FDA Perspective on Ensuring Quality: Risk-Based Monitoring

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FDA Perspective
Clinical Development: The Desired State

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

(Janet Woodcock, CTTI Monitoring Workstream #3 Workshop)

Quality Data=Data Fit for A Purpose

- Data that are sufficiently accurate to support FDA regulatory decisions and statements made in labeling.

- Data that has been acquired in a manner that has not jeopardized the rights, safety, or welfare of trial participants

FDA Regulatory Requirements Clinical Trial Quality

- 21 CFR 312 broadly describes sponsor responsibilities for clinical trials
  - Selection of qualified investigators
  - Ensuring the trial is conducted according to the investigational plan
  - Review and analysis of accumulating evidence relating to product's safety and effectiveness

Monitoring trial progress

Why Is This So Important?

- A successful quality management system
- Maintains data integrity and the safety of trial participants (and patients in the post approval realm) within, and across, clinical development programs.
- Makes available beneficial new therapies for patients based on a foundation of high-quality evidence
- Improves efficiencies and optimizes resource utilization (Industry, Regulators, Healthcare system)

Risk Evaluation and Management

- What is Severity?
  - Minor Transcription error
  - Over-dosage multiple subjects with associated resulting SAEs
- What is Scope?
  - Clinical Investigator site specific issue
  - Systemic study issue
  - Systemic sponsor issue
- What are consequences/potential consequences

Guidance for Industry

Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Office of Good Clinical Practice (OGCP)
Office of Regulatory Affairs (ORA)
August 2013
Procedural

OMB Control No. 0910-0733
Expiration Date: 03/31/2016
See additional PRA statement in section VII of this guidance.

- "This guidance focuses principally on monitoring, which is one aspect of the processes and procedures needed to ensure clinical trial quality and subject safety. Monitoring is a quality control tool for determining whether study activities are being carried out as planned, so that deficiencies can be identified and corrected. Monitoring, or oversight, alone cannot ensure quality. Rather, quality is an overarching objective that must be built into the clinical trial enterprise. FDA recommends a quality risk management approach to clinical trials and is considering the need for additional guidance describing this approach."

