Human Research Seminar Series

How to Maintain Research Data

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How to Maintain Research Data

Contribution to Science

• Provide generalizable knowledge to the scientific community
• Uncovering better ways to treat, prevent, diagnose and understand human disease
• Other
Research

• **Research** is a systematic investigation designed to develop or contribute to generalizable knowledge.


• **Clinical research** is medical research that involves … carefully conducted investigations that ultimately uncover better ways to treat, prevent, diagnose and understand human disease.


Ensuring Credible/Reliable Data and Enhancing Subject Safety

• **Proactive approach** – begin the compliance process before the study starts:
  > KNOW THE PROTOCOL; *is the current protocol on file?*
  > Understand what is required before the study starts
  > Self-monitor your studies (QA activities)
  > Know your SOPs, processes and institutional requirements
  > Educate
    • Study staff
    • Ancillary staff
    • Investigators, residents, fellows
    • Subjects
Why are Monitoring Site Visits and Audits Performed and What’s the Difference?

- Ensure that the rights and welfare of research subjects are protected
- Ensure that the trial is being conducted in a way that supports credible data collection and submission
- Evaluate compliance with institutional and federal requirements

Research Oversight

- FDA (Oversees Drugs/Devices/Biologics)
- OHRP (Oversees Human Research)
- Sponsor
- Institution (Einstein IRB, JCAHO, Cancer Center, etc.)
- PI
- External DSMB
- Internal DSMC
# Methods of Ensuring Compliance

- **Sponsor**
  - Monitoring Site Visits (quality control)
  - Sponsor Audits (quality assurance)

- **FDA**
  - Inspections

- **Institutional**
  - SOPs

- **Einstein IRB**
  - Audits
  - Adverse Event Review
  - Progress Reports

- **DSMB / DSMC**
  - Periodic review of data and subject safety

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# How is Compliance Determined?

Do you comply with:
- IRB Policies & Procedures and reporting requirements
- SOPs – Departmental / Institutional
- Federal Regulations (FDA, OHRP) & GCPs
- DSMC / DSMB reporting requirements
- Investigational plan / sponsor requirements

Do you have evidence of compliance through appropriate documentation practices?
Federal Regulations & Guidance Documents

- Regulations – CFR Title 21 = “Must”
  - GCP regulations 21 CFR Parts 50, 54, 56, 312, & 812
  - Records and Reports
- Guidance Documents = “Should” (FDA’s current thinking on how to comply with the regulations)
  - GCP guidance documents include ICH E6

Compliance with Einstein IRB Policies

- Required Documentation for the Conduct of Research Involving Human Subjects (1/13/2012)
  - [http://www.einstein.yu.edu/docs/administration/institutional-review-board/policies/Documentation.pdf](http://www.einstein.yu.edu/docs/administration/institutional-review-board/policies/Documentation.pdf)

- Audit and Inspection Guidelines (1/13/2012)
  - [http://www.einstein.yu.edu/docs/administration/institutional-review-board/policies/audit.pdf](http://www.einstein.yu.edu/docs/administration/institutional-review-board/policies/audit.pdf)
Definitions

- ICH – E6 Good Clinical Practice (GCP): Consolidated Guidance
  > Section 1: Glossary
  > Section 8: Essential Documents for the Conduct of a Clinical Trial (8.2 before; 8.3 during; 8.4 after completion or term.)
  > Section 8.4.7: Final report by investigator/institution to IRB/IEC where required...

What is an Audit?

- A systematic and independent examination of trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s). [ICH E6 Glossary]
Types of Audits

- **Routine** – Usually random, studies may also be selected because of high enrollment
  > FDA, Einstein IRB, Sponsor
- **Directed** (for cause) – Response to a complaint or identified non-compliance
  > FDA, Einstein IRB, Sponsor
- **Educational** – Request from site or Einstein IRB
  > Einstein IRB

What is Reviewed?

- **Essential Documentation** - Permits evaluation of the conduct of a trial and the quality of the data produced
  > Core Documents (regulatory binder)
  > Protocol Related Documents
  > Drug / Device / Biologic Control (receipt, dispensing, accountability, maintenance)
  > Source Documents (Subject Related)
- **Other** – Responsibilities, communication, processes, SOPs, Interviews
Essential Documentation:
Core Documents

Examples include:
- 1572
- Delegation of authority & Key Personnel
- Conflict of interest
- Einstein IRB documents / communication
- Sponsor communication (e.g. monitoring site visit letters)
- CVs, licenses, lab certificates
- Receipt and submission of amendments
- External AEs
- Progress reports

Essential Documentation:
Protocol Related

Examples include:
- Logs (screening, eligibility, enrollment)
- Case Report Forms (tools used for data analysis)
- Data Collection Tools
- Specialized study-related processes (lab collection, processing, shipment)
- Most recent protocol and past protocols including amendments
- Protocol Deviation and Corrective Action
- Adverse Event Documentation
- Revisions to ICD
- DSMB/DSMC Reports.
Essential Documentation: Drug/Device/Biologic Control

