LESS IS THE NEW MORE

ALTERNATIVE MODELS FOR SOURCE DATA VERIFICATION (SDV)

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Agenda

- Guidelines for Industry Regarding Risk Based Monitoring
- Alternative Models for Source Data Verification (SDV)
- Costs of Implementation
- Study Characteristics vs Monitoring Approach
100% SDV Approach - Disadvantages

- Human review process is only 85% accurate
- Capturing only certain types of errors (e.g. Protocol violations, transcription errors etc.) referring to a site accuracy, not clinical competency
- Focus on catching mistakes, not on preventing them
- CRAs have perspective limited to sites under current revision (no cross-site perspective)
- CRAs’ individual approach and preferences towards SDV managing and selection
- Resource and time consuming

Based on FDA statements – typically only 30% of submitted data are the most essential for drug approvals.
Guidelines for Industry

2. Reflection paper on risk based quality management in clinical trials, November, 2013
„Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring” (FDA)

„(…) use of alternative monitoring approaches should be considered by all sponsors, including commercial sponsors, when developing risk-based monitoring strategies and plans.”

“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.”
The combination of these (inspections) findings and the high cost of the oversight of clinical trials strongly suggests that current approach to clinical quality management is in need of review and reorientation.

There is a need to find better ways to make sure that limited resources are best targeted to address the most important issues and priorities, especially those associated with predictable or identifiable risks to the wellbeing of trial subjects and the quality of trial data and results.
What Does the Future Hold? 2013 vs 2015

**Figure 2.** Utilization of three monitoring models today and in 2015.

*Source: Industry Standard Research*

What does the Future Hold for Clinical Monitoring?, Applied Clinical Trials, September 2013: 3-7.
Alternative Models of SDV

- Adaptative Monitoring
- Targeted Monitoring
- Remote/Centralized Monitoring
- Risk-based Monitoring
Initial visits are 100% SDVd and if no significant issues are identified then adjustment is performed.

Adaptative Monitoring (2)

**PROS**

- Possibility of significant reduction of number of MV and associated costs.
- Focuses on key variables.

**CONS**

- Resource utilization is highly variable (unpredictable).
- Add complexity to the monitoring process.
- Might require extensive negotiations with a Regulatory Agency.

**Technology needs**

- Formula/tool for adjustment SDV decrease based on error rate/quality issue assessment.
Targeted Monitoring (1)

Targeted SDV prioritizes critical data and uses random sampling methods to select data for SDV during on-site monitoring visits.

There are two basic ways in which targeted SDV could be planned:

**FIXED FIELDS APPROACH**

- 100% SDV of 1-3 firstly enrolled patients
- 100% SDV of data points which are high risk and critical (e.g. ICFs, efficacy endpoints, safety)

**RANDOM FIELDS APPROACH**

- 100% SDV of 1-3 firstly enrolled patients
- 100% SDV of critical data points plus random statistical sampling verification
Targeted Monitoring (2)

**PROS**
- Has potential to improve safety oversight, data quality, protocol adherence and overall trial validity while reducing costs and time.
- Focuses on key variables.
- Better utilization of time spent at the site.

**CONS**
- Adds complexity to the monitoring process.
- Risk of not revealing critical findings.

**Technology needs**
- Risk Assessment tools to be used during start up phase of the study to identify critical/essential data points to be SDV.
- Algorithm/tool to support random sampling method to select data to SDV.
Remote/Centralized Monitoring (3)

"Centralized monitoring is a remote evaluation carried out by sponsor personnel or representatives (e.g. clinical monitors, data management personnel or statisticians) at a location other than the sites at which the clinical investigation is being conducted."

- **CENTRAL MONITORING TECHNIQUES (EXAMPLES):**
  - Monitor clinical data quality (outliers, consistency, completeness).
  - Analyze site characteristics/ performance metrics (e.g. number of reported AEs, PDs, SF rate data entry timelines).
  - Identify significant concerns with non-critical data that may not have been focus of on-site monitoring.
  - Check submitted documents (e.g. eTMF checklists).
  - Complete administrative and regulatory tasks.

FDA, August 2013
Remote/Centralized Monitoring (2)

**PROS**

- Analyse data in real-time (use of statistical methods to trace discrepancies and outliers).
- Allows to identify issues/critical areas faster.
- Better utilization of time spent on-site.
- Look at data from wider perspective (across systems, sites, countries etc.).

