

Planning for FDA Clinical Site Inspections: Are You at Risk?

Catherine M. Anderson, Ph.D., RAC

29 April 2010

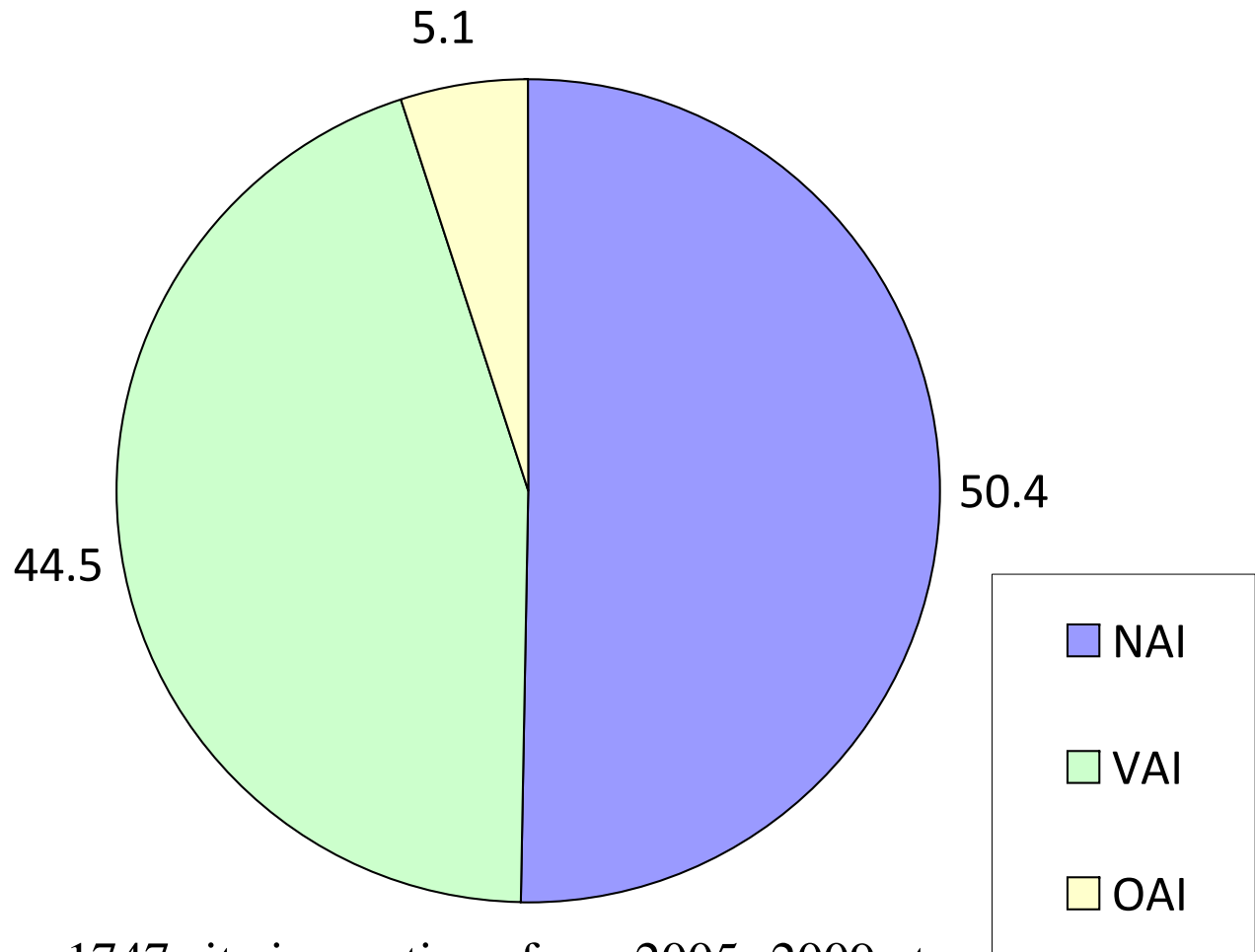
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Outcome of FDA



Inspections (2005-2009)*

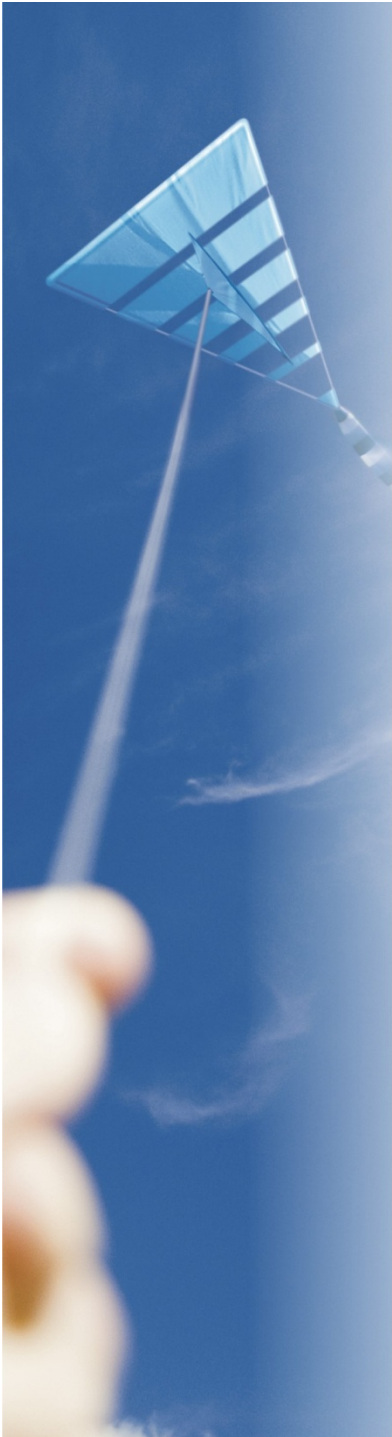


* Based on 1747 site inspections from 2005- 2009 at <http://www.accessdata.fda.gov/scripts/cder/CLIL>



Outline

- Responsibilities
- Inspection Process
- Inspection Outcome
- Inspection Preparation and Response



Responsibilities

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Sponsor Responsibilities



CFR 312.50-312.59

- Maintain IND
- Select qualified investigators
- Provide investigators all necessary information
- Inform FDA and investigators promptly of new AEs/risks

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Sponsor Responsibilities (2)



- Ensure adequate monitoring
- Ensure investigation is conducted per protocol
- Control shipment/disposal of drug

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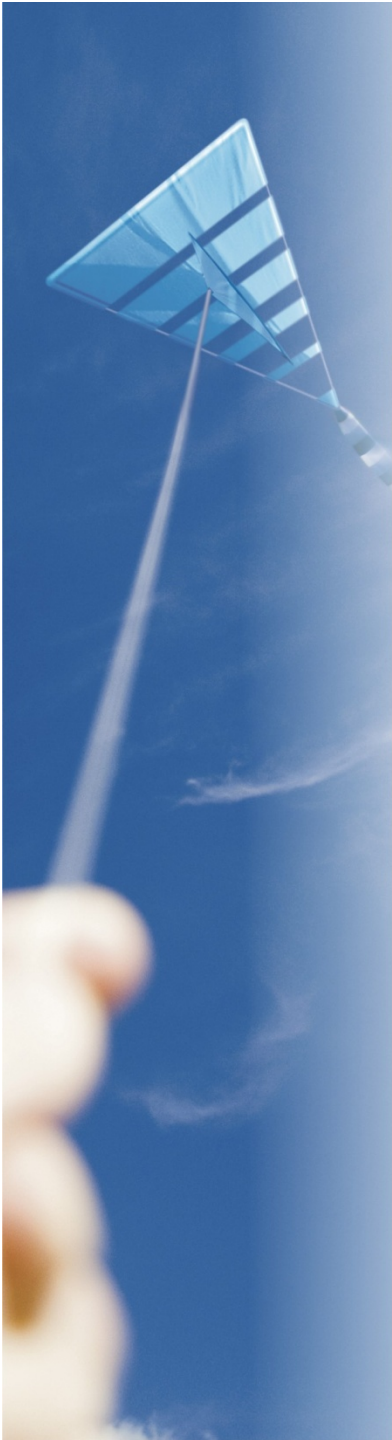


Investigator Responsibilities



- CFR 312.60-312.69, 56.108
- Follow the approved protocol or investigational plan and regulations
- Protect subjects
- Control investigational product
- Report AEs appropriately
- Ensure adequate IRB review
- Maintain adequate and accurate records

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Investigator

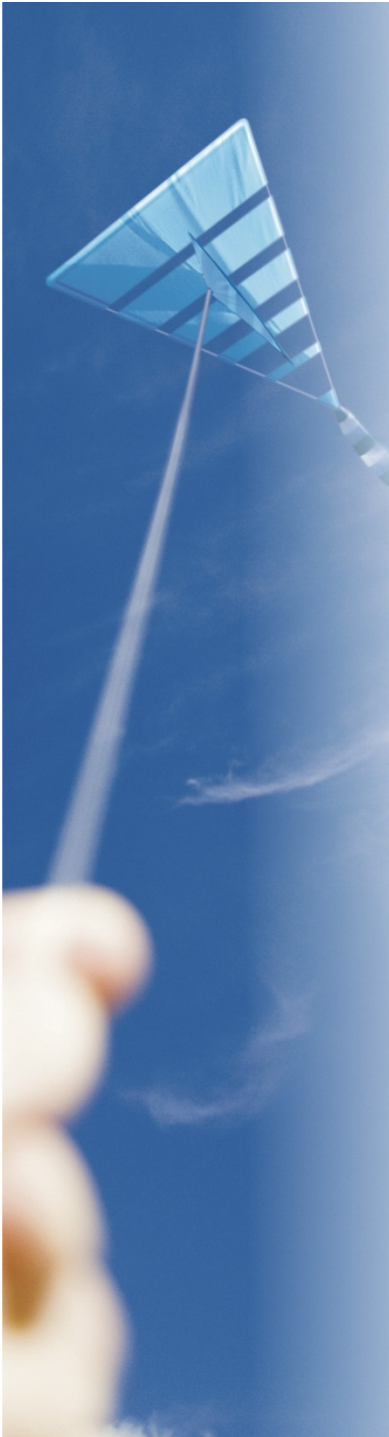


Responsibilities Example

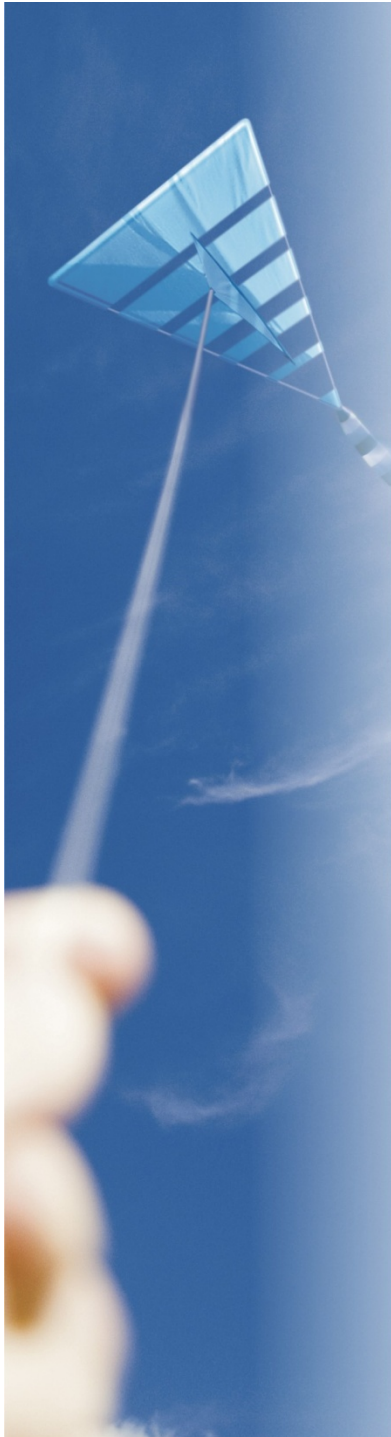
Holub, Richard, MD 01-Oct-08

You failed to ensure that the investigation was conducted according to the signed investigator statement and investigational plan [21 CFR 312.60].

