Risk-based Monitoring Overview & Case Study

24 April 2015
Today’s presenter:

Lynn King
Senior Director of Clinical Monitoring
TKL Research

- Clinical Research Professional
- 23 years of experience in the drug-development industry
- 16 years of management
- hands-on monitoring and project management
- coaching, mentoring and training roles in both the CRO and Pharmaceutical environments
Agenda

- Brief overview of Risk-based Monitoring
- Project risk assessment
  - Risk assessment tools
- Establishing monitoring strategy
  - Centralized monitoring
  - On-site monitoring
- Clinical Monitoring Plans
- Identifying critical data

*Items in quotes or noted with an asterisk (*) are from the FDA Guidance “Oversight of Clinical Investigations-A Risk-Based Approach to Monitoring” August 2013*
Please indicate your organization type.

- Pharmaceutical Company
- CRO
- Clinical Site
- Other
Please indicate your current functional area role.

- Project Manager
- Clinical Research Associate
- Management
- Quality Assurance
- Data Management/Statistician
- Regulatory Specialist
- Other
Monitoring Approaches

100% SDV

Targeted SDV

Reduced SDV

Risk-based Monitoring
Quality (& Risk) Management
How does this affect your development program?

<table>
<thead>
<tr>
<th>FDA expectations in audits</th>
<th>Review of team roles and responsibilities</th>
<th>Efficiency and cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Workforce impact</td>
<td>Investigational site staff impact</td>
<td>Data Quality</td>
</tr>
</tbody>
</table>
“This guidance describes strategies for monitoring activities that reflect a modern, risk-based approach that focuses on critical study parameters and relies on a combination of monitoring activities to oversee a study effectively. “

“For example, the guidance specifically encourages greater use of centralized monitoring methods where appropriate.”

FDA Guidance on Risk Based Monitoring

Design tailored monitoring plan for each trial

Use various monitoring approaches that fit risk assessment for specific study

Plan should address subject population needs specific to trial

Address data integrity risks specific to trial
## Types of Monitoring Defined in Guidance

<table>
<thead>
<tr>
<th>On-Site Monitoring</th>
<th>Centralized Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>• In-person evaluation</td>
<td>• Remote evaluation of data</td>
</tr>
<tr>
<td>• Assure study documentation exists</td>
<td>• Checks of range and completeness of data</td>
</tr>
<tr>
<td>• Identify data entry errors</td>
<td>• Review data distribution</td>
</tr>
<tr>
<td>• Assess site staff compliance and training</td>
<td>• Identify high risk sites</td>
</tr>
<tr>
<td>• Drug accountability</td>
<td>• Statistical analysis to identify data trends</td>
</tr>
<tr>
<td>• Quality of overall conduct</td>
<td>• Conduct SDV if possible</td>
</tr>
</tbody>
</table>
Centralized Monitoring

**Routine review of data**
- Missing/inconsistent data
- Data outliers
- Protocol deviations
- Regulatory review

**Statistical analyses to find data trends**
- Standard checks of range, consistency and completeness
- Check for unusual distribution of data (at one site and across sites)

**Site performance metrics**
- Screen failure rates that are unexpected
- Withdrawal rates
- Eligibility violations
- Data reporting delays
- Remote SDV if possible
Centralized Monitoring Example

Time between Expected and Actual Visit

Visit 1

Visit 2

Visit 3

Typically found at a site visit on individual subject basis
- Sometimes found during listing reviews
- Better approach: review consistently
Centralized Monitoring: P-Chart

Questionnaire Completion by Study Visit

Visit 1

Visit 2

Visit 3

Visit 4

Possible compliance issues

ACCELERATED STARTUP. QUALITY RESULTS.
Examples of Alternative Monitoring*

- Interaction with site staff
- Review of processes and records at each site
- Source data verification

• “...sponsor should consider which source records are likely to provide the most meaningful information”
• “...it may be sufficient to compare the most critical data points for a sample of subjects and study visits as an indicator of data accuracy.”
Multidisciplinary Team Approach

- Data Monitor
- Statistician
- Data Manager
- Project Leader
- Safety Associate
- Regulatory Associate
“Sponsors should prospectively identify critical data and processes that if inaccurate, not performed, or performed incorrectly, would threaten the protection of human subjects of the integrity of the study results.”
Risk Assessment Tools

Considerations

• Chance of errors occurring
• Impact of errors on subject protection and data integrity
• Ability to detect errors

Tools

• Risk Assessment and Categorization Tool (RACT) developed by TransCelerate Biopharma Inc
• Risk Ranking Tools
• Risk Management software
Have you ever implemented a monitoring plan using a risk-based approach?
Monitoring Plan