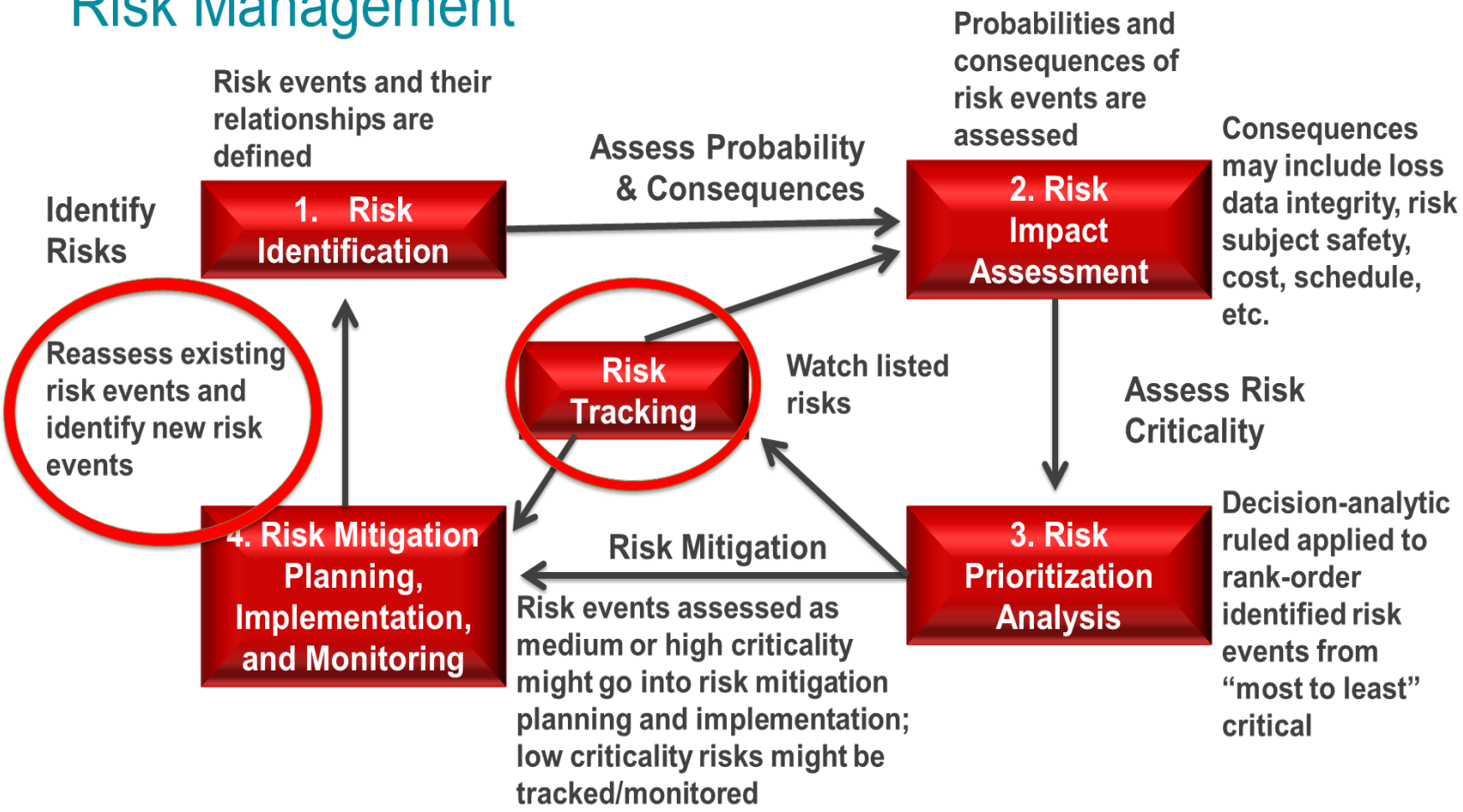
Need for Change: Traditional Reactive Approach ….. to Proactive Quality and Risk Based Approaches

Quality Management Systems

Quality by Design

Risk Based Monitoring

Risk Management



Suggestions on Documentation

- Quality Management System/Risk Management Plan:
  - Critical data and processes identified
  - Risk identification and evaluation process
  - Plans for risk control (mitigation, monitoring, etc.)
  - Ongoing risk tracking and review process (planned and actual)
  - Decision process used to determine need for CAPA versus ongoing plans to track issue
  - Reporting on deviations occurring from planned risk management plans

Overview: FDA Monitoring Guidance

Intent 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 Guidance Recommends

- **Protocol be considered blueprint for quality**
- Emphasizes need for a well-designed and articulated protocol
- Conduct of a risk assessment to identify and evaluate risks to critical study data and processes
- Monitoring plan be designed to address important and likely risks identified during risk assessment

Monitoring Plan Development Important 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 and quantity of data

Documentation Requirements

- Documentation should include:
  - Who conducted monitoring and when
  - Data and/or activities reviewed
  - Description of non-compliance, data irregularities, other deficiencies identified
  - Corrective actions implemented, if indicated

Discourages "One Size Fits All" approach to monitoring

http://kids.niehs.nih.gov/games/illusions/lots_of_illusions.htm

Experiences from the Real World (FDA Perspective)

A Phase 3 Study

- Single Primary Endpoint – Based on central laboratory parameter

- IMPORTANT Secondary Endpoints to determination of risk versus benefit of investigational product
  - Change in glucose control
  - Change in blood pressure

Study Outcome

- Primary Endpoint: A “Win”

- Secondary Endpoints:
  - For some IP improves outcome

    BUT
  - On others IP appears to worsen outcome

FINDINGS UNEXPECTED ARE THEY RELIABLE?