Examples include:
- Inspection of the study drug
- Drug Accountability Log (when applicable)
- Device Accountability Log (when applicable)
- Shipping Documents for Device / Drug
- Blinding and un-blinding Plans/documentation
- Temperature logs
- Labeling
- Orders / prescriptions
- Administration records

Essential Documentation: Subject Related

Review of case histories. Examples include:
- Laboratory/Procedural Results
- Original Signed Consent Form(s) & HIPAA Authorizations
- Physical exams, Vital Signs, Weight, BMI
- Written Documentation of Study-Related Visits
- Completed Diaries and Questionnaires
- Hospital, Clinic, Research Records
- Clinical Observations/Evaluations
- Study drug start/stop times
- Deviation submissions
- Corrective & preventative actions.
Essential Documentation: Subject Related

• Examples of what we look for…
  > Are informed consents signed, dated and complete?
    • Was the process documented adequately?
  > Were procedures performed after consent was signed?
  > Were procedures completed according to the protocol?
  > Is there a source for the data recorded on the CRF?
  > Was there adequate investigator supervision?
  > Was delegation of authority appropriate?
  > Did the subject experience adverse events?
    • Were adverse events reported accurately and with timeliness?
  • Is the documentation attributable, legible, contemporaneous, original and accurate?

Other

• Staff Interviews
  > Aware of regulations and Einstein IRB requirements
  > Understand sponsor requirements
  > Understand the protocol
• Adherence to SOPs
  > Do you adhere to your SOPs
• Responsibilities
  > Are the responsibilities that are delegated appropriate
  > Is there evidence of adequate PI supervision
• Processes
  > Do your processes support safety of subjects and credible data
Overall Review

• Is documentation:
  > Organized
  > Complete
  > Up-to-date

• Is there:
  > Evidence of appropriate and timely review of study related procedures (CS/NCS)
  > Signatures, indicating review and approval, from appropriate members of the research team
  > Timely responses to requests from the sponsor, Einstein IRB

Elements of Data Quality

• Are study-related activities ALCOA:
  > Attributable
  > Legible
  > Contemporaneous
  > Original
  > Accurate
Common Findings

- Informed consent deficiencies
- Study records – deficiencies in case histories
- Compliance with IRB policy – Adverse event policy
- Protocol deviations

Informed Consent Deficiencies

- ICD dated by someone other than the subject
- IC documentation does not include either a time or a statement that the consent was obtained prior to initiation of study procedures
- Original consent could not be found (copy only)
- Lack of documentation that the subject received a copy of the consent
FDA Warning Letter Excerpts

“Subject signed the consent form on [redacted]; however, the witness signed the consent on [a different date].”

“Subjects signing the informed consent in most cases did not complete dates. It appears that the study coordinator…completed the date.”

“You failed to provide study subjects with a copy of their signed informed consent document.”

“The original consent forms could not be located for 18…subjects enrolled in the study. Copies were available in study binders and subject charts.”

How to Avoid

• Do not try to be helpful and date the consent for subjects or investigators
• Take time to document the informed consent process – include the time that the consent was obtained and a statement that consent was obtained prior to study related procedures (if that was the case–should always be the case)
• After giving a copy of the consent to the subject, document
Deficiencies in Study Records
Inadequate or Inaccurate Case Histories

Common Findings:
> Pencil, white-out, illegible entries
> Revisions to source or CRF without initials/date
> Revisions to CRFs without rationale in source
> CRF does not match source documentation
> PI signature and/or date missing on essential documents (eligibility, consent note, queries, CRFs, adverse event submissions)
> Source missing
> Inaccurate / missing times / dates of procedures
> Documented assessments of CS labs/procedures missing

Documentation of case histories is essential to verify that study activities were done appropriately.

FDA Warning Letter Excerpts

“Records…were written in pencil, and many entries are illegible.”
“Entries were obscured by correction fluid.”
“There is no documentation of the name or initials of the person making entries in the records.”
“Source data for various assessments could not be located.”
“There is no record of who administered the study drug…Without a record of who administered the study drug, you cannot assure that these injections were performed by a member of the blinded study team.”
FDA Warning Letter Excerpts

“There was no supporting data...to confirm information contained in their case histories to demonstrate their eligibility...”

“The CRF contained blank fields.”

“Number of discrepancies were noted between source documents and data recorded on the CRFs...[CRF] indicates that a pericardial effusion was present, but echocardiogram report...states that no pericardial effusion was present.”

