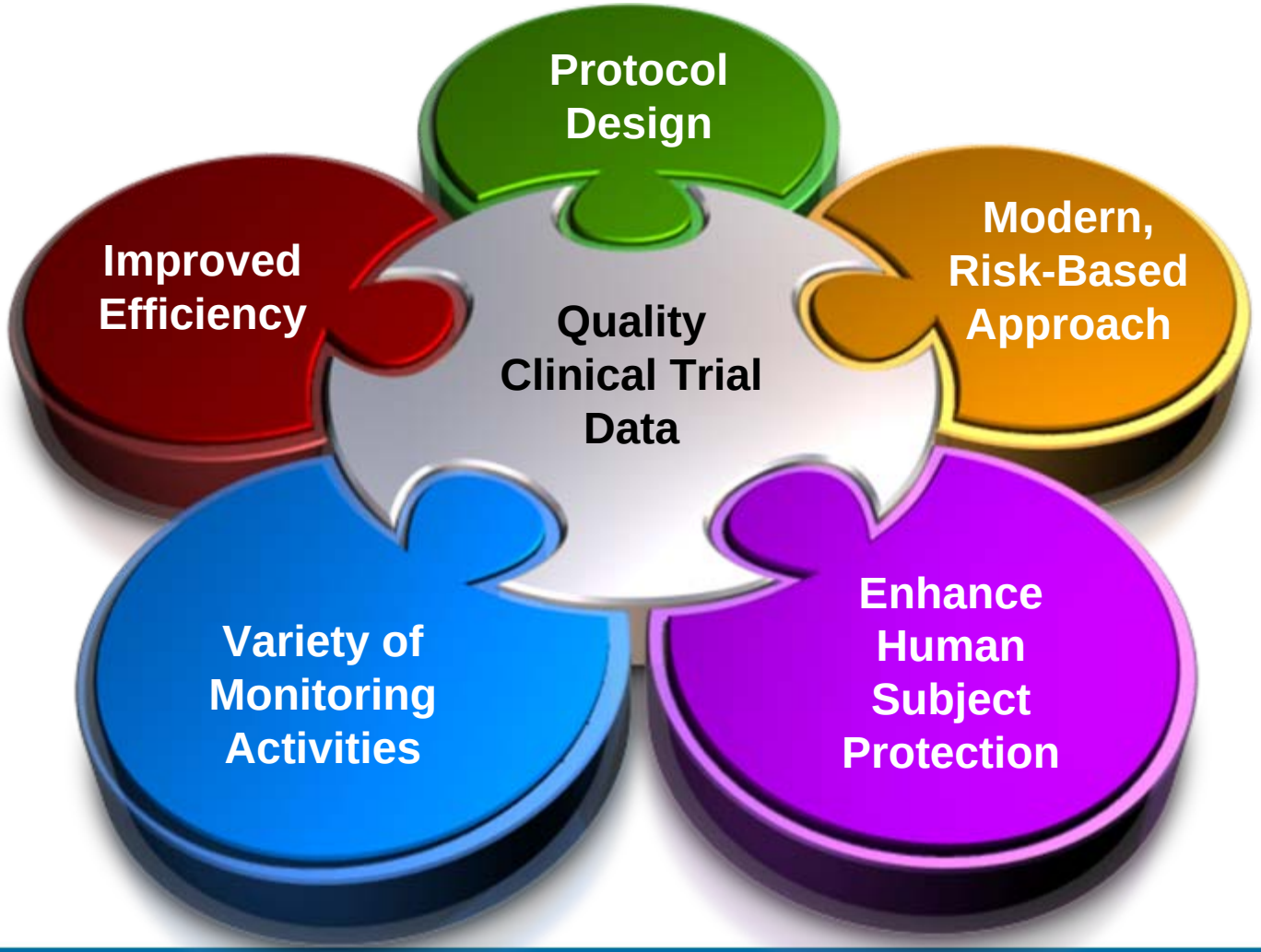
Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring (Draft Guidance)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Center for Drug Evaluation and Research (CDER)
Office of Good Clinical Practice (OGCP)

Chrissy J. Cochran, Office of Compliance, CDRH
Ann Meeker-O'Connell, Office of Scientific Investigations, CDER
Stephanie Shapley, Office of Medical Policy, CDER

