



U.S. Food and Drug Administration

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# Effective and Efficient Oversight of Clinical Investigations

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# Objectives

- Part 1
  - Describe FDA's view of the roles and responsibilities of sponsors and contract research organizations (CROs)
  - Discuss practical considerations for clinical trial conduct and oversight
  - Discuss specific considerations with outsourcing
- Part 2
  - Discuss CDER's inspection process

# Shared Goals

- Safe and Effective Products
- “Clear path” - predictability in review and approval
- Based on clinical trials that
  - Produce High quality data
  - Protect participants’ rights, safety, and welfare

# What is Quality in a Clinical Trial Context ?

- The ability to *effectively and efficiently* answer the intended question about the benefits and risks of a medical product (therapeutic or diagnostic) or procedure while assuring protection of human subjects.\*
- Data that are fit for purpose

\*Clinical Trials Transformation Initiative at: <http://www.trialstransformation.org/scope>

## Current Oversight Models for Clinical Trials May Be Outmoded

- Reactive and premised on retrospective detection of errors
- Lack of proportionality
- Resource intensive
- May not optimally address significant risks to trial integrity, particularly systemic error

# Systemic errors can render trial data unreliable

- Poorly designed protocols and ancillary documents
  - Inadequate attention to study feasibility
  - Inconsistencies within protocol / between protocol and other study documents
- Poorly executed protocols
  - Inability to verify critical efficacy and safety data
  - Missing data for critical endpoints
- Inadequate internal processes to ensure
  - Integrity of critical study activities (e.g. randomization)
  - Study and vendor oversight
  - Data quality control
  - Appropriate statistical analysis

## Analysis of OSI Reviews of Marketing Applications<sup>1</sup> Indicates Opportunities for Improvement Remain



### Current Trends in FDA Inspections Assessing Clinical Trial Quality: An Analysis of CDER's Experience

by Ann Meeker-O'Connell and Leslie K. Ball

1. *Meeker-O'Connell and Ball*  
*FDLI Update 2011;2: 8-12*

104 original and supplemental NDAs/ BLAs reviewed by OSI from 1QFY10 to 1Q FY11

- Rejection of data for 4% of clinical investigators inspected in association with the related NDAs and BLAs
- Significant data integrity concerns affected 5 inspected applications (5%)
- Some systemic errors persisted due to deficits in sponsor monitoring, but had a **root cause in study design and planning.**
- For 2/5 applications, concerns arose solely from **internal processes** at the sponsor and CRO, unrelated to clinical investigator activities

# Inefficient practices may consume valuable resources and inadvertently detract from quality

## Case Study: Clinical Trial Monitoring

- Millions of data points collected on a clinical trial; Not all used in regulatory decision-making.<sup>1</sup>
- OSI focus: critical errors in endpoint and safety data
- Industry standard for monitoring:
  - 100% source data verification at the clinical site
  - “The flexibility in the GCP guidelines is not often utilized”<sup>2</sup>
- FDA regulations permit a variety of monitoring approaches

1: *Assuring Data Quality and Validity in Clinical Trials for Regulatory Decision Making: IOM Workshop Report 1999.*

2: *Sensible guidelines for the conduct of large randomized trials. Clin Trials 2008 5: 38*

# FDA's Clinical Trial Regulations

## FDA Oversight:

- Institutional Review Boards (IRBs)
- Sponsors/Monitors
- Contract Research Organizations (CRO)
- Clinical Investigators

FDA regulations govern the approval, conduct, review and reporting of clinical research intended for submission

- 21 CFR Part 50: Protection of Human Subjects
- 21 CFR Part 54: Financial Disclosure
- 21 CFR Part 56: Institutional Review Boards
- 21 CFR Part 312: Investigational New Drugs (IND)
- 21 CFR Part 314: New Drug Applications (NDA)

**These are legally enforceable requirements.**

# Key Sponsor Responsibilities under 21 CFR Part 312

*Clinical investigation* means any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of this part, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice.