How to Avoid

• Don’t use pencil or white out
• Don’t obscure original entries, line through (once), initial & date
• Write the corrected entry and the reason for the correction is generally included
• Maintain accurate records of study related activities
• Ensure that there is a source for each CRF entry
• Maintain source data with research record
• Ensure the timely review of study labs/procedures
  > Assessment, initials/date of Investigator (documented in subject chart)
Deficiencies in Compliance with IRB Policies

- Inaccurate information
- No notification
- Late submission
- No follow-up
- Assessment of event by unqualified personnel

FDA Warning Letter Excerpts

Failure to comply with IRB reporting requirements:

"Your IRB requires that a written report of the death of any research subject be made within ___ business days...five or more subject deaths have not been reported to the IRB."
How to Avoid

- Know your AE reporting policies:
  - Sponsor’s policy
  - Einstein IRB policy
- Submit reports & complete notifications with timeliness
- If you are unsure about reporting criteria, call the Einstein IRB
- Make sure that your report is complete prior to submission (evaluated by PI/Co-I, personally signed and dated).
- Keep track of AE reports and submit a follow-up report when new information becomes available.

Deviations

- A protocol deviation/violation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change.
- Protocol deviation is also used to refer to any other, unplanned, instance(s) of protocol noncompliance.
- For example:
  - Situations in which the investigator failed to perform tests or examinations as required by the protocol or
  - Failure on the part of study subjects to complete scheduled visits as required by the protocol.
FDA Warning Letter Excerpts

"An ultrasound was not done at six months for subject."

"Numerous assessments were not completed as required by the protocol."

"Physical exam at six months was not done for subject."

"You did not conduct certain follow up visits or document efforts to locate missing subjects."

"An ultrasound was not done at six months for subject."

“Although laboratory samples were taken for certain tests, including the hematology, biochemistry, coagulation and/or the test,…these laboratory samples were not performed within the protocol specified time periods…”

How to Avoid Unplanned Deviations

• Know the protocol, ask questions
• Pay attention to monitoring visit letters / reports
• Perform timely self-monitoring of protocol adherence
• Carefully monitor those activities that are delegated to others
• Educate and re-educate when necessary
Unplanned Deviations that Already Occurred

- Sometimes, despite your best efforts, deviations will occur. Here’s what you need to do:
  - Document and submit to the Einstein IRB and notify sponsor
  - If serious or multiple deviations occur:
    - Find the root cause and develop a Corrective And Preventative Action (CAPA) plan
    - Monitor the success of the CAPA plan
    - Develop internal processes to address issues

Identify, Correct, Prevent, Implement and Evaluate

Corrective And Preventative Action (CAPA) Plans
- Identify the circumstance that led to the issue
- Describe how it was corrected
  - Generally, only data errors can be “corrected.” Other problems, e.g., wrong drug given or vital signs not taken, can’t be corrected, but you can find a way to prevent future occurrences.
- Develop a plan to prevent future occurrences
- Implement the plan
- Evaluate the success of the plan
Prepare for a Monitoring Site Visit or Audit

- Make sure your regulatory documents are organized and complete
  > Ensure that logs are completed
  > Appropriate review, signatures and dates are completed
  > The records are organized
  > Up-to-date recurring documents are in place:
    • Examples - CVs, licenses, COIs, lab certificates
    • Delegation of authority
- Make sure that requested documents are available for review prior to the site visit/audit (you will receive a list of documents ahead of time)

Prepare for a Site Visit or Audit

- Have study records ready for all subjects requested:
  > Original informed consent forms
  > Source documents
  > CRFs
  > Drug accountability
- Schedule appointments with ancillary departments (pharmacy, radiology, etc.)
- Schedule an exit visit with the PI
- Prepare a space for the visit that is private, quiet and has access to a copier and Internet
During the Visit

- Prepare for a general discussion about the study
- Ask for help – when you don’t know something, ask the PI, Einstein IRB, or sponsor
- Ask questions
- Be available for questions

What Happens After the Audit?

- The PI will receive a report with the findings
- The PI will have an opportunity to respond
  > Non-significant findings may result in a CAPA plan and directed education
  > Significant findings of non-compliance will be reviewed by the Joint Executive Committee
    - The Joint Executive Committee decides what actions to take including:
      - Corrective and preventative actions
      - Education of investigator / staff
      - Suspend or terminate the study (or all of the PI’s studies)
      - Report to OHRP or FDA
    - The Department Chair and the administrative representative are notified of the findings
Start Preparing for Your Next Site Visit/Audit NOW!

- Be proactive
  - Set up processes before the study starts (troubleshoot)
  - Monitor Study Team turn-over (SSL, Delegation Log, etc.)
  - Prepare source document templates:
    - Increase accurate data collection & decrease deviations
- Be vigilant
  - Develop an internal QA process to monitor the study
    - Address deficiencies promptly
    - Develop CAPAs / processes that address deficiencies
- Seek knowledge regarding:
  - Federal regulations (Title 21 CFR) & Guidance Docs (ICH-E6)
  - State / institutional requirements
  - Trends in research

Education & Training Opportunities

- Einstein IRB
  - Seminars
  - On-site education to meet specific needs
  - Educational site visits
  - Monitoring
  - Assistance with developing “source templates”
  - Assistance with creating study document binders
- NIH, OHRP, Mayo, CITI (free)
- Professional Associations (ACRP, SOCRA)
- Mentoring with someone more experienced
- Attend local in-services
Questions?