October 2011

Introduction



Outline

- Background of clinical trial monitoring- requirements and practices
- Overview of FDA's draft guidance
- Discussion of monitoring recommendations

FDA Regulatory Requirements for Monitoring

- Effective monitoring is critical to
  - Human subject protection
  - Conduct of high-quality studies
- FDA IND and IDE Regulations
  - Obligate sponsors to oversee their clinical trials
    - 21 CFR 312.50 and 812.40: Sponsors are responsible for ensuring proper monitoring of the investigation
    - 21 CFR 812.25(e): Requires written monitoring procedures
  - Are not specific about how sponsors are to conduct monitoring

Types of Monitoring

- On-Site Monitoring- In person evaluation carried out by sponsor personnel or representatives at the site.
  - To identify data entry errors and missing data in source records and case report forms
  - To assess compliance with protocol and test article accountability
  - To assess investigator supervision

Types of Monitoring

- Centralized Monitoring- Remote evaluation carried out by sponsor personnel or representatives at a location other than the site.
  - Standard checks of range, consistency, completeness of data
  - To identify unusual distribution of data
  - To identify higher risk sites to target on-site monitoring
  - Routine review of data in real time

Current Practices

- Wide range of monitoring practices
  - Periodic, frequent visits with 100% source data verification
- Reactive and premised on retrospective detection of errors
- Oversight efforts not commensurate with risks
- May not optimally address significant risks to trial integrity, particularly systemic error
- Resource intensive
- **FDA's withdrawn guidance on the monitoring of clinical investigations does not reflect FDA's current recommendations**

Why is Guidance Needed?

- To improve quality and integrity of data
- To enhance human subject protection
- Inefficient practices may consume valuable resources and not add to quality
- To improve effectiveness of monitoring
- To reflect changes in clinical trial enterprise
- **To inform industry of FDA's support of alternative approaches**

Overview: FDA Monitoring Draft Guidance

- Goal: To enhance human subject protection and clinical trial data quality
- Focuses on clinical investigators' conduct, oversight, and reporting of an investigation
- Makes clear that sponsors can use a variety of approaches to fulfill monitoring responsibilities
  - "No single approach to monitoring is appropriate or necessary for every clinical trial"

Overview: FDA Monitoring Draft Guidance

- Intends to assist sponsors in developing risk-based monitoring strategies and plans
  - Tailored to the specific human subject protection and data integrity risks of the trial
  - Focuses on critical study parameters
  - Encourages use of a combination of monitoring activities
  - Encourages greater reliance on centralized monitoring practices, where appropriate

FDA Monitoring Recommendations

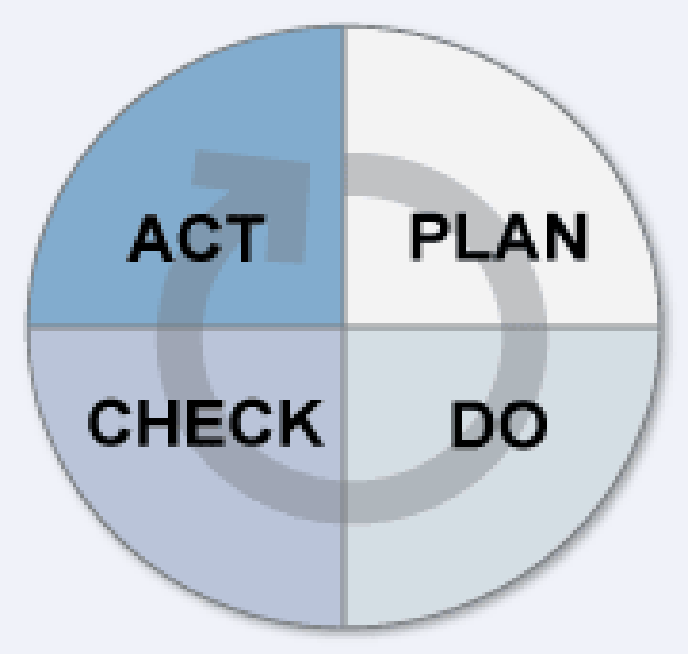
- Conduct a risk assessment to identify and evaluate risks to critical study data and processes

- Design a monitoring plan tailored to address important and likely risks identified during risk assessment

Risk Assessment

- 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?