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“Study coordinators who administered the informed consent, determined subject eligibility and dispensed study drug were not listed on the Form FDA 1572, Statement of Investigator. By performing these significant study activities, the study coordinators should have been listed.”



Bioresearch



Monitoring Program

- Inspections and data audits for FDA regulated research:
 - Clinical Investigators
 - Sponsors/CROs/Monitors
 - IRBs
 - Nonclinical Labs
 - In Vivo Bioequiv.
- Program Objectives:
 - Protect research subjects
 - Verify quality and integrity of data



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Inspection Authority

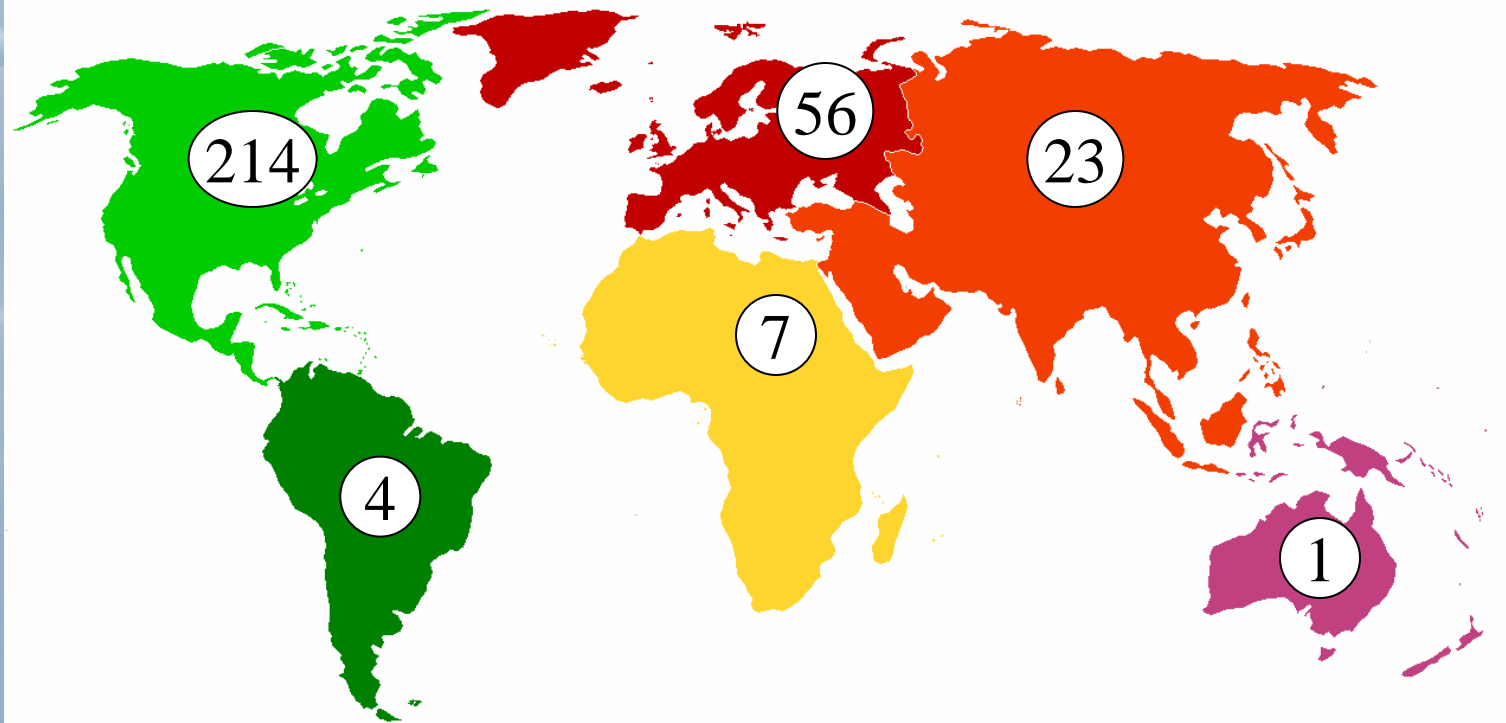


CFR 312.58, 312.68, 812.145

- FDA will have access to investigator and sponsor records/reports
 - May copy and verify if necessary
- Investigator is not required to release subject names
 - Unless...

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FDA Inspections 2009



* Based on 305 Clinical Site Inspections in 2009 at
<http://www.accessdata.fda.gov/scripts/cder/CLIL>

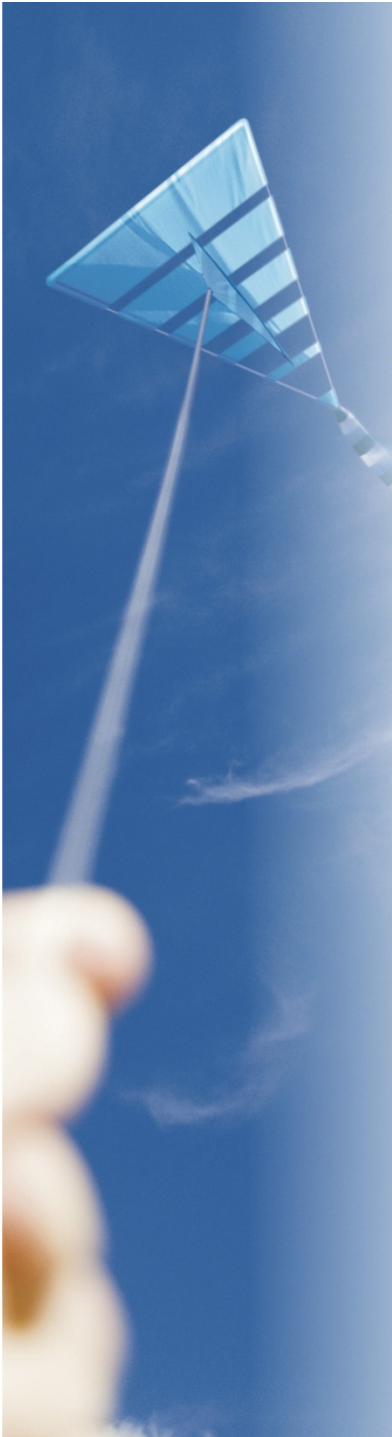


Inspection Triggers



- Routine inspection
 - Verify data submitted to FDA (ex: NDA)
 - FDA compares information at the site to submissions by the sponsor
- For cause inspection
 - Complaint about site's conduct of study
 - Compliance follow-up
 - FDA compares source documents with CRFs, etc.

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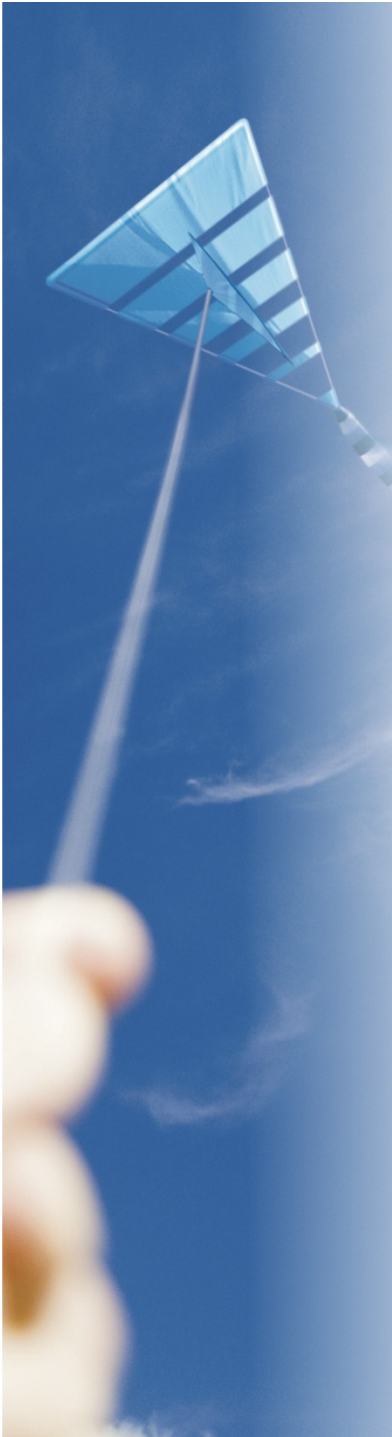


Site Selection



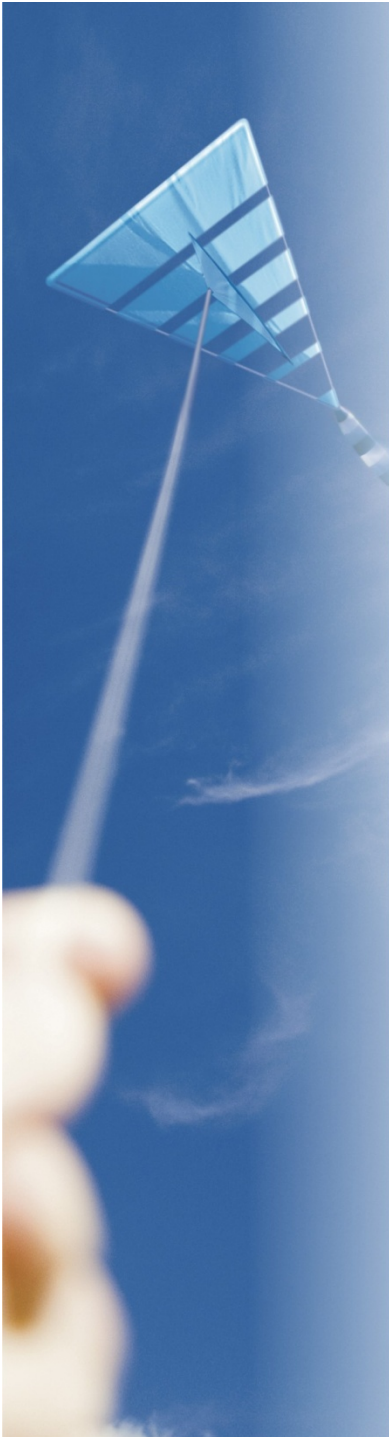
- Importance of site to study results/product approval
- Potential concerns at the site
 - SAEs
 - Whistle blower
 - Financial interest
 - Safety/efficacy data inconsistent with other sites

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Inspection Overview

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Notice of Inspection/Arrival



- Typically will be notified of inspection
- Upon arrival, the FDA Investigator:
 - Provides credentials to most responsible person
 - Issues Form FDA 482
 - Obtains list of studies performed by the investigator