• Any questions, please contact the Einstein IRB
• East Campus:
  > Jacqueline Rowan, QA Coordinator
  > 718-430-2268
  > jacqueline.rowan@einstein.yu.edu
• West Campus:
  > Kathleen O'Connor, QM Analyst
  > 718-920-4151 x228
  > koconno@montefiore.org

Einstein IRB Contact Information

**East Campus IRB**
- Belfer Building, Room 1002
  1300 Morris Park Avenue
  Bronx, NY 10461
- Phone: 718-430-2237
- Fax: 718-430-8817

**West Campus IRB**
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  Bronx, NY 10467
- Phone: 718-798-0406
- Fax: 718-798-5687

Website: [http://www.einstein.yu.edu/irb](http://www.einstein.yu.edu/irb)
Includes: Policies and Procedures,
Submission Guidelines, Forms, and
Educational Materials
Required Documentation for the Conduct of Research Involving Human Subjects

An inspection of required research documents may be conducted by a research sponsor, Contract Research Organization, Einstein IRB or Regulatory Agency, such as the FDA or OHRP. These inspections are part of the process to confirm the validity of the trial conduct, the integrity of data collected and confirm that any unanticipated problems have been properly reported.

Required documents are those which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator with accepted standards of research practice and applicable regulatory and institutional requirements.

Terms:

OHRP: The Office for Human Research Protections (OHRP) is involved in the protection of the rights, welfare, and well being of subjects involved in research conducted or supported by the U.S. Department of Health and Human Services (HHS).

FDA Regulated Product: FDA regulated products include but are not limited to human drugs, devices, therapeutic biologicals, vaccines, tissue, blood, and other products derived from living sources, instruments or products used for treating or diagnosing disease.

IND: The clinical investigation of a drug that is not marketed requires submission of an Investigational New Drug (IND) application to FDA. The clinical investigation of a marketed drug requires submission of an IND application to FDA unless the clinical investigation meets certain conditions.

IDE: An investigational device exemption (IDE) allows an investigational device to be used in a clinical study in order to collect safety and effectiveness data.

Minimal Risk: The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Required documents should be maintained by the investigator in printed form or on a secure server. Documents should not be maintained exclusively on a flash drive or email archive. The investigator is to keep the original signed copy of the consent form and HIPAA authorization. A copy or second signed original should be provided to the participant and filed with the clinical record.

Required documents are listed below.

I. All Research: (Includes human subjects research that poses only minimal risk to the subject)

1. General Research Protocol Application and all related documents (with signatures)
2. Initial IRB Approval letter
3. Protocol
4. Protocol Amendments
5. IRB Approval letter for each amendment
6. All IRB approved versions of Informed Consent Forms & HIPAA Authorization Forms (unless the consent requirement has been specifically waived by the IRB)
7. Progress Report Form submitted to the IRB and all related documents (with signatures)
8. IRB Recertification letters
9. Deviation Reports submitted to the IRB and IRB acknowledgements
10. Adverse Event Reports submitted to the IRB
11. All monitoring reports (if third party monitoring is done)
12. Subject Identification Log
13. Completed Case Report Forms or Data Collection Forms (as applicable)
14. Original Signed Informed Consent Forms
15. Correspondence with study sponsor or outside agencies (if applicable)

II. All Research involving greater than minimal risk to the subject:
All of the above (1-15) and:
16. Data Safety Plan and Reports (if applicable)

III. All Research involving a drug or therapeutic device
All of the above (1-16) and:
17. Delegation of Authority/ Signature Log
18. For Drug Studies: Drug Accountability Log and shipping records (when Investigator is providing the drug to subjects).
19. For Drug Studies: Pharmacy Waiver (if not using the MMC Pharmacy for Drug Storage and Dispensing)
20. For Drug Studies: Investigator’s Brochure or Product Insert
21. For Device Studies: Device Accountability Log and shipping records (when the Investigator provides the device to subjects)
22. For Device Studies: Device Manual
23. Decoding Procedures (if trial is blinded)
24. Instructions (if any) for handling of investigational products

IV. All research involving a FDA regulated product with an IND/IDE (PI is not IND/IDE holder)
All of the above (1-24) and
25. CV – Principal Investigator
26. Source Documents (including, for example, progress notes, physical exams, ecgs, lab reports etc.)
27. For Drug Studies: Form 1572 – Statement of the Investigator
28. For Device Studies: Investigator Agreement
29. CV of Subinvestigators
30. Laboratory normal values for all lab tests used (Outside Labs only) – MMC normal values are available on the MMC Intranet – Department of Pathology
31. Lab certificates for all labs used (Outside Labs only)- MMC Lab Certificates are on file with the Department of Pathology 920-2456
Audit and Inspection Guidelines

I. Purpose

Research is subject to audit and inspection by regulatory agencies, including the Food and Drug Administration (“FDA”) and Office for Human Research Protections (“OHRP”). Federal law allows an FDA investigator who provides written notice (Form 482) and shows appropriate credentials to enter a regulated establishment. FDA has broad authority to inspect equipment, materials, products, labeling and certain records. An inspection can be comprehensive, focused on a specific issue or set of issues, or in response to a reported problem. Investigation techniques may include observing operations, examining equipment, reviewing documents, collecting product samples, and interviewing employees. Likewise, OHRP has broad audit and inspection powers to ensure protection of human subjects in research. Any external investigation, inspection or other external review and its outcome must be reported to the Einstein IRB Director.