- Maintaining an **effective IND** with respect to the investigations
- **Select qualified investigators** and provide them with the information needed to conduct the investigation properly
- **Monitoring** the progress of all clinical investigations being conducted under an IND
- Ensuring investigation(s) are **conducted in accordance with the general investigational plan and protocols** in the IND
- Promptly **securing compliance or ending** a non-compliant investigator's participation in the investigation

# Key Sponsor Responsibilities

- Reviewing and evaluating the evidence relating to the safety and effectiveness of the drug as it is obtained from the investigator
- Ensuring that FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to a drug
- Halting study in case of unreasonable risk to subjects
- Ensuring that foreign clinical studies not conducted under an IND whose data have or will be submitted to FDA meet the GCP requirements outlined 21 CFR 312.120
- Recordkeeping and record retention

## 21 CFR 312.120 - Foreign clinical studies not conducted under an IND

Conditions of FDA acceptance of non-IND foreign trials to support an IND or marketing application:

- Well-designed and well-conducted trial
- Conducted in accordance with good clinical practice (GCP)
- Must provide information describing the actions the sponsor or applicant took to ensure that the research conformed to GCP
- FDA able to validate the data through an onsite inspection if necessary

# Collaboration of International Regulators

- FDA-EMA GCP initiative: 18 month pilot initiated Sept 2009; Report issued July 2011\*
  - Inspections: joint, parallel and sequential
    - Confidence building exercise
    - Comparison of practices
  - Information sharing on marketing applications
  - Sharing information on best practices/guidances
- Goal:
  - Harmonization where possible
  - Leveraging of finite resources
- Continuing collaboration with EMA
- Extending collaboration efforts to other regulatory authorities

<http://www.fda.gov/downloads/InternationalPrograms/FDABeyondOurBordersForeignOffices/EuropeanUnion/EuropeanUnion/EuropeanCommission/UCM266259.pdf>

# Requirements Evolve...

## One Example

### 1. Reporting Information Regarding Falsification of Data

- *Proposed rule* published February 19, 2010
  - <http://edocket.access.gpo.gov/2010/pdf/2010-3123.pdf>
- Requires sponsors to promptly report information to FDA about known or suspected falsification of data in the course of:
  - Reporting study results or
  - Proposing, designing, performing, recording, supervising, or reviewing studies
- Applies to studies with human or animal subjects, whether
  - conducted by or
  - on behalf of a sponsor or
  - relied on by a sponsor

## Example 2: Title VIII of Food and Drug Administration Amendments Act of 2007 (FDAAA)

- Mandates that:
  - for certain "applicable clinical trials"
  - the "responsible party" must:
    - Register the trial
    - Provide periodic updates (e.g. recruitment status) and
    - Report results
- "Responsible party"
  - i.e. the sponsor or designated principal investigator
  - The responsible party **must** have control of the data
  - If a clinical trial is being conducted under an IND or IDE, then the IND/IDE holder usually will meet the definition of responsible party under Title VIII.

# What is an Applicable Clinical Trial under FDAAA, Title VIII?

**Drugs and Biologics:** Controlled, clinical investigations, other than Phase I investigations, of a product subject to FDA regulation

**Devices:** Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric post-market surveillance studies

- **SEE:**  
[prsinformations.clinicaltrials.gov/ElaborationsOnDefinitions.pdf](https://prsinformations.clinicaltrials.gov/ElaborationsOnDefinitions.pdf)

# Obligations under FDAAA, Title VIII

- Reporting requirements
  - Registration **and** Results
- Certification to FDA of compliance with law:
  - Form FDA 3674
  - Submitted with FDA drug / biologic / device applications /submissions
- Inclusion of required language in informed consent forms for applicable clinical trials
- Certification of compliance submitted with grant progress reports
  - Oversight of any FDA grants
  - Similar requirements apply to other HHS grants

# Additions to CPGM

- March 11, 2011: Release of revised Compliance Program Guidance Manual (CPGM) CP 7348.810, Sponsors, Contract Research Organizations, and Monitors
- Includes section on “Registration of Studies on ClinicalTrials.gov” assessing, among other things:
  - Evaluation of sponsor compliance with SOPs (if any) for complying with the requirements associated with ClinicalTrials.gov.
  - Determination of whether the trial(s) being inspected was/were registered on ClinicalTrials.gov, if required.
  - For registered trials, assessment of timing of registration vs. date first subject enrolled
  - For registered trials, determination of whether primary and secondary outcome measures are captured in ClinicalTrials.gov and are generally accurate

# FDA Guidance, Information Sheets, and Notices

- Our regulatory world is very complex
- Regulations at a high level
- Need more detailed interpretation but want flexibility to evolve with science and technology changes
- Guidance
  - Represents the Agency's current thinking on good clinical practice (GCP) and the conduct of clinical trials

## **Not binding on FDA or the public**

- “An alternative approach may be used if such approach complies with the relevant statute or regulations”