Approach

• Clear and concise
• Eliminate redundant information
• Modify during study as needed

Content

• Study background
• Risk assessment with rationale
• Study-specific monitoring strategy and information
• Documentation and communication of findings
# Monitoring Plan Example

## I. Overview of the Monitoring Plan
- **A. Purpose**
- **B. Study Objectives**
- **C. Risk Assessment**

## II. Trial Management
- **A. Monitor Training**
- **B. Visit Scheduling**
- **C. Visit Reporting**

## III. Monitoring Activities
- **A. Source Data Verification**
- **B. Case Report Forms**
- **C. Query Management**
- **D. Essential Document Review**
- **E. Remote Data Review**
- **F. IP Accountability**
- **G. Communications**
- **H. Protocol Deviations**
- **I. Issue Escalation/Resolution**

## IV. Quality Assurance Audits

## V. Safety Monitoring
- **A. Adverse Event Procedures**
- **B. Serious Adverse Events**
Case Study

Phase II randomized, double-blind study

Mild to moderate atopic dermatitis

20 US sites, 10 ex-US sites

195 subjects screened, 121 subjects randomized

- 11,217 CRF pages completed
- 68% data fields SDV completed
# Case Study: Monitoring Strategy

<table>
<thead>
<tr>
<th>Review Tier</th>
<th>SDV Requirements</th>
</tr>
</thead>
</table>
| Tier 1A: 100% SDV Tier    | 100% SDV of all data variables for first subject randomized at every site  
• 100% of critical variables plus 100% of non-critical variables  
If the data quality at the site is acceptable for first subject, move to Random SDV |
| Tier 1B: Random Tier      | 25% of Subjects [randomly assigned, runs in parallel with Tier 2];                                                                                   |
| Tier 2: Critical Variable Tier | 75% of Subjects [randomly assigned, runs in parallel with Tier 1B];  
• 100% of ONLY critical variables                                       |
Case Study: Visual of Monitoring Strategy

<table>
<thead>
<tr>
<th>Projected Enrollment per Site</th>
<th>Subj 1</th>
<th>Subj 2</th>
<th>Subj 3</th>
<th>Subj 4</th>
<th>Subj 5</th>
<th>Subj 6</th>
<th>Subj 7</th>
<th>Subj 8</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Data Points</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SDV Requirements</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tier 1A:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First subject enrolled</td>
<td>100%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tier 1B:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25% of subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100% Critical Variables and 100% Non-critical Variables</td>
<td></td>
<td>100%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tier 2:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>75% of subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100% of Critical Variables</td>
<td>&lt;100%</td>
<td>&lt;100%</td>
<td>&lt;100%</td>
<td>&lt;100%</td>
<td>&lt;100%</td>
<td>&lt;100%</td>
<td>&lt;100%</td>
<td></td>
</tr>
</tbody>
</table>
Case Study: Critical Variables Identified

- ICF/Assent
- PK ICF
- Childbearing Potential
- Target Lesion Identification
- % BSA
- Inclusion/Exclusion Criteria
- AEs/SAEs
- Overall Investigator Global Assessment score
- Overall Eczema Areas and Severity Index score
- VAS score
- QOL Assessments
Case Study Lessons Learned

✓ Definition of roles and expectations at study start is critical
✓ Communication pathways must be established and maintained
✓ Risk assessment discussions across functions
✓ Clinical Monitoring Plan should be concise with critical study-specific information
✓ Provide examples during training for monitoring escalation and triggers for additional monitoring
✓ Ensure system capabilities of EDC for implementing monitoring plan
“Although sponsors can transfer responsibilities for monitoring to a CRO, they retain responsibility of oversight of the work completed by the CRO…”

Considerations

• Establish clear understanding of responsibilities
• Share information for risk assessment
• Evaluate monitoring practices and plans in partnership and prospectively
• Communicate effectively and in a timely manner
What is the most difficult challenge in implementing RBM in your organization?

- Buy-in/support in organization
- Having the right staff to implement
- Risk assessment processes/tools
- Writing CMPs
- Establishing centralized monitoring processes
- Not sure
Summary

Risk-Based Monitoring Guidance Overview

- Risk Assessment/Quality Management
- Identifying Critical Variables
- Monitoring Approaches
- Clinical Monitoring Plan

Case Study

- Importance of CMP
- Tools for monitoring strategy
- Communication and planning is critical
Summary


TransCelerate Biopharma Inc. (http://www.transceleratebiopharmainc.com/assets/risk-based-monitoring/)
Thank you for your participation

Contact Information for follow-up questions

Lynn King
Senior Director, Clinical Operations
Head, Clinical Monitoring
TKL Research
201-587-0500  x5218
lking@tklresearch.com