II. Recommendations

A. Preparing for the inspection

1. When an inspector from a regulatory agency calls to schedule an inspection, ask the following:
   a. Inspector name, agency and contact information
   b. The name of the PI being inspected
   c. What studies are being inspected
   d. The reason for the inspection
   e. Does the inspector want specific personnel available?
   f. Does the inspector want specific documents available?

2. Document any telephone conversation(s) that occur between the inspector and the study staff.

3. Print any records specifically requested in advance by the inspector. The inspector is not authorized to review documents using MMC electronic medical Records systems. Hard copies should be provided.

4. As soon as you are notified of an impending inspection, notify the following parties. Include the study name, the IRB number, and the date of the inspection:
   a. All study staff
b. Department Chair
c. Sponsor (if applicable)
d. Einstein IRB Manager (in all cases)
e. BRANY IRB Manager (if applicable)
f. Montefiore Research Billing Compliance Analyst
g. The Department of Pharmacy (if applicable)

5. The inspector will usually request that the inspection take place within 10 days. This request should be accommodated.

6. Reserve a room in a private area for the inspection. The room should contain no files or records. Make sure that there is a copy machine located close to the room.

7. Identify a person who will serve as an escort and oversee the inspection. This person is usually a research coordinator familiar with the study. The escort will serve as a guide and general study contact person. The escort will need to accompany the inspector when touring the facility and be readily available to the inspector at all times but does not need to be always present in the room while the inspector is reviewing documents.

8. Ensure that all study documentation, including informed consent forms, source documents, CRFs, regulatory documents, and sponsor correspondence are available for review by the inspector, if requested.

9. Keep all study documents and records ready and accessible, but do not volunteer a list of them to the inspector. Always wait for a specific request to provide information.

B. During the Inspection

1. The Principal Investigator (PI) or his/her designee should meet the inspector and receive and, in the case of an FDA inspection, sign the FDA form 482 “Notice of Inspection.” Request to see the inspector’s identification if he/she does not present it to you.

2. The inspector may request a tour of the facility areas where the research took place. The escort should accompany the auditor at all times during the tour.

3. Provide the inspector only with files that have been requested.

4. The inspector may request copies of some documents. Remove subject identifiers from the copies given to the inspector. Make a copy for yourself of any documents that are requested by the inspector.

5. The PI should set aside time each day to talk with the inspector, as well as being available for any questions that may arise.
6. Answer all questions from the inspector honestly and completely. Listen carefully to the question and only answer what was asked. It is OK to defer to the PI or other study staff if you don’t know the answer. Keep a log of questions asked by the auditor.

7. How to answer Questions:
   a. Be concise; answer only the question that is asked
   b. Always be clear and honest in your answers
   c. Do not provide information that the inspector has not asked for. When answering questions, do not guess or speculate. If you don’t know the answer, write down the question and refer it to the appropriate person (PI or other study staff.)

C. After the inspection
   1. The inspector will hold an exit interview at the conclusion of the audit. At a minimum, the escort, PI, and a representative from the Einstein IRB should attend this interview. The purpose of this interview is to review the findings and deficiencies, if any.

   2. Findings will be reviewed during the exit interview
      a. The escort should document the conversation, specifically noting observations, recommendations, comments, and commitments.
      b. If any deficiencies were found during an FDA inspection, they will be noted on the FDA Form 483. The PI should forward a copy to the Einstein IRB Director.

   3. A corrective or preventative action plan, if indicated, should be submitted to the IRB in advance of submission to the Regulatory Agency.

   4. All correspondence received from regulatory agencies before, during and after the inspection should be submitted to the IRB.

For questions, contact the Einstein IRB Director at 718.430.2237.
Dear Dr. Picus:

Between October 14 and 28, 2009, Ms. Kathleen Swat, representing the Food and Drug Administration (FDA), conducted an investigation and met with you, to review your conduct of the following clinical investigations:

- Protocol (b)(4), entitled (b)(4) of the investigational drug (b)(4), performed for (b)(4).
- Protocol (b)(4), entitled (b)(4) of the investigational drug (b)(4), performed for (b)(4).
- Protocol (b)(4), entitled (b)(4) of the investigational drug (b)(4), performed for (b)(4).