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Duration of Inspection

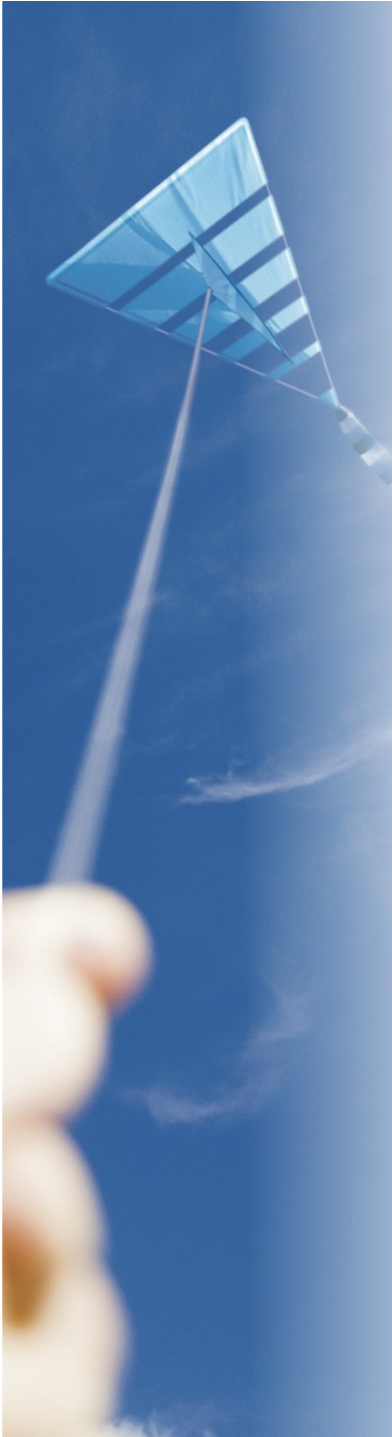


- Factors

- Complexity of study
- Availability/organization of records
- Extent of operations at facility
- Cooperation of firm
- Findings

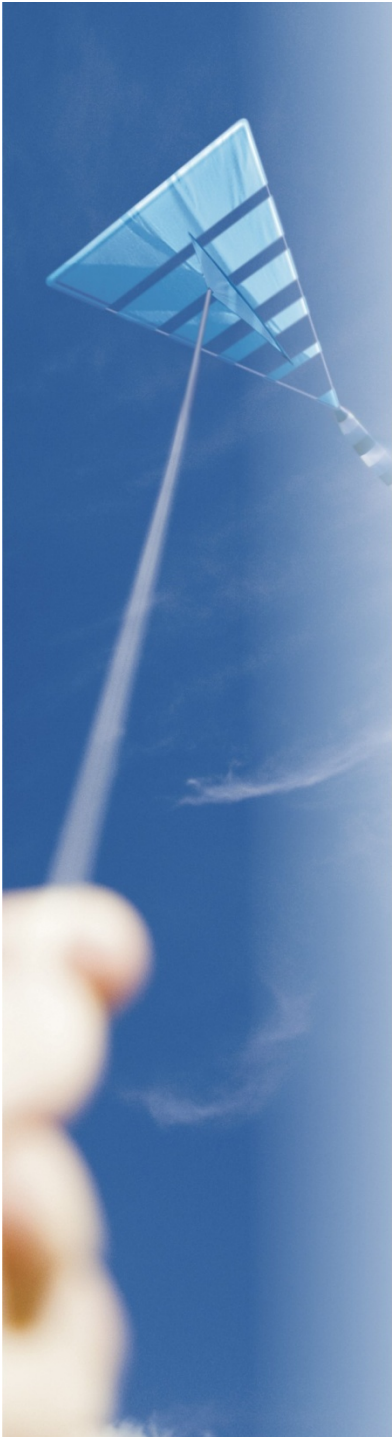


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Site Procedure Review

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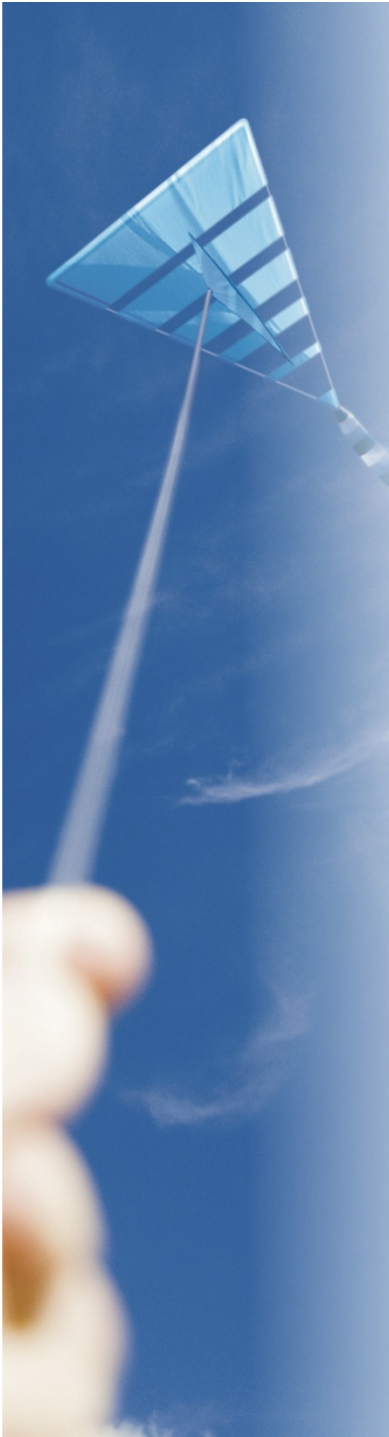


Site Procedures



- Investigator oversight
- Protocol responsibilities
 - Who verified inclusion/exclusion, obtained ICF, collected AEs, etc.
- Location of study procedures
- Process for recording data
- Accountability for the test article

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Protocol



- How the protocol was followed for:
 - Inclusion/exclusion criteria
 - Enrollment
 - Randomization
 - Administration of product
 - Frequency of observations
 - Required procedures & evaluations
 - AEs

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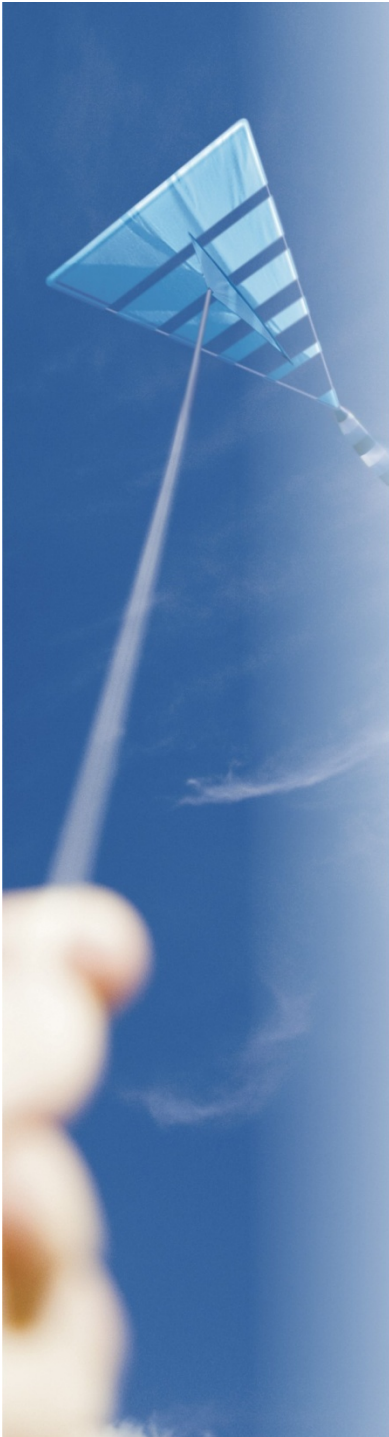
Protocol Example

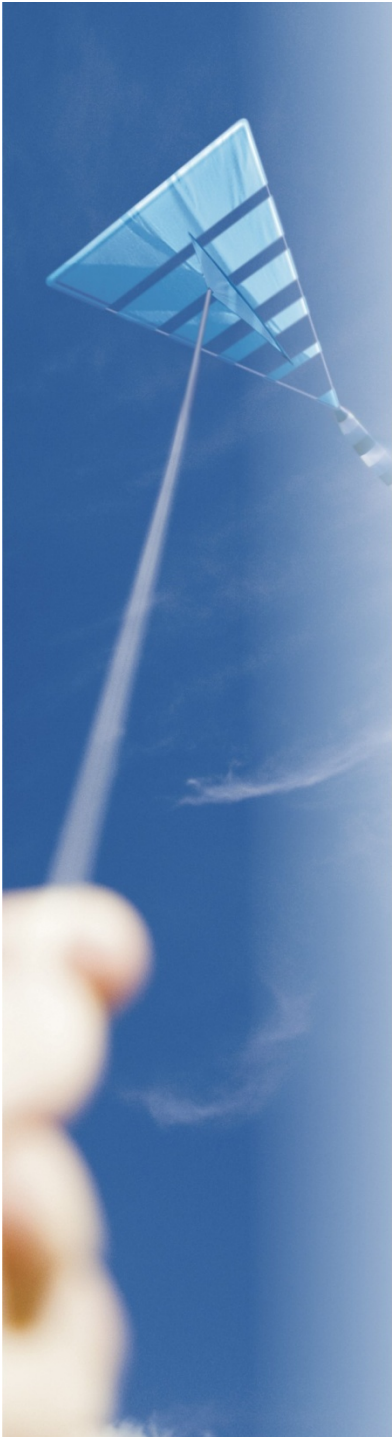


Wright, Richard A, MD 02/18/2009

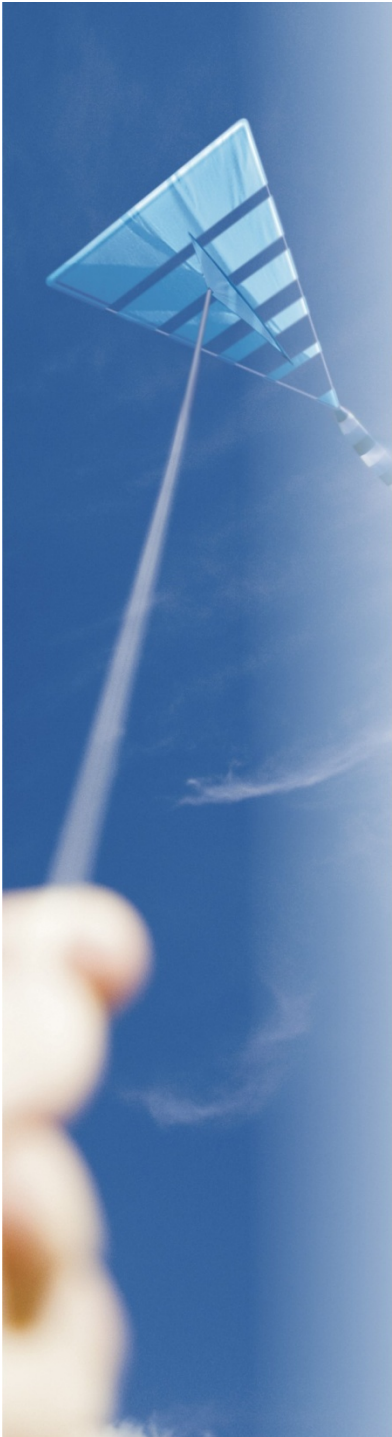
You failed to conduct the studies, or ensure they were conducted, according to the investigational plan.

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“...subjects with abnormal laboratory values were to be excluded from the study. For five of sixteen enrolled subjects, you did not review the screening laboratory results until after the subjects were enrolled in the treatment phase of the study. Because subjects with abnormal laboratory values were to be excluded, the protocol required you to review subjects' lab results prior to their enrollment in the treatment phase.”



