Risk based approaches to monitoring of vaccine clinical trials:

A quality driven and cost-effective model

Abby Abraham
Vice President – Clinical Solutions

www.algorics.com
Topics

• Industry challenge
  • Spiraling costs of clinical trials in drugs & vaccines
  • Current state of clinical trial monitoring
  • Monitoring outcomes & Quality

• Solution
  • What is RBM
  • How does it work?
  • How to implement?
  • Technology intervention

• A peek into data visualization and risk indication
• Benefits of using RBM
• Is RBM optional in the new world?
Affordability of medicines today

MEDICINES SHOULDN'T BE A LUXURY

www.medicines.org
Industry challenge
Vaccine development costs

• Spiraling R&D costs:

  • Vaccine R&D costs:
    • WHO estimates between US$163 & $518 Mn
    • US $500 Mn to US$ 1 Bn*

  • Clinical development is expected to be ~ 60 to 70% of total R&D
    • ~ $100 to $600 Mn USD

  • Clinical monitoring and management costs 35 to 55% of phase II & III clinical trials
    • ~ $44 Mn to $ 200 Mn

* Investing in vaccines for the developing world – PATH White paper, April 2009
Clinical trial monitoring - current state

**Current monitoring practices**

Current monitoring practices allocate monitoring resources uniformly among study sites, regardless of the risk to patients or clinical data from individual sites.

<table>
<thead>
<tr>
<th>Site</th>
<th>Site 1</th>
<th>Site 2</th>
<th>Site 3</th>
<th>Site 4</th>
<th>Site 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-risk site</td>
<td>40*</td>
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<tr>
<td>Medium-risk site</td>
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<td>Low-risk site</td>
<td>40</td>
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</tbody>
</table>

*Site monitoring relative costs (percent)
Monitoring outcomes – Critical findings (last 10 years)

Source: Uniting to achieve oversight compliance by Alan M, Patrica L presented at PCT EU Conference, 6 November 2013
Monitoring outcomes – Major findings (last 10 years)

EMA major findings (n=516)

- Monitoring: 11.0%
- Data management: 10.3%
- Essential documents: 10.3%
- SOPs: 10.0%
- Protocol (other aspects): 9.1%
- CRF/diary reporting: 8.3%
- Protocol (selection criteria): 6.8%
- Qualifications / training: 6.4%
- Protocol (safety reporting): 5.0%
- Protocol (efficacy aspects): 4.8%
- Protocol (efficacy aspects): 4.3%
- Document control / personnel: 2.9%
- Contract / Agreements: 2.7%
- Protocol (efficacy aspects): 2.1%
- Protocol (efficacy aspects): 2.1%
- Facilities / equipment: 1.7%
- Direct access to data: 0.8%
- Audit: 0.6%
- Randomisation / blinding: 0.4%
- Randomisation / blinding: 0.2%

Source: Uniting to achieve oversight compliance by Alan M, Patrica L presented at PCT EU Conference, 6 November 2013
Gap in monitoring methodology

Current approaches

Traditional on-site monitoring

Intensive manual analysis
Solution
Solution (RBM)

Risk-based monitoring

A risk-based monitoring approach allows for the identification of risk at individual sites and allocates monitoring resources to optimally address and mitigate patient safety and data quality risk.

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<th>Low-risk site</th>
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</thead>
<tbody>
<tr>
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<tr>
<td>Site 5</td>
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</tbody>
</table>

*Site monitoring relative costs (percent)
What is Risk based monitoring?

- Identify risks
- Plan and prioritize risks
- Monitor prioritized risks
How does it work?

Risk-Based Monitoring (RBM) Methodology - High Level Process Map and Associated Tools

1. Risk Assessments
   - Complete Risk Assessment Categorization Template (RACT)
   - Define at the Program Level
   - Reassess at the Protocol Level

2. Critical Variables
   - Includes Critical Data and Processes

3. Risk Plan
   - Develop Integrated Quality and Risk Management Plan (IQRMP)
   - Define Central, Off-site, and On-site Monitoring Activities and other risk mitigation activities in Functional Plans (e.g. Monitoring Plan, Data Plan)

4. Monitoring Execution
   - Execute Monitoring Activities
How to implement?

1. Identify Key Risk indicators/Quality indicators
2. Use data visualizations
3. Layer it with thresholds
4. Use outputs for monitoring objectively
5. Use Statistical algorithms to grade risks
Fundamental requirement – Data confluence

Insight – Subject, Site and country level

CTMS
IXRS
ePRO
eTMF
eDC
other data sources
Monitor based on risks
Expected Quality & Cost benefits

Risk Based Monitoring Case Study:
Lessons from a 3,389-subject Global Phase III Trial

Oct 06, 2015  By Lisa James
Applied Clinical Trials
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)
Office of Regulatory Affairs (ORA)
August 2012

European Medicines Agency
Science Medicines Health

Reflection paper on risk based quality management in clinical trials

Draft agreed by the Clinical Trial Facilitation Group (CTFG) for release for consultation
31 May 2013
Draft adapted by the Good Clinical Practice (GCP) Inspectors Working Group for consultation
14 June 2013
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5 August 2013
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10 February 2012
Agreed by the Clinical Trial Facilitation Group (CTFG) for publication
10 September 2013
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12 September 2013

Keywords:
Quality Management, Risk Management, Quality Assurance, Risk Control, Clinical Trials
Thank you