**CONS**

- Requires launching of an office based team.
- Not a stand alone method – requires hybrid with other on-site monitoring approach.

**Technology needs**

- Real-time access to data hosted by IVRS/IWRS, EDC, CTMS, central laboratory, safety systems and other data repositories.
- Algorithm/tool to support statistical methods to trace discrepancies and outliers etc.
Risk-based monitoring approach focuses on the **high risk data points** (data points which are **prone to mistakes** or difference in interpretation or transcription and which have a **high impact on the quality** of the data and the outcome of the study).

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**A) Protocol risks:**
- Therapeutic area
- Drug safety profile
- Invasiveness of the drug

**B) Study site risks:**
- Site Experience
- Site location

**Algorithm’s real time evaluation of dynamic risks e.g.:**
- Number of AEs
- Number of PD/PVs
- Primary/secondary efficacy range

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**Tailored Risk-based Monitoring Plan**
**Risk-based Monitoring – RBM (2)**

- **Trigger Types**
  - Protocol-based (e.g. in case of death, critical outliers etc.)
  - Volume-based (archived collection of estimated amount of data)
  - Time threshold (certain amount of time elapsed)

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**On-site Monitoring Visit**
Risk-based Monitoring – RBM (3)

Figure 1. An internal study found triggering techniques reduced site visits, while increasing on-site CRA utilization.

What does the Future Hold for Clinical Monitoring?, Applied Clinical Trials, September 2013: 3-7.
**Risk Based Monitoring – RBM (4)**

**PROS**

- Analyse data in real-time (use of statistical methods to trace discrepancies, outliers, alert signals etc.).
- Focuses on critical data points.
- Allows to identify issues/critical areas faster.
- Better utilization of time spent on-site and decrease of monitoring visit hours.
- Triggers action in results of situation at the site.

**CONS**

- Risk of improperly allocating monitoring resources.
- Risk that algorithms predict high-level risk across all sites (negligible impact on saving costs).
- Risk of not revealing critical findings.

**Technology needs**

- Robust predictive modelling tool using sophisticated statistical algorithms that take into account variables/risks such as historical data and the statistical distribution of patients.
- An electronic system – capable of extracting data from multiple sources (EDC, IVRS, CTMS etc.) – being able to translate the event into trigger.
- Scheduling tool.
Reductions of costs are unlikely in small (phase 1/2a) studies and studies with high safety risk profiles (e.g. Oncology). Significant savings can be gained in large phase 2b/3 studies.
Costs of Implementation (2)

<table>
<thead>
<tr>
<th>Study Phase</th>
<th>Preferred Monitoring Approach</th>
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<tbody>
<tr>
<td>Phase I</td>
<td>Traditional monitoring models</td>
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<td>Phase III</td>
<td>Triggered and hybrid monitoring models</td>
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<tr>
<td>Phase IV</td>
<td>Suited for Non-Traditional models</td>
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Clear and focused objectives (valid endpoints).

Multidisciplinary team (Biostatisticians, Data Managers, CPLs, Medical Monitors) involved in all phases of the study.

Tailored Monitoring Plan.

Well designed eCRF that collects „adequate case histories”.

Clear training strategy- for both internal and site staff.
“Risk Based Monitoring (RBM) is evolving into a standard expectation for SDV and study management in general. KCR would like to be on the forefront to implement such solutions with our customers.

As RBM involves a various approach to SDV, it is critical for KCR to identify the best solution for our customers’ projects to meet the quality and efficiency expectations.

Knowing our clients’ options towards RBM is critical. We see a commoditization of CRA site activities as it comes to SDV and other GCP related topics. Therefore Risk Based Monitoring will help to optimize further the use of CRA time at sites.”

Mike Jagielski, President & CEO of KCR
References:

7. Overcoming the Concerns Associated with Risk-Base Monitoring, Applied Clinical Trails, September 2013: 21-23.
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About KCR

KCR is a European Contract Research Organization (CRO) with a dynamic team of nearly 300 professionals operating across 18 countries in Europe as well as the U.S.

With 17 years of experience, more than 350 trials executed, over 30,000 patients recruited and almost 3,000 sites contracted, KCR is a strategic solutions provider and a reliable alternative to global CROs, delivering the all-important flexibility.

We provide services on long standing global or local contracts to 12 out of the Top 20 Global Pharma companies, and have been granted by 3 of them with the Preferred Provider certification.

KCR offers clinical development support via 3 types of professional services:
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- Functional Service Provider (FSP)
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