Site Document Review

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Commonly Reviewed Items



- Patient data
 - CRFs, ICFs, medical records
- Drug/device disposition logs
- Staff training records
- Date of IRB approval of documents
- Enrollment log
- Communication with monitors

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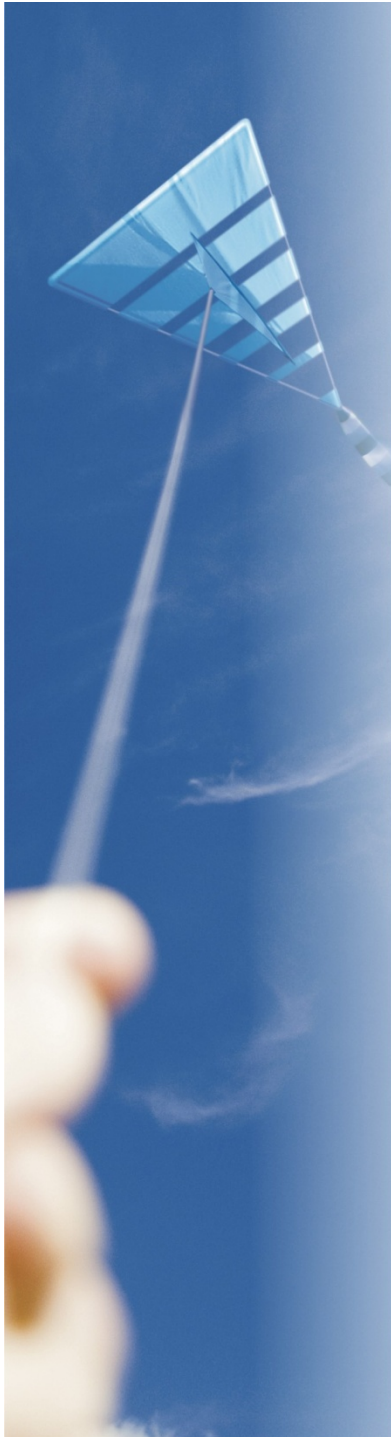
Recordkeeping



- Attributable
- Legible
- Contemporaneous
- Original
- Accurate



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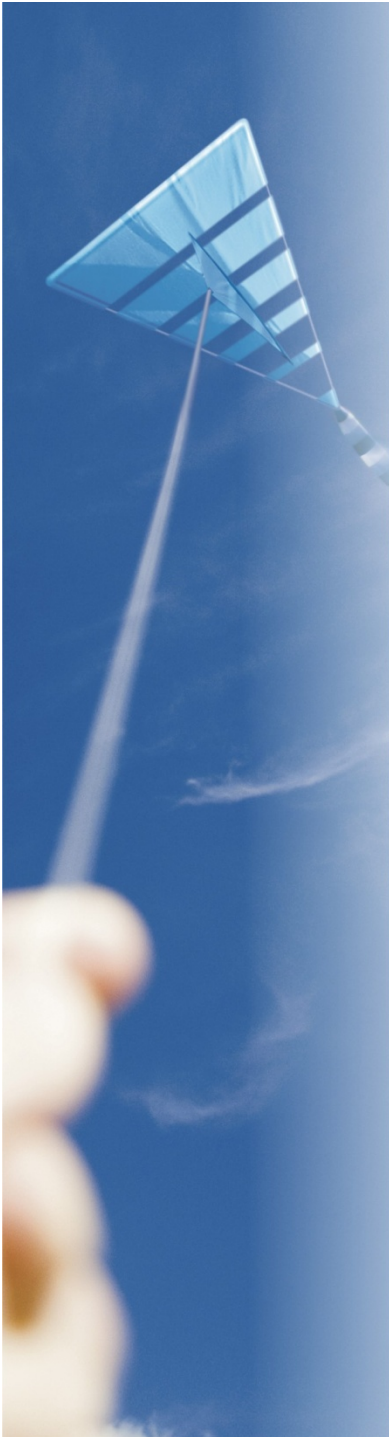
Recordkeeping Example



Hijazi, Saad, M.D. 5/19/09

You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual [21 CFR 312.62(b)].

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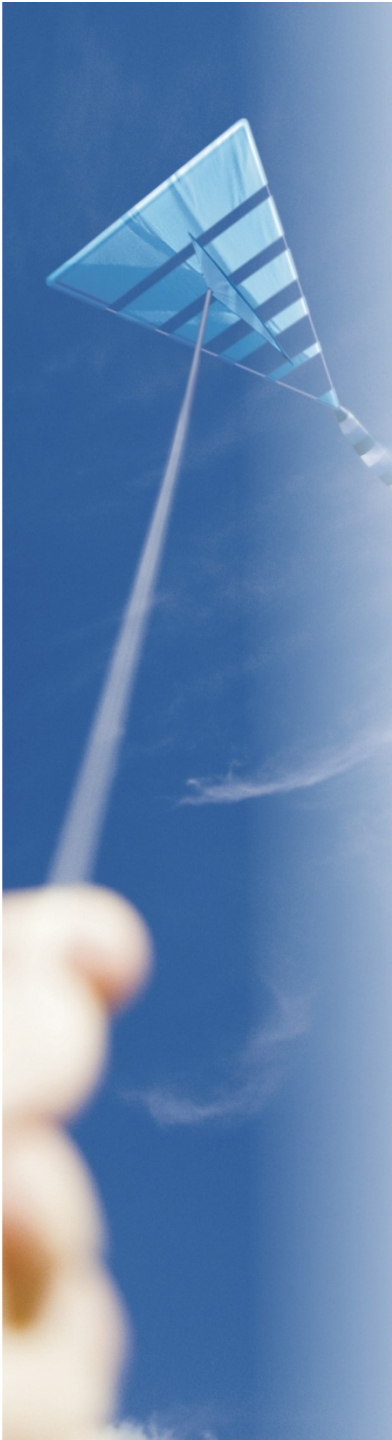
“In FDA’s review of the source documents ... there were numerous instances where either information entered into the CRFs did not match the information in the source documents or information in the source documents was changed after the subject had completed the study, up to two years post-completion, and it could not be determined where the information related to the change was derived.”



Electronic Records

- If electronic data and collection methods are defined in the protocol
 - Procedures for creating, modifying, maintaining and transmitting e-records
 - Record retention procedure
- Inspect electronic records (current/archived)
 - Accessibility
 - Audit trail

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Electronic Records Example



Bruce Branitz, M.D.

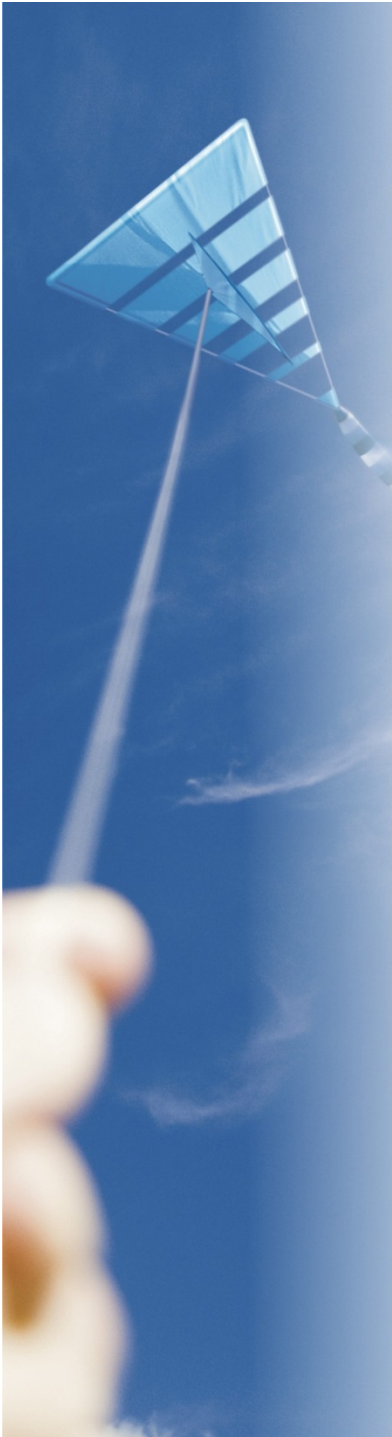
You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual

[21 CFR 312.62(b)].

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“The FDA investigator's review of the electronic CRFs (eCRFs) for the Novartis study revealed discrepancies. When the FDA investigator requested hard copies of the eCRFs, you were unable to provide copies of the eCRFs. Your study coordinator informed our investigator that the eCRFs were maintained by another firm and that you had no access to that eCRF database.”

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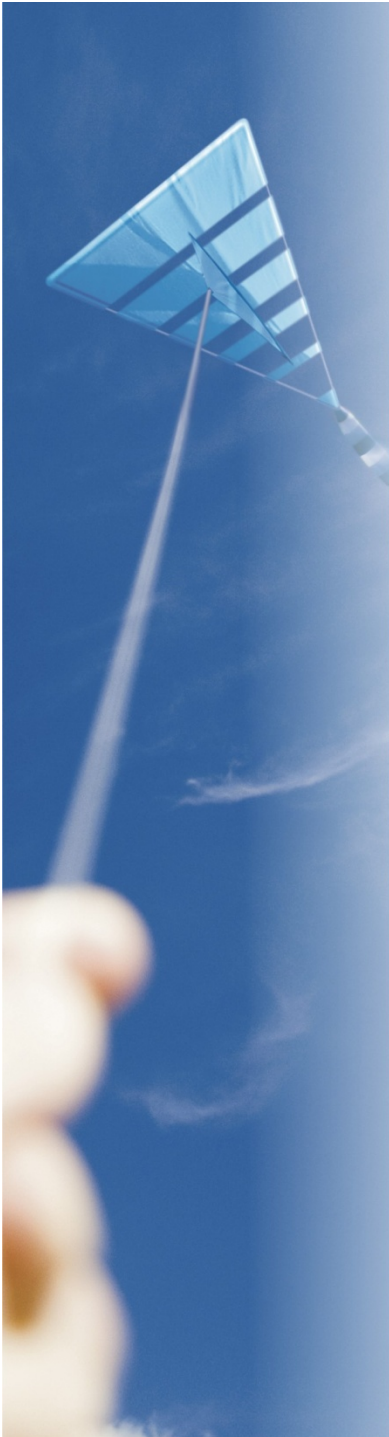


Medical Records



- Physician's progress notes, hospital charts, nurses' notes, etc.
- Pertinent data before and after study participation

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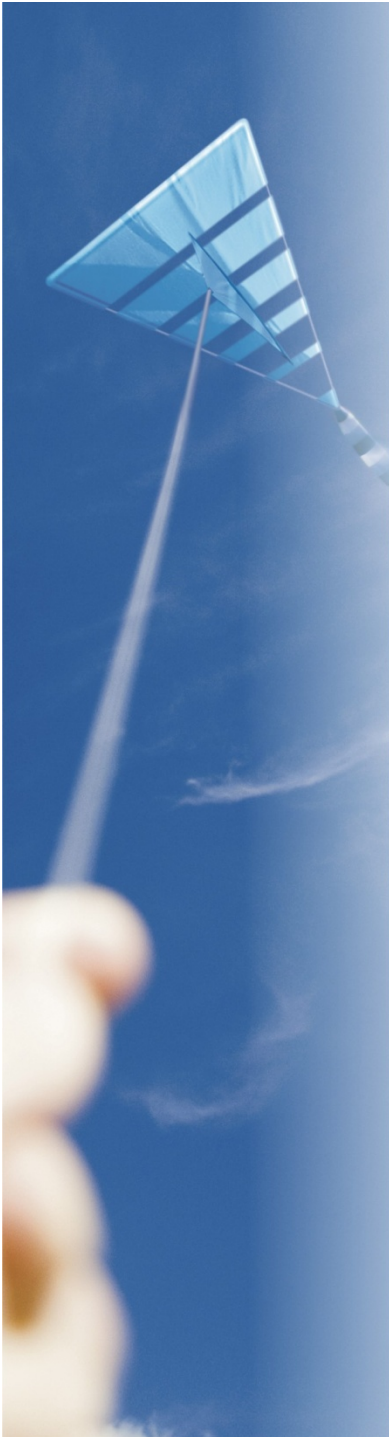


CRFs



- Source of information
- Process for obtaining and recording data (and corrections)
- Responsibility

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Test Article



- Personnel authorized to administer or dispense
- Documentation related to
 - Quantity
 - Shipment, receipt, and storage conditions
 - Labeling
 - Utilization, return and destruction
- Unused supplies

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Drug Accountability

Example



Desai, Virendra M., MD 3-2-2009

You failed to maintain adequate and accurate records for disposition of drug [21 CFR 312.62(a)].