Traditional approach to evaluation of data quality and integrity

- Sponsor Monitoring
  - Source Document Verification
  - Fixed Monitoring Schedule
- Sponsor Quality Audits
- Regulatory Inspections

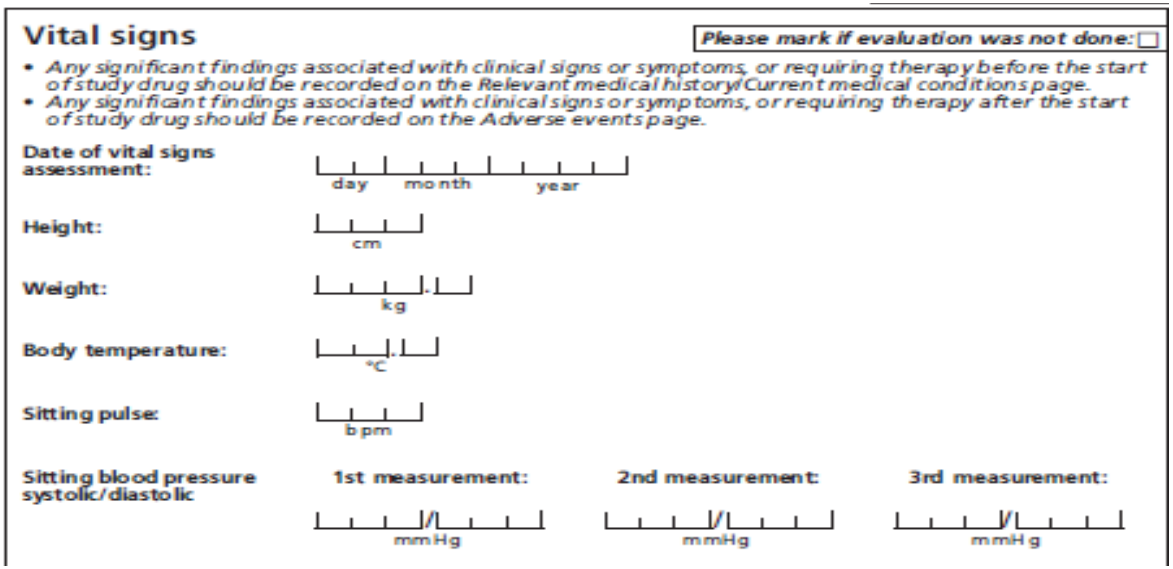
Finding on Site Inspection

Table: Blood Pressure Values

Sub. #	Visit	date	Sitting diastolic	Sitting Systolic	Sitting diastolic	Sitting Systolic	Sitting diastolic	Sitting Systolic	Standing Diastolic	Standing Systolic
9	4	10/10/08	110	90	110	90	108	86	106	78
9	5	10/27/08	110	96	112	94	112	96	112	90
9	6	11/11/08	102	80	102	80	100	78	98	78
9	7	11/25/08	110	90	110	90	105	85	100	84
9	8	12/10/08	120	80	120	80	116	80	110	76
9	9	01/09/09	118	80	118	80	116	80	110	76
9	10	02/09/09	110	80	110	80	110	80	100	78
9	11	03/10/09	110	80	110	80	110	80	100	78
9	12	04/10/08	120	80	120	80	118	80	110	78
9	13	05/08/09	110	80	110	80	110	80	106	76
9	14	05/09/09	110	78	110	78	106	78	106	78
9	17	05/30/09	108	78	108	78	104	78	100	76
9	of safet	07/16/09	100	78	100	78	100	78	100	74

Protocol "Blueprint"

- At each visit, three manual sitting BP measurements were to be recorded and averaged. They must agree by ±5 mm HG (no up or down rounding allowed). If the measurements did not agree they were to be repeated after 5 minutes.



Vital signs

Please mark if evaluation was not done: ☐

- *Any significant findings associated with clinical signs or symptoms, or requiring therapy before the start of study drug should be recorded on the Relevant medical history/Current medical conditions page.*
- *Any significant findings associated with clinical signs or symptoms, or requiring therapy after the start of study drug should be recorded on the Adverse events page.*

Date of vital signs assessment: day month year

Height: cm

Weight: kg

Body temperature: °C

Sitting pulse: bpm

Sitting blood pressure systolic/diastolic

1st measurement:	2nd measurement:	3rd measurement:
mmHg	mmHg	mmHg

What happened?