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to help ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection, Ms. Swat presented and discussed with you Form FDA 483, Inspectional Observations. We acknowledge receipt of your responses dated November 11, 2009, and January 6, 2010, to Form FDA-483. We wish to emphasize the following:

1. You failed to personally conduct or supervise the clinical investigation [21 CFR 312.60].

When you signed the Statement of Investigator (Form FDA 1572) for the above-referenced clinical trials, you agreed to take on the responsibilities of a clinical investigator at your site. Your general responsibilities as a clinical investigator include ensuring that the clinical trial is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; protecting the rights, safety, and welfare of subjects under your care; and ensuring control of drugs under investigation [21 CFR 312.60]. By signing a Form FDA 1572, you specifically agreed to personally conduct the clinical trial or to supervise those aspects of the trial that you did not personally conduct. While you may delegate certain study tasks to individuals qualified to perform them, as a clinical investigator, you may not delegate your general responsibilities. Our investigation indicates that your supervision of personnel to whom you delegated study tasks was not adequate to ensure that the clinical trial was conducted according to the signed investigator statement, the investigational plan, and applicable regulations, and in a manner that protected the rights, safety, and welfare of human subjects. Your failure to adequately supervise led to significant problems with the conduct of the study described below.
2. You failed to ensure that the investigation was conducted according to the investigational plan, and you failed to protect the rights, safety, and welfare of the subjects under your care [21 CFR 312.60].

As the clinical investigator, you are responsible for ensuring that the investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations, and for protecting the rights, safety, and welfare of study subjects. Failure to adhere to protocol-specified procedures compromises the safety and welfare of subjects enrolled in the clinical investigation. Specifically:

a. Protocol (b)(4) specified that blood samples for chemistry and hematology should be drawn and the test results should be reviewed within the 24 hours prior to dose administration. The protocol further specified that Liver Function Test (LFT) results must be reviewed for dose modification and withholding of treatment.

Our investigation found no documentation that Subject 040-001’s LFT results were reviewed by you or your research staff for the protocol-specified procedures for dose modification and withholding treatment, and the subject was dosed on April 3, 2009.

On (b)(6), Subject 040-001 was taken for emergency medical care with symptoms of vomiting and fever. Subject 040-001 was pronounced dead on (b)(6), by the attending physician, with the cause of death being attributed to cardiac arrest due to severe metabolic acidosis due to multiorgan failure.

In a follow-up case report form dated October 7, 2009, you reported that Subject 040-001 died of liver failure. You reported that the death was not due to a gastrointestinal stromal tumor (GIST), and that the relationship of the death to the study drug was “probable.” You also documented the protocol deviation that Subject 040-001 was treated on April 3, 2009, with elevated LFT, although the protocol specified that the dose should have been withheld.

b. Protocol (b)(4) specified that study drugs were to be prepared by the pharmacist or designee who was trained in the safe handling and administration of a cytotoxic agent.

The Infusion Preparation Log for Subject 040-001 documents that study drugs were prepared on March 24, March 27, March 31, and April 3, 2009, by an individual identified only by the initials (b)(6). There was no documentation in the study records that (b)(6) was the pharmacist or designee, or that (b)(6) had been trained in the safe handling and/or administration of a cytotoxic agent.

In your response dated November 11, 2009, you acknowledge that a number of procedures were not appropriately followed, that the abnormal laboratory results were not reviewed by staff prior to treatment, and that the study drug was not withheld as the protocol specified. Further, you indicated that you failed to maintain an accurate Delegation of Authority log that identified (b)(6) and the responsibilities delegated to (b)(6).

We acknowledge your response that you have implemented a formal double check process that requires proof that one registered nurse (RN) documents his/her review of the laboratory values and that a second RN documents a separate and independent review, prior to the Pharmacy dispensing study medications. Your response is acknowledged and is acceptable if implemented as proposed. In addition, you further indicated that you are revising staffing, so that all matters pertaining to studies will be performed by a restricted subset of trained research staff members. We acknowledge your response. However, we are concerned that the response is not adequate to prevent future recurrence of the violation noted above.

3. You failed to obtain informed consent in accordance with the provisions of 21 CFR Part 50 [21 CFR 312.60].

Except as provided in 21 CFR 50.23 and 21 CFR 50.24, no investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative [21 CFR 50.20]. Informed consent must be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time consent [21 CFR 50.27(a)].

For Protocol (b)(4), Subject 040-001’s screening date was reported as March 19, 2009. The subject signed the IRB-approved informed consent on March 24, 2009. However, source records for Subject 040-001 document that study-related tests and procedures were performed prior to the date of consent. A blood sample was collected for study screening on March 12, 2009; the investigational dose was prescribed on March 20, 2009; and subject randomization occurred on March 23, 2009. Study-qualifying electrocardiograms (ECG), an eye examination, and a blood draw were performed on March 23, 2009.