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“Our investigation found numerous discrepancies between the dose#/kit #/vial # dispensing records kept by the unblinded pharmacy and what was recorded on the Drug Accountability Forms ... Specifically, the same dispensing vials from the same kits were documented as being dispensed to one subject ... and to a different subject ... In addition, drug dispensing information was missing for several subjects ...”



Informed Consent



- Presence of required elements
 - 21CFR50.25(a)
- Signatures/dates
- Assent for pediatric subjects + consent by parents
- Most current IRB approved version

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Outcome of Inspection

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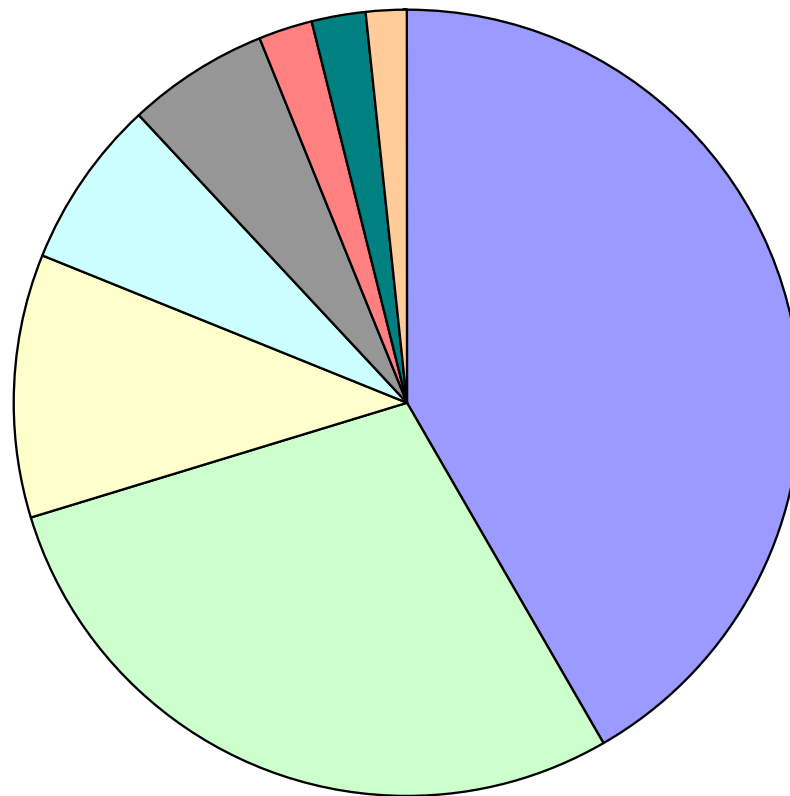
After an Inspection



- Exit interview with the clinical investigator
- Establishment Inspection Report
 - NAI: No Action Indicated
 - VAI: Voluntary Action Indicated
 - OAI: Official Action Indicated

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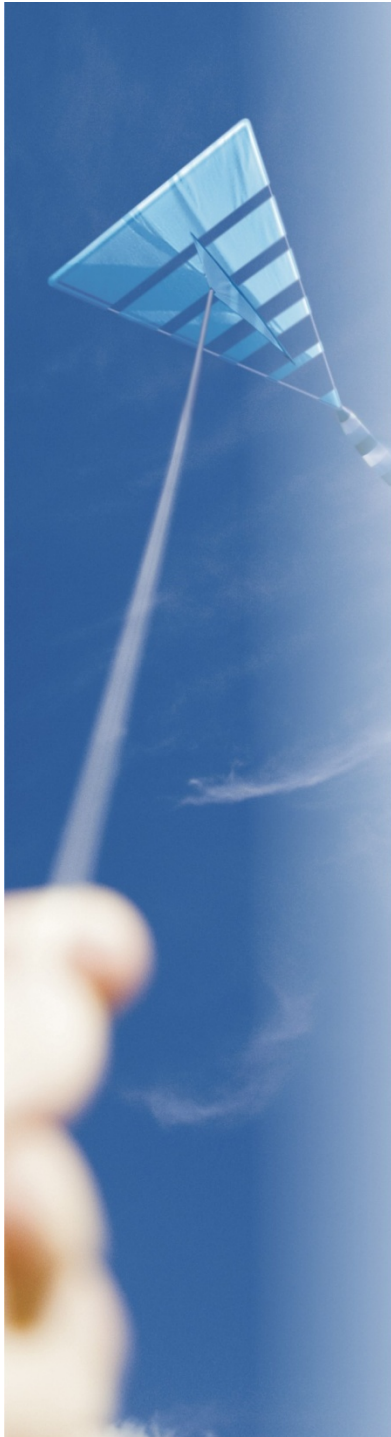
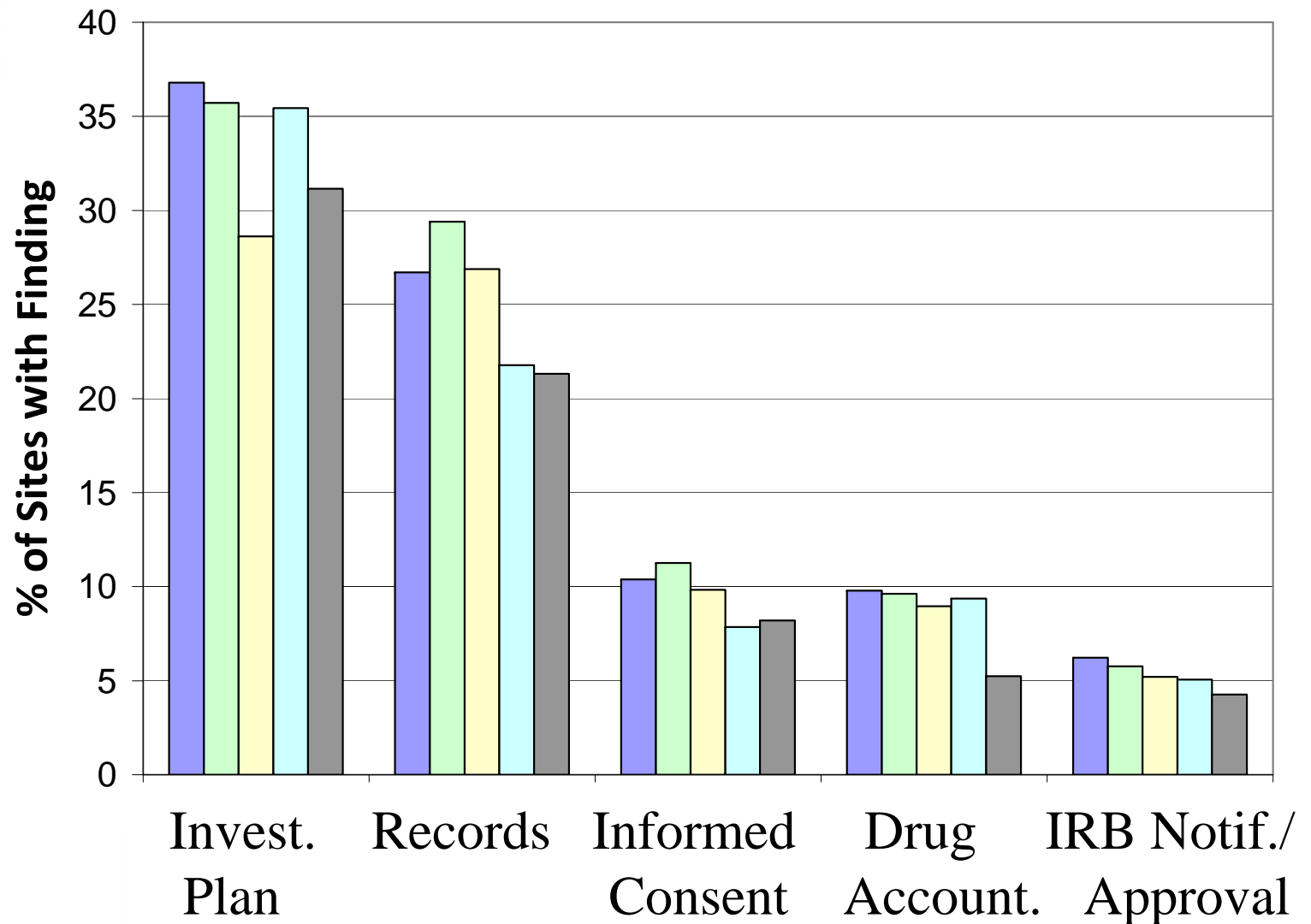
2009 Inspection Deficiencies

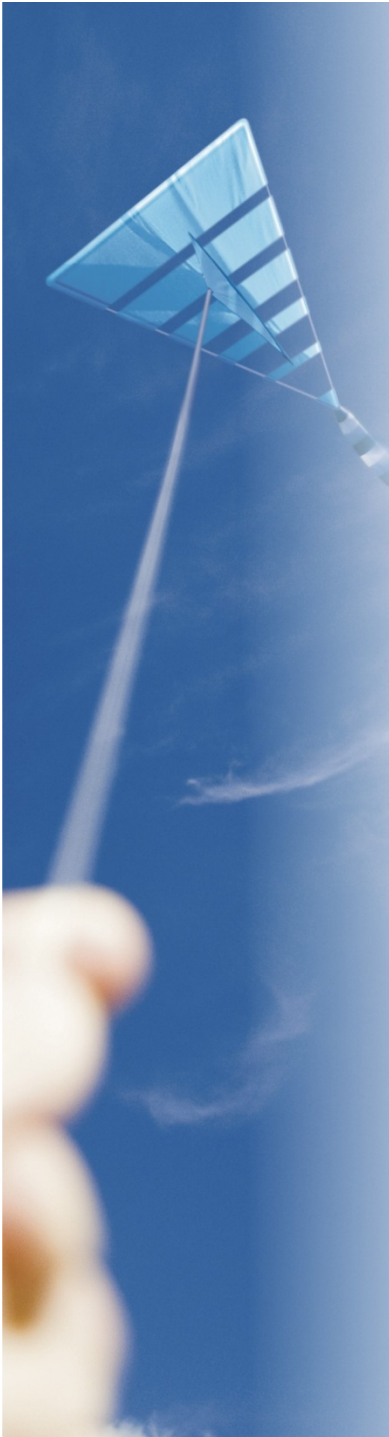


- Failure to follow investigational plan
- Inadequate, false, or unavailable records
- Inadequate informed consent/documentation
- Inadequate drug accountability
- IRB notification/approval
- Delegation of authority/supervision
- Failure to report adverse drug reactions
- Miscellaneous