Monitoring as a Component of Quality Risk Management



- **Plan – Identify quality objectives and metrics and risks to quality to develop quality management plans (e.g., monitoring plan)**
- **Do – Study conduct**
- **Check – Measure/monitor**
- **Act – Respond to deviation**

http://www.iso.org/iso/catalogue/management_standards/understand_the_basics.html

Protocol Design and Monitoring

- **"The most important tool for ensuring human subject protection and high-quality data is a well-designed and articulated protocol."**
  - Prospectively identify the important risks to subject safety and data reliability
  - Tailor and conduct the protocol to eliminate or mitigate those risks
  - Monitoring is one tool in a quality toolbox designed to mitigate and/or manage risks

What Should be Monitored?

- Some data and processes may need more intensive monitoring
  - Critical study endpoints, protocol-required safety assessments, withdrawals
  - Protocol eligibility criteria
  - Study blind
  - Informed consent
  - Test article administration and accountability

Monitoring Plan

- Trial specific
- Describes monitoring methods, responsibilities, and requirements
- Components to consider
  - Description of monitoring approaches (e.g., timing, intensity, activities, documentation)
  - Communication of monitoring results
  - Management of noncompliance
  - Training and study-specific information
  - Monitoring plan amendments

Monitoring Plan

- **Focus on critical data and processes**
- Types, frequency, and intensity of monitoring will depend on factors considered during risk assessment
  - Complexity of study design
  - Types of endpoints
  - Clinical complexity of subjects
  - Investigator experience
  - Relative safety of product
  - Quantity of data
  - Stage of study

Documentation of Monitoring

- Who conducted and date
- Data and activities reviewed
- Description of non-compliance, data irregularities, other deficiencies
- Actions taken or recommended

Ensuring Study Quality

- Investigator training and communication
- Delegation of monitoring to a contract research organization