# Clinical Trial-Related Guidance (Examples)

<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidanceInformationSheetsandNotices/default.htm#notices>

- Electronic Source Documentation in Clinical Investigations (Draft) 2010
- Investigational New Drug Applications (INDs)—Determining Whether Human Research Studies Can Be Conducted Without an IND (Draft 2010)
- Safety Reporting Requirements for INDs and BA/BE Studies (Draft)(2010)
- Adverse Event Reporting to IRBs – Improving Human Subject Protection (2009)
- Establishment / Operation of Clinical Trial Data Monitoring Committees (2006)
- Using a Centralized IRB Review Process in Multicenter Clinical Trials (2006)
- Use of Clinical Holds Following Clinical Investigator Misconduct (2004)
- Financial Disclosure by Clinical Investigators (2001)
- ICH E6 Good Clinical Practice: Consolidated Guidance (1996)

# FDA Guidance Documents May Also Evolve

## **EXAMPLE: Draft Clinical Monitoring Guidance**

(published 29 August 2011)

- FDA regulations are not specific about how sponsors are to conduct monitoring of clinical investigations and, therefore, are compatible with a range of approaches to monitoring
- FDA last provided comprehensive guidance on appropriate monitoring of clinical investigations in 1988
- FDA recently withdrew this guidance
- Comments on draft guidance due by November 28, 2011

# New Draft Monitoring Guidance

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2 results for "FDA-2011-D-0597"

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Title	Document Type	Agency	ID	Posted Date	Actions
<a href="#">Draft Guidance for Industry; Oversight of Clinical Investigations; A Risk-Based Approach to Monitoring</a>	Other	FDA	FDA-2011-D-0597-0002	08/29/2011	<a href="#">Submit a Comment</a> <a href="#">Open Docket Folder</a>
<a href="#">Draft Guidance for Industry; Availability: Oversight of Clinical Investigations; A Risk-Based Approach to Monitoring</a>	Notice	FDA	FDA-2011-D-0597-0001	08/29/2011	<a href="#">Submit a Comment</a> <a href="#">Open Docket Folder</a>

Comments Due Nov 28, 2011 11:59 PM ET

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# FDA Draft Clinical Monitoring Guidance Overview

- Focus is on monitoring of clinical investigators
- Makes clear that sponsors can use a variety of approaches to fulfill their responsibilities related to monitoring
- “No single approach to monitoring is appropriate or necessary for every clinical trial.”
- Recommends that sponsors develop a monitoring plan that is:
  - Tailored to the specific human subject protection and data integrity risks of the trial.
  - Ordinarily, includes a mix of centralized and on-site monitoring practices.

# Potential Monitoring Activities

- On-site monitoring
  - Focusing on key data and processes
- Remote monitoring
- Data management metrics and trending
- Statistical monitoring to assess data trends across sites and trials
- Data Mining

# FDA Draft Monitoring Guidance Recommendations

- Identify critical study data and processes, e.g.
  - Endpoints
  - Serious Adverse Events
  - Randomization / Blinding
  - Consent
  - Eligibility Criteria
- Perform and document a risk assessment to identify risks to these critical data and processes
  - What could go wrong?
  - What would be the impact?
  - Could we detect it?

“Before setting out to identify and mitigate risks it is first necessary to establish the priorities that need to be addressed .... It is the risks that are a significant threat to those priorities that most merit the allocation of resource in their mitigation.”

European Medicines Agency (EMA) Draft Reflection Paper on Risk-Based  
Quality Management in Clinical Trials (4 August 2011)

# Draft Guidance: Considerations in Developing a Monitoring Plan

- Risk assessment should inform development of monitoring plan
- Considerations
  - Complexity of study design
  - Types of study endpoints
  - Clinical complexity of study population
  - Geography
  - Relative experience of clinical investigator
  - Electronic data capture
  - Relative safety of investigational product
  - Stage of the study
  - Quantity of data



# Draft Monitoring Guidance: Elements of a Monitoring Plan

- Should include:
  - Description of monitoring approaches
  - Communication of monitoring results
  - Management of non-compliance
  - Training and study-specific information
- Monitoring plan amendments
  - Should define events or triggers for plan update

# Draft Monitoring Guidance: Recommendations for Documenting Monitoring Activities

- Should include:
  - Who conducted, what was reviewed, and date
  - Description of non-compliance, data irregularities, other deficiencies identified during review
  - Corrective and preventive action plans, including identification of accountable/responsible person(s)
  - Data and/or activities reviewed
- Should be provided to appropriate management for review, and as necessary, follow-up

How do we apply these regulations and use these guidance documents to **effectively and efficiently conduct and oversee trials**, avoid **systemic errors** and **facilitate quality trials**?