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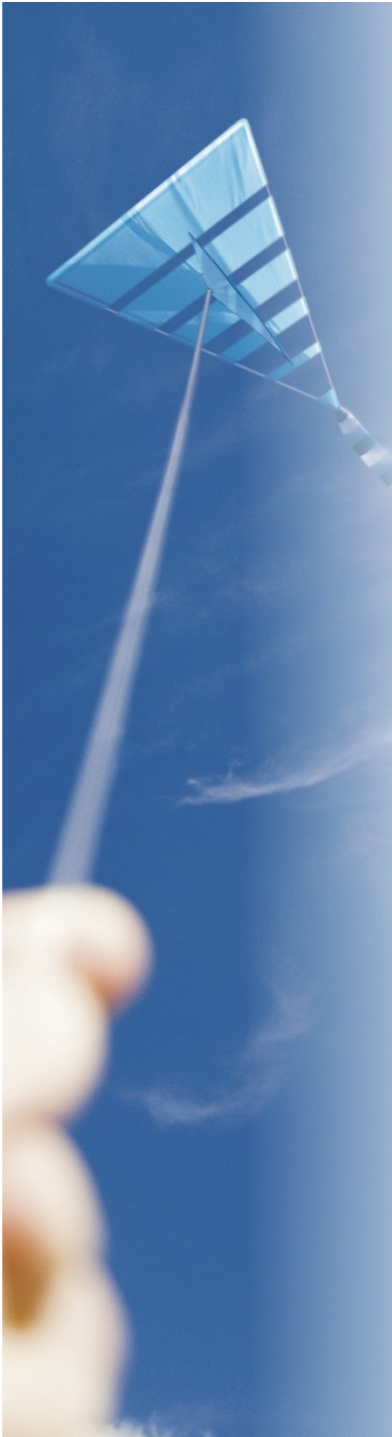
2005-2009 Inspections





Warning Letter

- 15 day response
- Posted on FDA web page!
- If response insufficient, potential actions:
 - Reinspection
 - Regulatory meetings
 - Clinical hold
 - Disqualification of the investigator
 - Civil money penalties



Inspection Preparation

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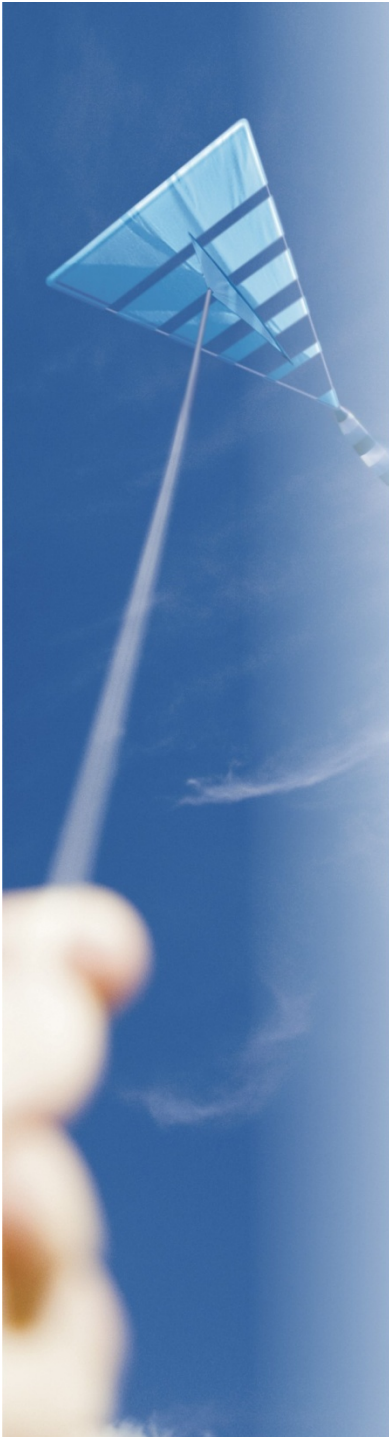
Preparing for the Inspection



- Decide who will interact with FDA
- Be sure critical personnel will be available
- Review site/PI history with FDA
- Reserve a suitable place
- Review critical documents
 - Ensure easily accessible



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At the Inspection



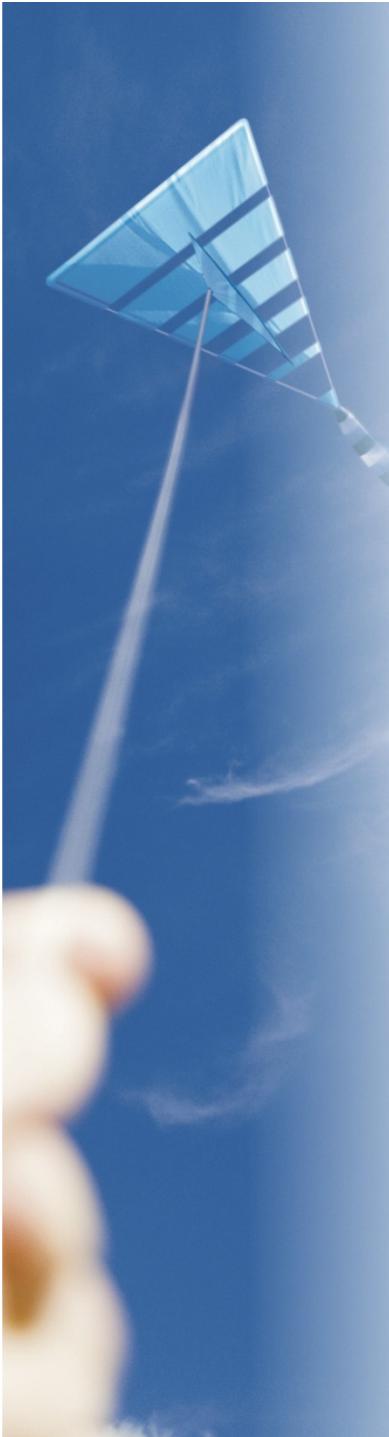
- Be prepared to tour the facilities
- Don't offer extra information
- Don't be argumentative
- Ask questions to prevent misunderstandings

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Response to FDA

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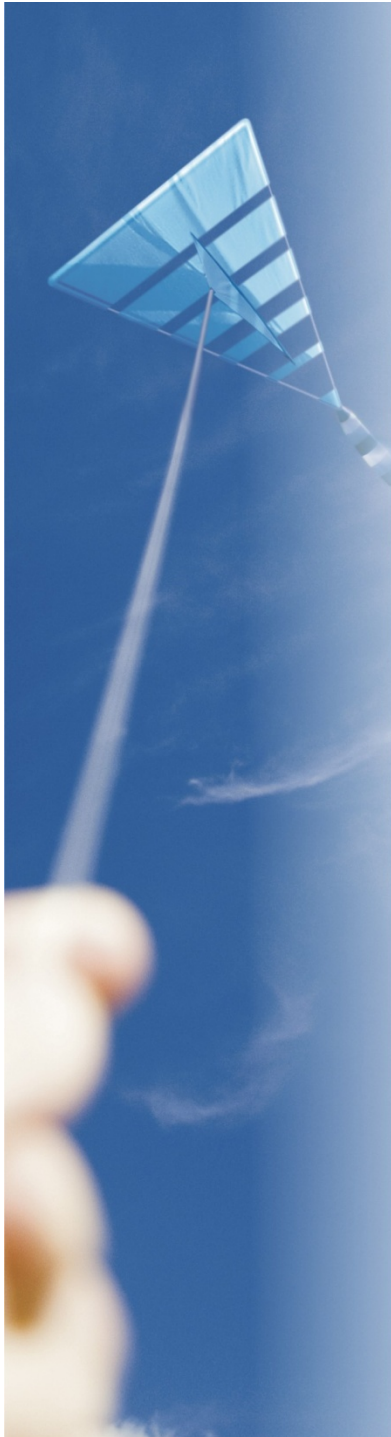
Responding to FDA Findings



There is no regulatory requirement to respond to a 483 ...but you should!

- Establishes credibility
- Demonstrates a commitment to correct issues
- Could prevent further FDA action (Warning Letter)

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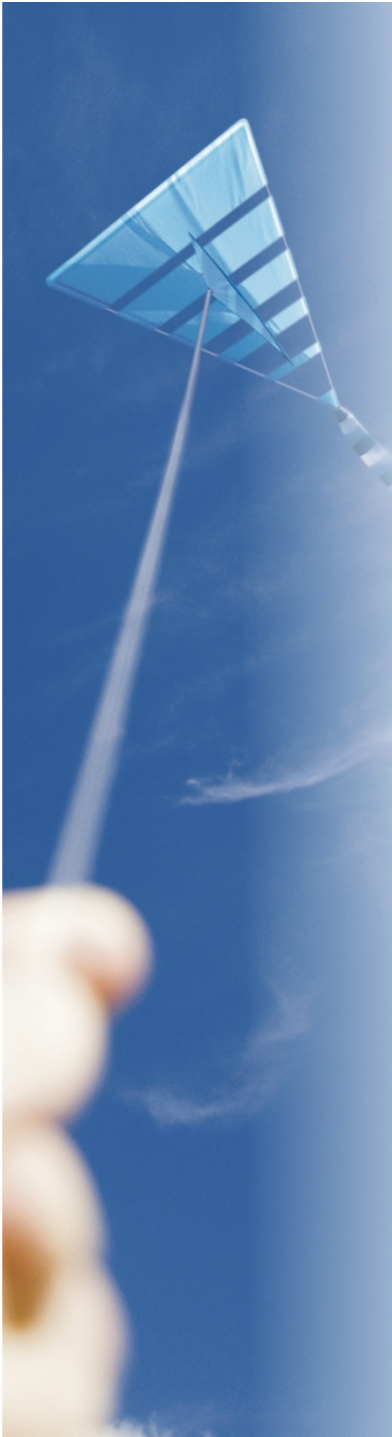


Providing a Complete Response



- Assess each observation
 - specifics
 - system-wide implications
 - global implications
- Develop a plan for immediate, short-term, and long-term CAPA

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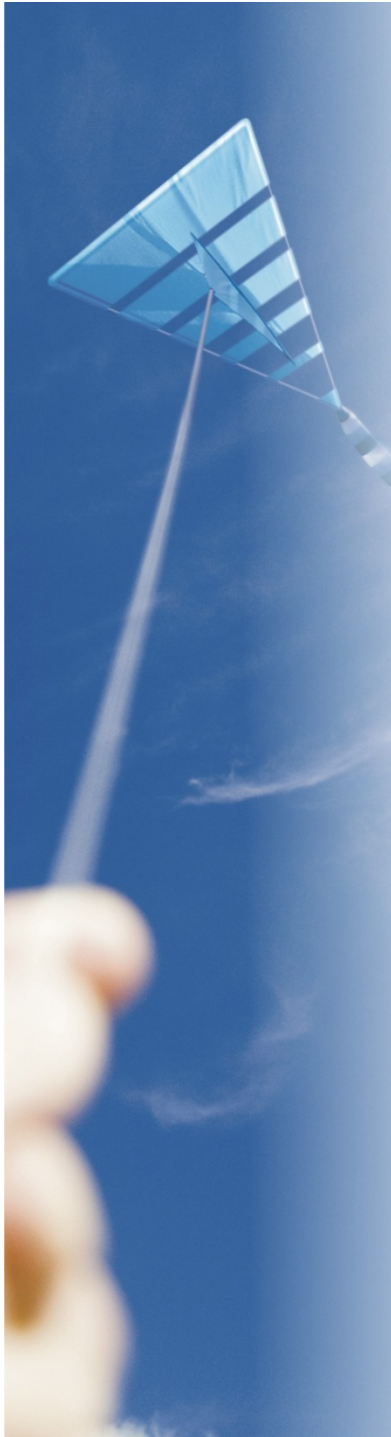


Providing an Effective Response



- Include a commitment from senior leadership
- Address each observation separately

