Managing Clinical Operations Risks

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Disclaimer

The views and opinion expressed in this slides are that of the presenter and do not necessarily reflect the views and opinions of ii4sm ltd.
Goal

• Risk-based Approach to Clinical Operations is an emerging risk management discipline

• Measurement of structural and operational risks

• Risks have large impact on whole organisation: legal, financial and reputational consequences
Clinical Development

Phase I
Dosage/Safety
First testing 20-100 volunteers

Phase II
Safety/Efficacy
20-500 patients

Phase III
Safety/Efficacy
500-20000 patients

Phase IV
Safety/Efficacy in ‘real life’
Up to 50,000 patients

Clinical Operations
• Protocol Design
• Study Set-up
• Feasibility/Recruitment
• Data Management
• Monitoring
• Study Site Management
• Drug Safety

-...
A global Phase III trial

6 continents
850 study centers
18,000 patients

Source: ct.gov: trial NCT01663402
Consequences of not having Risk Management in Clinical Operations

• Possible Public Health Consequences
  - Harm to clinical trial participants
  - Delayed market availability of new therapy
  - Market Approval of unsafe or ineffective therapy
  - Loss of public confidence in pharmaceutical industry

• Possible effect on drug application
  - Non-market approval/ delayed market approval
  - Additional clinical trials if data are insufficient
  - Warning letters, investigator disqualifications, congressional hearings, criminal investigations...

→ Financial, Legal and Reputational Impact
Some recent examples...

Health Canada Suspends License
Chemical Testing Laboratory
Falsified Results

FDA issues cefotibiprole Complete Response Letter
due to unreliable and unverifiable trial data

Cetero files for bankruptcy after it faked
clinical trial data

CRO Cetero Research filed for bankruptcy after FDA accusations
of faking clinical trials and manipulating lab data. The allegations
involved Cetero's Houston facility and have been investigated
for the last 2 years.

An investigator site inspection by FDA revealed serious violations of
Title 21 CFR including failure to ensure that informed consent...

Shares of Peregrine Pharmaceuticals Inc
plunge on unreliable trial data

Company blames unreliable trial data on error by contract researcher
Found discrepancies while preparing to meet with regulators
Shares, which had risen tenfold during the summer, fell as much as 85%
Shares of Peregrine Pharmaceuticals Inc. (PHMI) plunged as much as 85% Monday, after

I-1 issues warning letter to Johnson & Johnson
regarding the failure to ensure proper monitoring of
the clinical trials, the reports say accountability for CROs is weak.

Few sponsors report having robust measures to ensure
conducting by contractors are safe and ethical, indicating no evidence of exerting real influ-
contracts conduct trials.
Regulatory Drivers & group initiatives

- FDA Final Guidance for all clinical trials – Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring – Aug 13
- MHRA Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products. Oct’ 11
- EMA Reflection Paper on Risk-Based Quality Management in Clinical Trials - Nov ‘13
- ICH guidance Q10 (Pharmaceutical Quality Systems – Jun ‘08), Q9 (QRM – May ‘06), Q8 (Pharmaceutical Development - Jun ‘06)

- CTTI
- TransCelerate

- Quality Risk Management
- Quality by Design
- Risk-based Monitoring
Cost driver

Average per-patient trial costs across all therapeutic areas

Source: Pharmalot Cutting Edge Informatics 26 July 2011
Clinical Operations – today

- **Protocol Design, Study set up**
  - Complex
  - Increasing number of procedures
  - Poor study set up

- **Trial Site Performance**
  - Study management lacks oversight
  - Queries after on-site visit and review
  - Reactive

- **Monitoring**
  - Rigid Monitoring Visit Schedules (4 – 8 weeks)
  - Intensive 100% SDV of all data points

- Complex and poor study design introduce risks later on
- Fire fighting of issues
- High cost due to high amount of monitoring visits
RM in Clinical Operations – where to start

Protocol Design, Study set up (Quality-by-Design)
- Patient safety, data quality, compliance
- Impact on Monitoring Planning

Trial Site Performance
- Key Risk Indicators
  - Flagging of problem sites
  - Adjustment of Monitoring Approach

Risk Based Monitoring
- Focus on sites with findings
- Focus on data that matter

- Thorough study design reduces risks later on
- Some findings can be solved remotely
- Reduction of monitoring visit frequency and costs
RM in Clinical Operations – how to do it

Protocol Concept

Quality-by-Design

Clinical Trial Process

Trial Site Performance

RM in Clinical Operations – how to do it

Control Risk
- On-Site/Remote Monitoring
- Risk Mitigation

Assess Risk
Calculate and identify risk entities with increased Risk (key risk indicators)

Collect Data
From CTMS, eCRF, clinical DB, questionnaires

Adapt Plan
- Monitoring Plan
- Risk Mitigation Plan

Generate Risk Reports
Key Risk Indicators (KRIs)

• KRI values of a trial site are calculated by using site metrics
• Outlier identified when a KRI value exceeds a predefined threshold
• KRI signals indicate outliers by turning from green to red
• KRIs cover many aspects of trial site performance, e.g.
  - Patient Safety
  - Patient Recruitment
  - Site Performance
  - Data Quality
  - Vendor Performance
Trial Site Report Example

Detailed Key Risk Indicator Assessment Report

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- **KRI Threshold exceeded**
- **within KRI Threshold**
- **KRI turned off**
Significant Savings of Risk-based Approach per Study

Cost: Initial estimates show potential of risk-based monitoring to save 15 to 20% in study portfolio costs

Source: Risk-based monitoring Reduce clinical trial costs while protecting safety and quality. PwC, March 2013
Summary

• Current situation in Clinical Operations is unsustainable

• Risk-based Approach to Clinical Operations is an emerging risk management discipline

• Measurement of structural and operational risks is key to operational excellence

• Risks have large impact on whole organisation: legal, financial and reputational consequences

• Increased resource effectiveness with risk driven resource allocation

• Significant cost savings can be achieved while maintaining patient safety, data quality and compliance
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