In your response dated November 11, 2009, you acknowledge that you failed to obtain written consent from the subject prior to conducting all screening procedures, but that you documented the subject’s verbal consent process in study records. The regulations require that informed consent be signed and dated by the subject or the subject’s legal
representative prior to the subject’s involvement in the investigation [21 CFR 50.20]. Failing to obtain adequate informed consent jeopardizes the safety and welfare of enrolled subjects by denying them an opportunity to assess the risks and benefits of their participation in the clinical investigation.

We acknowledge your response. However, the response is not adequate, because you did not propose corrective actions to prevent future recurrence of the violation noted above. In particular, your response did not indicate that you properly understand the regulations for obtaining the legally effective informed consent of the subject.

4. You failed to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects [21 CFR 312.62(a)].

Drug accountability records are incomplete and inaccurate for Protocol (b)(4). There are discrepancies in dates, lot numbers, and drug identification numbers. Examples include but are not limited to the following:

a. Master Investigational Product Accountability Records do not account for all study drug received on September 29, 2009. Kits 754083, 765462 and 842798 listed on the Proof of Receipt record were not documented in the Master Investigational Product Accountability Record.

b. Investigational drug received on October 07, 2009, boxes 00690997 and 00696204, are documented twice in the Drug Accountability Records.

c. Subject Specific Investigational Product Accountability Records for Subject 6111-08201 lack complete documentation for IV Bag Size, Total Volume Prepared, and Number of IV Bags Used.

We note your acknowledgment that you failed to maintain adequate and accurate drug accountability records. We also acknowledge the corrective actions, described in your written response, that you have taken to prevent drug accountability discrepancies in the future. We find these corrective actions adequate, if implemented as proposed.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical study of an investigational drug. It is your responsibility to ensure adherence to each requirement of the law and relevant FDA regulations. You should address these deficiencies and establish procedures to ensure that any ongoing or future studies will be in compliance with FDA regulations.

Within fifteen (15) working days of your receipt of this letter, you should notify this office in writing of the actions you have taken to prevent similar violations in the future. Failure to adequately and promptly explain the violations noted above may result in regulatory action without further notice.

If you have any questions, please contact Constance Cullity, M.D., M.P.H., at 301-796-3397; FAX 301-847-8748. Your written response and any pertinent documentation should be addressed to:

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Good Clinical Practice Branch I
Division of Scientific Investigations
Office of Compliance
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Sincerely yours,
/S/
Leslie K. Ball, M.D.
Director
Division of Scientific Investigations
Office of Compliance
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.
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/s/
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Dear Dr. Snow:

Between April 27 and May 7, 2009, Ms. Barbara Wright, representing the Food and Drug Administration (FDA), conducted an investigation and met with you, to review your conduct of clinical investigations [protocol 008, parts A and B, both entitled "A multi-center randomized, double-blind, placebo-controlled trial of ibuprofen injection (IVIb) for treatment of pain in post-operative adult patients"] of the investigational drug ibuprofen (Amelior), performed for Cumberland Pharmaceuticals.

This inspection is a part of the FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report, the documents submitted with that report, and your written response dated October 16, 2009, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations. We are aware that at the conclusion of the inspection, Ms. Wright presented and discussed with you Form FDA 483, Inspectional Observations.

1. You failed to ensure that the investigation was conducted according to the signed investigator statement, in that you failed to personally conduct or supervise the clinical investigation [21 CFR 312.60].

When you signed the Statement of Investigator (Form FDA 1572) for the above referenced clinical trial, you agreed to take on the responsibilities of a clinical investigator at your site. Your general responsibilities as a clinical investigator include ensuring that the clinical trial is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; protecting the rights, safety, and welfare of subjects under your care; and ensuring control of drugs under investigation [21 CFR 312.60]. By signing Form FDA 1572, you specifically agreed to personally conduct the clinical trial or to supervise those aspects of the trial that you did not personally conduct. While you may delegate certain study tasks to individuals qualified to perform them, as a clinical investigator you may not delegate your general responsibilities. Our investigation indicates that your supervision of personnel to whom you delegated study tasks was not adequate to ensure that the clinical trial was conducted according to the signed investigator statement, the investigational plan, and applicable regulations, and in a manner that protects the rights, safety, and welfare of human subjects.
We note that your failure to adequately supervise this study led to significant problems identified below with the conduct of the study.

2. You failed to 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)].

   a. The primary efficacy endpoint of the protocol was to measure the reduction in the requirement for morphine use in the 24 hours following surgery measured by total morphine usage compared to placebo. We are unable to determine the total morphine dose administered to subjects as documented in the hospital records, compared to the documents in the subjects’ files. Examples include, but are not limited to, the following:

      i. Regarding Subject 3255, enrolled in protocol 008, part A, there are discrepancies in the total administered dose of morphine, as reflected in hospital records and the Case Report Form (CRF). The CPI-CL-008 Post Operative Pain Source Document and the CRF contain documentation of morphine administered consistently 40 or 41 minutes after the hour (e.g., 1340, 1440, 1541, 2241, etc.), and indicate that the subject was given a total dose of 37 mg of morphine between (b)(6). However, summing up the doses in the hospital Post Anesthesia Care Unit (PACU) report printed on (b)(6) (full year not legible) and the hospital Morphine Patient Control Analgesia (PCA) report reveals that the subject received a total of 18 mg of morphine between (b)(6). In addition, based on the hospital’s narcotic waste documentation, only a total of 15 mg of morphine was administered to this subject. A CRC Notes form in the subject’s case history addresses the discrepancy in the hospital records but does not offer any explanation; furthermore, it does not address the discrepancy between the total doses of morphine reflected in these hospital records and the CRF.