## Desired State for Clinical Development similar to Quality by Design in Manufacturing:

“Maximally efficient, agile clinical development programs that reliably produce high quality data\* and protect trial participants without extensive regulatory oversight”

\*Data that are fit for purpose

## Systematic, proportionate approach to clinical development

- Emphasis on process control
- At the trial level, the protocol is the blueprint for quality
  - Prospectively identify “what matters”
  - Consider the important risks to subject safety and data reliability
    - Risks may accrue from a variety of sources
  - Tailor the protocol and its delivery to eliminate or mitigate these important risks.
- Monitoring and auditing become tools in a quality toolbox, with flexibility in approaches

## A Cliff's Note Approach to Quality Risk Management for Clinical Trials

- Say what you do (PLAN)
- Do what you say (DO)
- Prove it (CHECK)
- Improve it (ACT)

# Considerations: Say what you do

## Governance

- Responsible, accountable individuals
- Interdepartmental coordination and exchange of information to enhance decision-making
- Oversight of outsourced activities



## Considerations: Say what you do

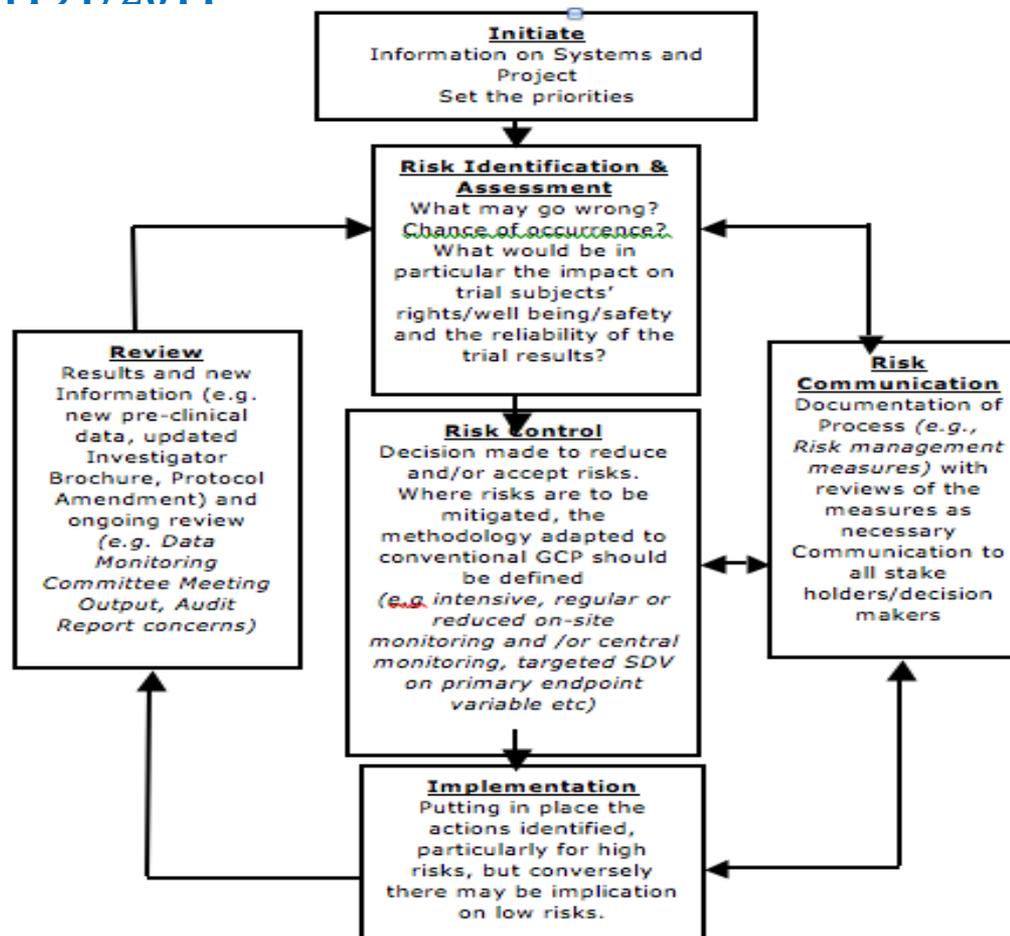
- Prospectively establish priorities and define requirements, processes, and responsibilities for key clinical trial activities
- At the trial level, this must **start with protocol development**
- Clearly define in the protocol the procedures and data that are critical to the reliability of the study findings.
  - Data that support primary and secondary endpoints
  - Data that are critical to subject safety, such as serious adverse events and events leading to discontinuation of treatment;