- FDA review of VS dataset submitted demonstrates the site is extreme outlier – lack of expected variability in BP assessments
- IR to Applicant - Applicant unaware of site issue and after further review and investigation of site remained unable to provide explanation/cause

BP data considered unreliable

Hindsight is 20/20 but…

- Could issue have been prevented?
  - Could protocol requirements for BP collection have been simplified?
- Could issue have been identified sooner?
  - Central Statistical Monitoring
- If identifiable, could contingency plan have been implemented successfully?
  - Remote or On-site intervention, Site staff training
  - Revisit protocol feasibility

A Phase 3 Study

- Complicated Bacterial Skin and Skin Structure Infections (cBSSSI)

- **Protocol "Blueprint":**
  - Infection was to be of severity that hospitalization was required for treatment
  - Randomization and first dose of study drug to occur on Day 1 (protocol stated this only in footnote on Study Procedures table)

Traditional approach to evaluation of data quality and integrity

- Sponsor Monitoring
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  - Fixed Monitoring Schedule
- Sponsor Quality Audits
- Regulatory Inspections

Finding on Site Inspection

- Nine subjects did not receive study drug for more than 24 hours after randomization, ranging from approximately 48 hours to eleven days post randomization.

What happened?

- Study drug was not available at site to dose subjects
- Beds were not available at site to admit subjects
- One subject randomized despite declining hospitalization when agreed that she would return several days later to begin treatment.
- Subjects placed at risk of worsening disease, sepsis, and death without treatment
- Did subjects have cBSSSI to start with?

Hindsight is 20/20 but…

- Could issue have been prevented?
  - Protocol clearer on requirements
  - IVRS
- Could issue have been identified sooner?
  - Central or remote monitoring time from randomization to dosing, subject enrollment-drug availability at site
- If identifiable, could contingency plan have been implemented successfully?
  - Enrollment halt pending drug resupply and site training

A Phase 3 Study

Protocol "Blueprint"

- Enrolled subjects to be hospitalized per protocol
  - BUT enrolled subjects may have been treated on outpatient basis via protocol waivers from CRO medical monitor (according to individual investigator sites' plans for outpatient)
- Study drug: Intravenous formulation relatively tight temperature storage requirements per protocol – once reconstituted required refrigeration and use within 16 hours

Traditional approach to evaluation of data quality and integrity

- Sponsor Monitoring
  - Source Document Verification
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Findings on Site Inspection

- Site outpatient dosing plan stated that the first dose of study medication was to be administered in clinic and remainder delivered daily and administered in subjects' homes by CRA
- Site administration records (source documents) documented multiple subjects receiving doses at the same time or overlapping times administered by the same CRA

What happened?

- Subject interviews reveal:
  - Site personnel dropped off study drugs and subjects self administered
  - Reconstituted drug doses for multiple days, at times entire treatment courses, were delivered to subjects homes at one time
- Fraudulent documentation practices
- Study drug administered well beyond stability – placed subjects at risk of inadequate treatment and adverse events due to infusion of particulate matter

Hindsight is 20/20 but…

- Could issue have been prevented?
  - Inclusion of plan for outpatient dosing in protocol, associated study documents, and monitoring plans
- Could issue have been identified sooner?
  - Would trend analysis have suggested more intensive on-site monitoring indicated?
- If identifiable, could contingency plan have been implemented successfully?

Take Home Points

- Quality cannot be monitored, audited, or inspected in retrospectively.
- Development of a Quality Risk Management Plan is strongly encouraged; a Risk-Based Monitoring Plan is one component the larger plan.

Take Home Points

- At the trial level, the protocol – or more appropriately the investigational plan – is the blueprint for quality.

- Risk-Based Monitoring is NOT a one size fits all approach to monitoring.