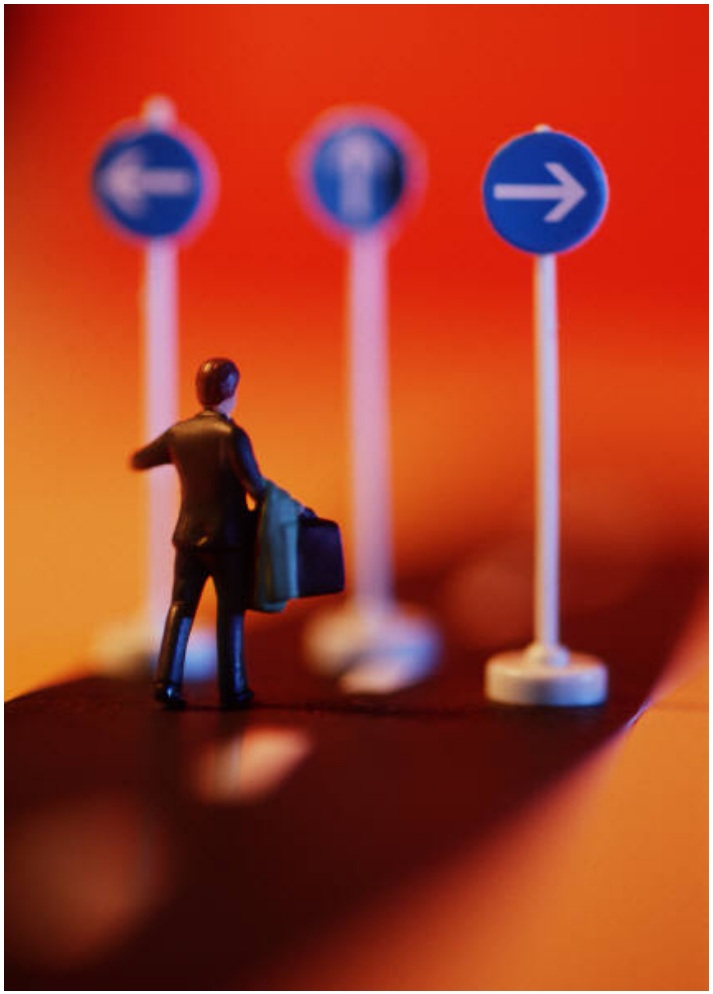
Summary

Risk-based approach

Not one size fits all

Document your plan

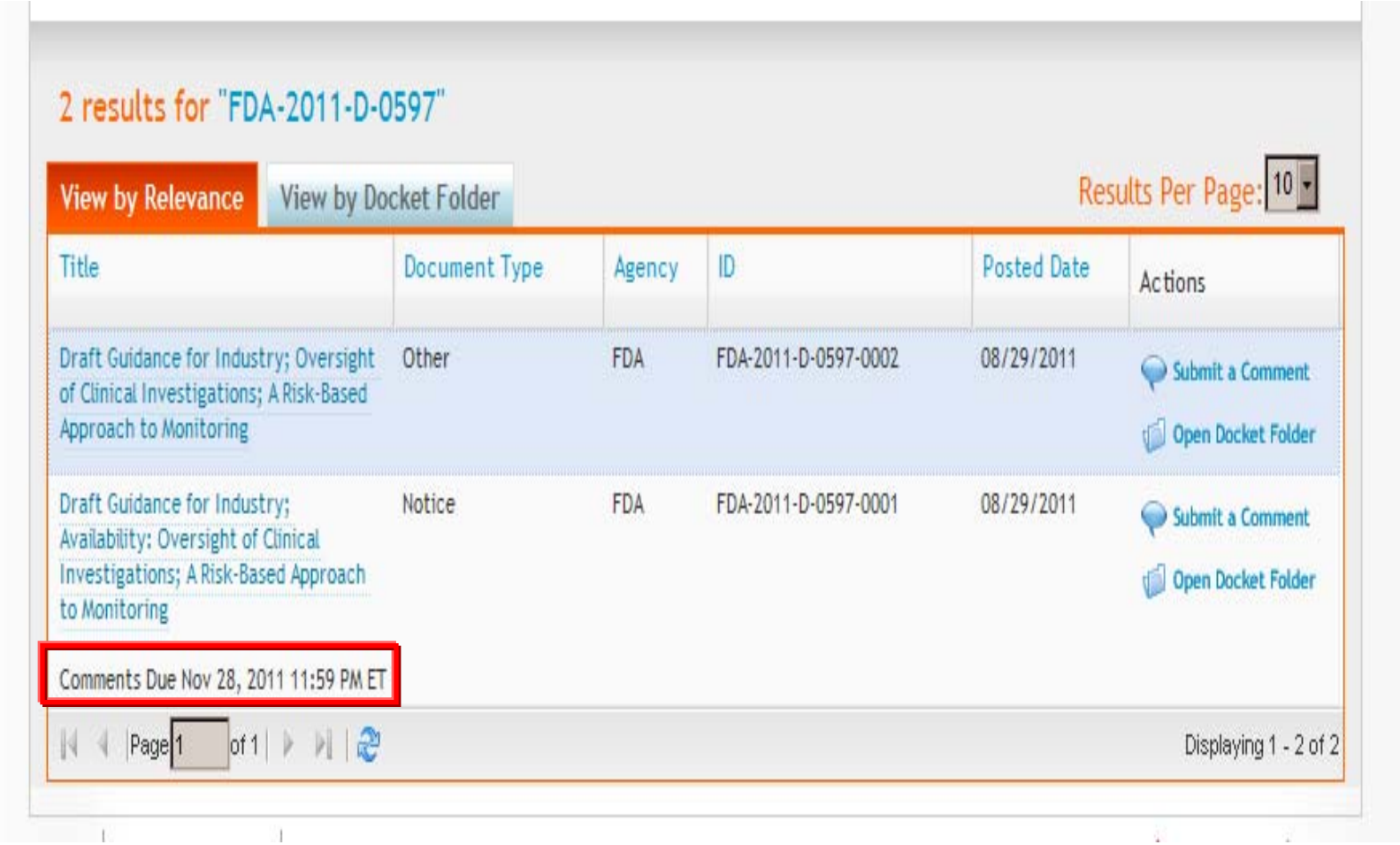
Next Steps



- Review and address comments to docket
- Determine internally the feasibility of prospective review of monitoring plans within CDER
  - Who?
  - Which trials?

How to Submit Comments

Regulations.gov



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

View by Relevance | View by Docket Folder

Results Per Page: 10

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

Comments Due Nov 28, 2011 11:59 PM ET

Page 1 of 1

Displaying 1 - 2 of 2

Internet Location

- Draft guidance: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269919.pdf