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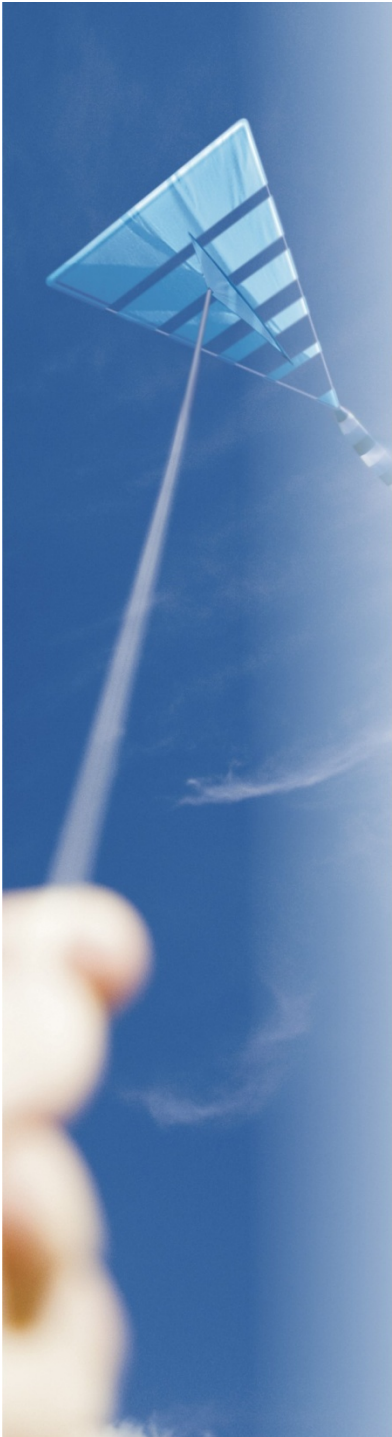


Providing an Effective Response (2)



- Provide CAPA accomplished/planned
 - Specific, complete, and realistic
 - Time frames for correction
 - Method of verifying/monitoring corrections
 - Submit documentation where possible
- **BE TIMELY**

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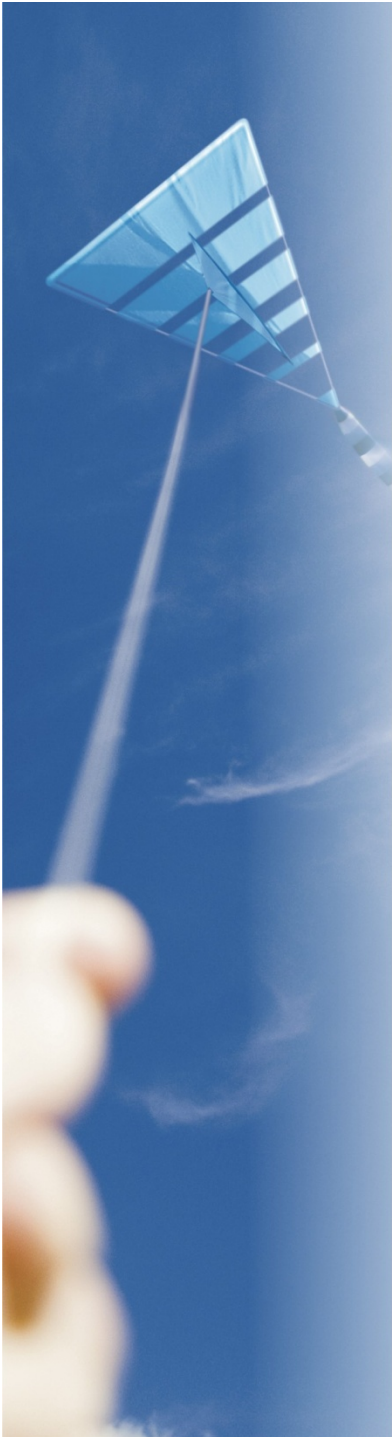
An Effective Response



Francisco Hernandez, M.D.

You failed to ensure that the investigations were conducted according to the signed investigator statement and investigational plans [21 CFR 312.60].

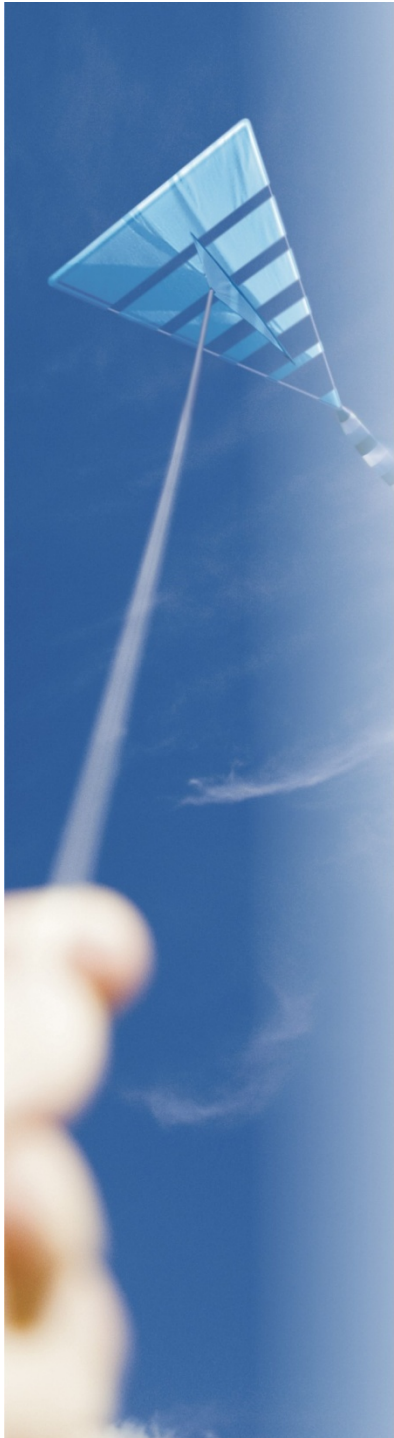
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“Of 15 subjects randomized in Protocol ..., 12 subjects were enrolled in violation of protocol inclusion and exclusion criteria.

In your response letter, you proposed corrective measures to avoid future violations pertaining to inclusion and exclusion criteria. Specifically, you outlined plans to present inclusion and exclusion criteria, thoroughly review past medical histories, and discuss borderline candidates in detail with your staff and the sponsor prior to enrollment decision-making. Additionally, you proposed measures to provide a clear separation of study procedures and clinical practice visits. These corrective measures are acceptable if implemented as proposed.”

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Discussion

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References



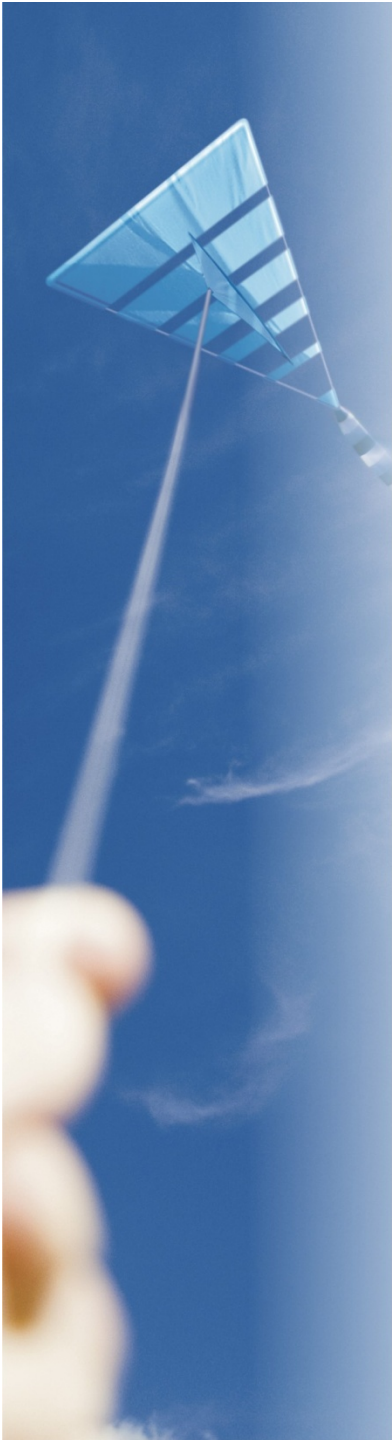
Information Sheet Guidance For IRBs,
Clinical Investigators, and Sponsors:
FDA Inspections of Clinical Investigators
(January 2006)

FDA Compliance Program Guidance
Manual for Clinical Investigator
Inspections

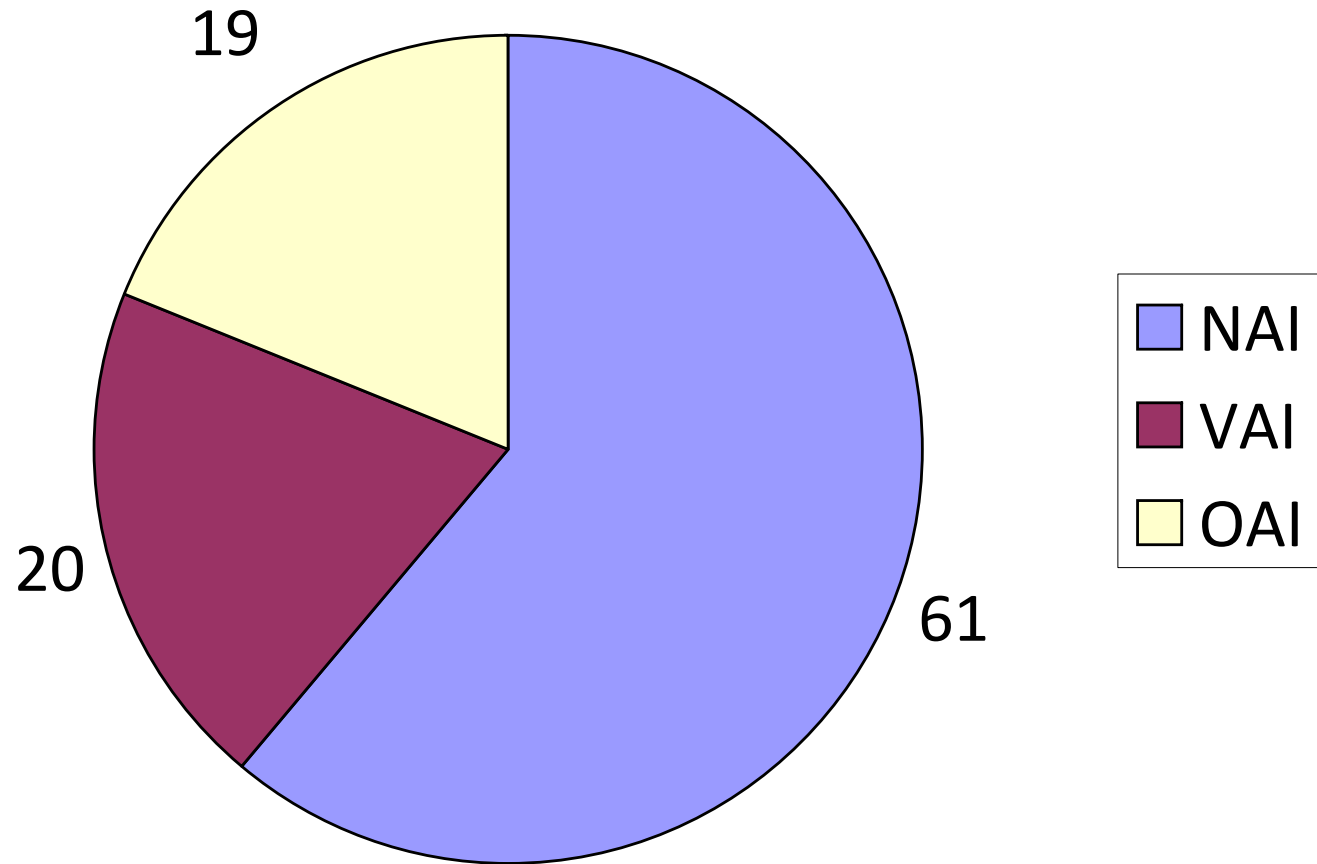
Inspection procedures for FDA personnel

Clinical Investigator Inspection List

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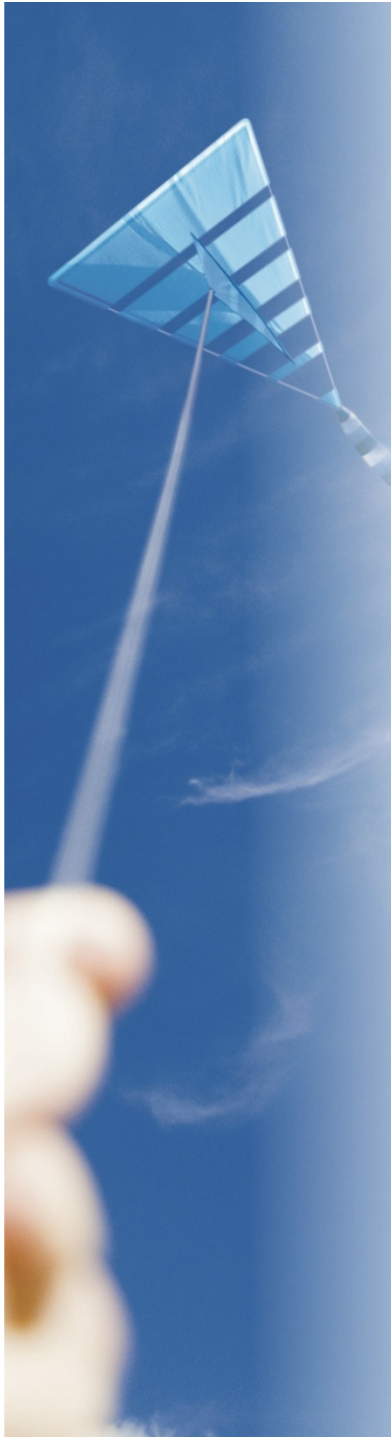