## Considerations: Say what you do

- Focus on these critical measurements and preventing important and likely sources of error in their conduct, collection and reporting.
- Questions to ask in identifying risks:
  - What could go wrong?
  - What must go right for us to succeed?
  - Where are we vulnerable?
  - How do we know whether we are achieving our objectives?
  - What activities are most complex? Which ones are regulated?
- *During protocol development*, determine
  - Which risks should be managed
  - What actions are necessary

# EMA draft reflection paper on risk based quality management of clinical trials -

EMA/INS/GCP/394194/2011



# Considerations: Say What You Do

- Preventive controls
  - Attempt to prevent undesirable events from occurring
  - Examples:
    - CRF design
    - Decreasing volume of data collected
- Detective controls
  - Attempt to detect undesirable events
  - Provide data about effectiveness of preventive controls
  - Examples:
    - Data monitoring and quality control
    - Functional line quality control



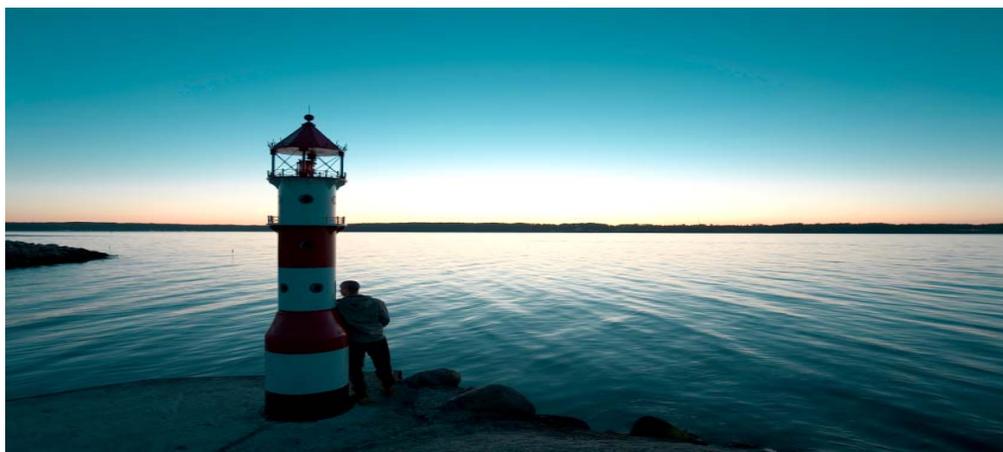
## Considerations: Do what you say

- Specific requirements, and responsibilities are communicated prospectively to:
  1. Affected company staff
  2. CRO and service provider personnel, and
  3. Clinical Investigators and their staff