      ii. Regarding Subject 7060, enrolled in protocol 008, part B, the CRF contains documentation to indicate that the subject was given a total of 20 mg of morphine between (b)(6). However, hospital records indicate that the subject received a different total amount of morphine. For example, the hospital PACU report dated (b)(6), indicates that the subject received a 10 mg dose of morphine; and the hospital Medication Administration Record (MAR) reveals that a total dose of 31.75 mg of morphine was administered to the subject via patient controlled analgesia between (b)(6). Viewed together, these two hospital records (the MAR and PACU reports) indicate that the subject received a total dose of 41.75 mg of morphine, not the 20 mg reported in the CRF.

      iii. Regarding Subject 6057, enrolled in protocol 008, part B, the CRF contains documentation to indicate that the subject was given a total of 26 mg of morphine between (b)(6). However, the hospital PACU report dated (b)(6), revealed that the subject received a 4 mg dose of morphine; and the hospital MAR revealed that a total dose of 39 mg of morphine was administered to the subject via PCA between (b)(6). Viewed together, these hospital records indicate that the subject received a total dose of 43 mg of morphine, not the 26 mg reported in the CRF.

      iv. Regarding Subject 8058, enrolled in protocol 008, part B, the CRF indicates that the subject was given a total of 48 mg of morphine (40 mg from PCA and 8 mg from PACU) between (b)(6). However, the PCA Patient Assessment 24 Hour Flowsheet indicates that a total dose of 17 mg of morphine was administered to the subject via PCA between (b)(6), not the 40 mg reported in the CRF.

   b. Regarding protocol 008, part A, there were discrepancies between the hospital records and other documentation in Subject 2256’s file regarding the time of study drug administration. Specifically, the hospital MAR indicates that Dose 2 of the study drug was to be administered at 14:20, but was given at 15:30. However, the CPI-CL-008 Post Operative Pain Source Document indicates that the subject received Dose 2 from 14:20-14:50.

   c. Regarding protocol 008, part B, there was a discrepancy between the hospital records and other documentation in subject 5059’s file regarding the time of Imitrex administration, a concomitant medication. Specifically, the hospital MAR indicates that Imitrex was given at 8:00 a.m. on (b)(6). However, the concomitant medications page of the CRF indicates that Imitrex was dispensed at 9:40 a.m.

3. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].

   a. Protocol 008, part A specified that if any adverse event (AE) occurs during or after dosing with the study drug, the investigator will record the following information on the appropriate pages of the CRF: the AE; whether or not
the AE was judged to be study drug related; the date and time of occurrence; date and time of resolution (or a statement to indicate that it is still ongoing); severity of the AE; seriousness of the AE; relationship of the AE to study drug administration; treatment used; and outcome of the AE. The Discharge Summary noted that Subject 1252 had an episode of about 48 hours of vomiting requiring intravenous fluids. However, vomiting was not reported as an adverse event on the CRF.

b. Protocol 008, part A specified that the study will be double-blind and that the subject, investigator, and sponsor will be blinded to the assigned treatment until all subjects have completed the protocol and after the study database has been analyzed. The protocol also specified that a subject's treatment assignment will be revealed only in the case of an emergency, when it would be imperative for the assignment to be known. Despite the absence of any indication that an exception was warranted, the hospital Medication Administration Record (MAR) for Subjects 2251 and 4251 revealed their particular treatment arm (400 mg of ibuprofen) to study staff, in violation of the protocol.

c. Protocol 008, part A specified that a physical examination was required during the screening/baseline period (Hour -72 to Hour 0). The protocol-required screening/baseline physical examination for Subject 2251 was performed on January 18, 2006. However, the surgery and subsequent treatment with study drug did not take place until (b)(6), which is more than 72 hours from the date of the screening physical examination.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical study of an investigational drug. It is your responsibility to ensure adherence to each requirement of the law and relevant FDA regulations. You should address these deficiencies and establish procedures to ensure that any ongoing or future studies will be in compliance with FDA regulations.

Within fifteen (15) working days of your receipt of this letter, you should notify this office in writing of the actions you have taken to prevent similar violations in the future. Failure to adequately and promptly explain the violations noted above may result in regulatory action without further notice. If you have any questions, please contact Constance Cullity, M.D., M.P.H., at 301-796-3397; FAX 301-847-8748. Your written response and any pertinent documentation should be addressed to:

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Sincerely yours,
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/s/

LESLIE K BALL
09/29/2010