2008 FDA Inspections of Sponsors and Monitors



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<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm134452.htm>



Sponsor



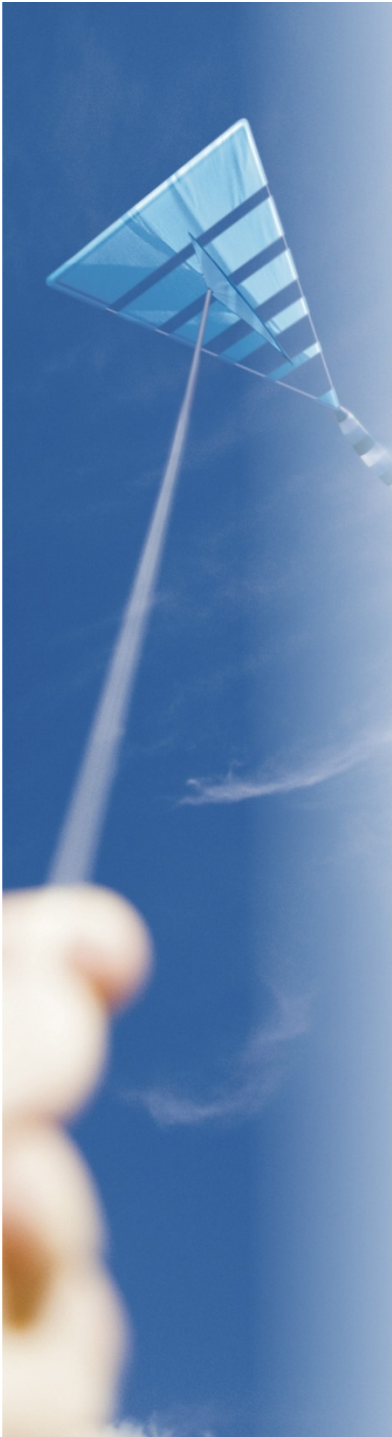
Responsibilities Example

Richard E. Ringel, M.D.

Failure to ensure proper monitoring of the clinical investigation. [21 CFR 812.40]

“You did not assure, according to the protocol and the Monitoring Plan, that data collection was overseen by an independent study monitor, nor that any monitoring of the study was conducted at any time.”

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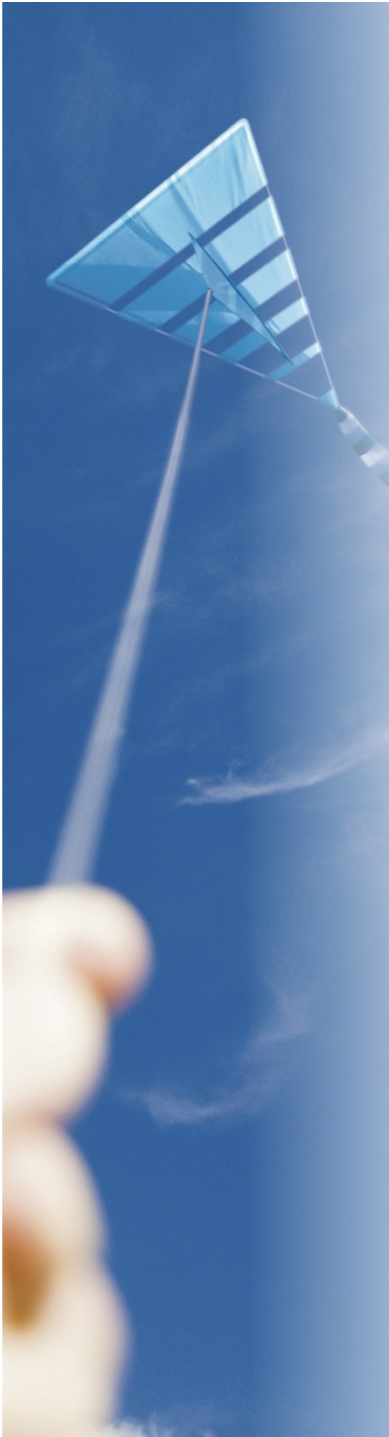


Investigator Responsibilities: Example

Brewer, George J. M.D. 1/14/09

You failed to assure that an IRB complying with applicable regulatory requirements was responsible for the continuing review and approval of a clinical study [21 CFR 312.66].

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“You continued to perform research activities during timeframes when the IRB's study approval was expired. Examples include, but are not limited to, the following: Study [redacted] lapsed in IRB approval from 3/19/93 until 4/29/93. During this timeframe subject [redacted] was enrolled (4/15/93).”



An (In)Effective Response



Holub, Richard, MD 01-Oct-08

“...You stated that the Form FDA 483 items were a reflection of the failure of a few clinical research coordinators to adhere to the established SOPs. You mentioned correctives actions that will be taken to assure that such errors are not repeated. These include the process used to select, train, and manage research staff, and SOPs governing the day-to-day work of the research division.

The response does not address oversight of the research activities by the clinical investigator and appears to place the burden of responsibility for the research activities on the study staff. Although hiring qualified staff and providing training may help with the performance of study related activities, this does not substitute for your responsibilities as the clinical investigator to supervise those aspects of the studies you delegate to research staff.”



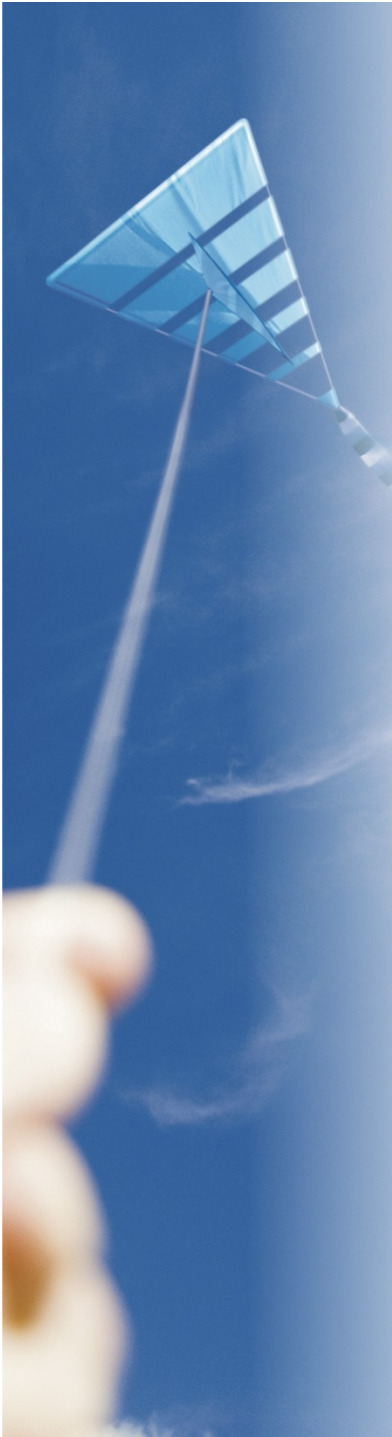
An (In)Effective Response



Desai, Virendra M., MD 3-2-2009

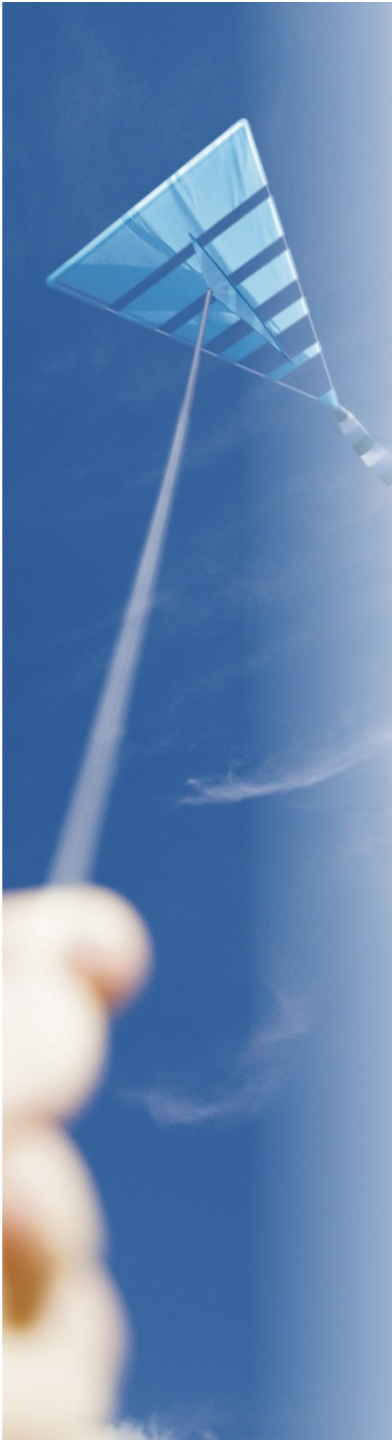
You failed to conduct the study
according to the investigational plan
[21 CFR 312.60].

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“Our investigation found that all 18 subjects randomized into the study received study drug prior to your review and assessment of their baseline laboratory results, thereby potentially compromising the safety of subjects in the study.

Your explanation provided in your written response to the Form FDA 483 is unacceptable. You stated in your response that, “section 5.2.2 of the protocol only indicates that central laboratory testing needs to be obtained...” ... page 58 of the protocol clearly states that “all screening/ predose assessments will be considered as baseline and must be performed and reviewed before randomization and dosing on Day 1...””



A Really Ineffective Response



Saudek, Christopher D., M.D. 13-Nov-08

Failure to submit an IDE supplemental application to FDA for approval of changes to an investigational plan. Failure to obtain FDA approval of the supplemental application before beginning part of an investigation.

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“During the FDA inspection, you told the FDA investigator that you did not know you were the sponsor of this study... We remind you that the original IDE approval letter addressed to you, included an attachment ... which describes your regulatory requirements.

... Your response is inadequate as it lacks a CAPA plan ... Please provide copies of policies/procedures that you have developed and implemented to ensure that future changes to the investigational plan will be submitted to FDA for approval”

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