# Considerations: Prove it

## Risk-based Monitoring

- Verify that critical activities, including QC, are carried out as planned

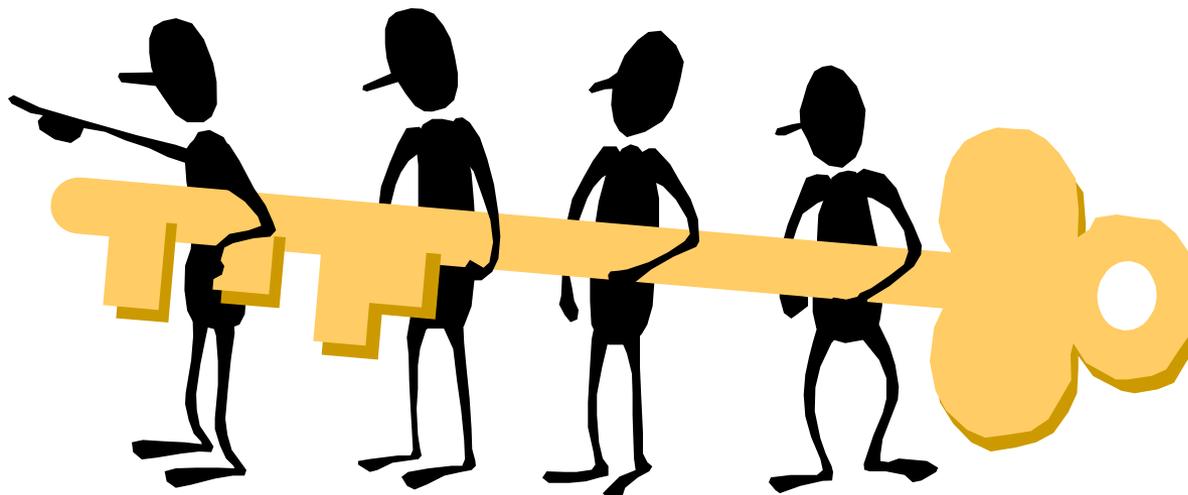


## Trend analysis: “Data as compliance intelligence”

- Proactively identify and evaluate compliance signals
- Identify and respond to unanticipated risks

# Improve it

- Corrective and Preventive Actions
  - Evaluate issue and solution broadly
  - Long-term and sustainable solutions
  - Follow-up on effectiveness
- Responses to changes in laws, regulations, guidance, business operating environment



# Contract Research Organizations

a person that **assumes**, as an independent contractor with the sponsor, **one or more of the obligations of a sponsor**, e.g., design of a protocol, selection or monitoring of investigations, evaluation of reports, and preparation of materials to be submitted to the Food and Drug Administration.

# Transfer of Obligations

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- 312.52 Transfer of obligations to a CRO
  - Any or all sponsor obligations may be transferred
  - Transfer must be described in writing
  - If not all obligations are transferred each obligation being assumed by the CRO must be described
  - If all obligations are transferred, a general statement is acceptable
  - Any obligation not covered in writing shall be deemed not to have been transferred

## CRO Responsibilities

- Any obligations transferred, in writing, to the CRO by the sponsor.
- CRO is subject to the same regulatory action as a sponsor for those obligations transferred to them.

## ICH E6 Good Clinical Practice:

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A sponsor may transfer any or all of the sponsor's trial-related duties and functions to a CRO, *but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor.*

## General quality considerations for outsourced activities:

- 1. CRO capabilities commensurate with activities to be transferred
- 2. Contract(s) and scope(s) of work clearly define responsibilities
- 3. Prospective attention to identifying and mitigating high-impact risks:
  - Inherent to outsourced activity
  - Inherent to outsourcing
  - Specific to a particular vendor
- 4. Defined oversight structure
  - Clear lines of communication
  - Triggers and process for issue escalation
  - Assessments of performance against pre-defined quality measures linked to focused on critical risks and outcomes

# Outsourcing: How problems arise

- Deficits in Key Documentation
  - Responsibilities not clearly transferred in writing
  - Sponsor / CRO have a different understanding of what was transferred in writing
    - Specific deliverables
    - Management of other 3<sup>rd</sup> parties?
  - Changes in duties over the course of a study are not documented in writing

# Example: Data Management

- Application review revealed errors in data related to safety parameters
- Errors primarily associated with scanning of faxed paper CRFs
- Sponsor vs. CRO
  - Pervasiveness of errors uncertain at filing for both parties
  - Lack of clarity on responsibilities for data management
    - Creation / maintenance of data management plans and charters
    - Routine QC during study conduct
    - Pre-filing data quality assessment

## Outsourcing: How problems arise

- Deficits in Governance
  - Lapses in communication of critical information
  - Limited real-time assessment of whether and how CRO is
    - Completing transferred responsibilities
    - Delivering against quality expectations

## Outsourcing: How problems arise

- Deficits in Governance (continued)
  - Lack of comprehensive root cause analysis and corrective action when issues are identified

## Example: PADE Reporting Warning Letter, January 28, 2011

- The "Adverse Event Reporting Form," used by your call center contractors for the receipt of adverse drug experience reports, fails to correctly identify the adverse outcomes required to determine the seriousness of an adverse drug experience. ...Indeed, it appears deficiencies in written procedures such as these may have contributed to the late reporting and non-reporting of 15-day reports that are identified in this warning letter.

# Thank You

- Questions?

# References

- FDA Draft Clinical Monitoring Guidance (29 August 2011)
  - <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269919.pdf>
- EMA Draft Reflection Paper on Risk-Based Quality Management in Clinical Trials (4 August 2011)
  - [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2011/08/WC500110059.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/08/WC500110059.pdf)