Risk-Based Monitoring (RBM): Opportunities and challenges in clinical development

PSDM (Pharmaceutische Statistiek en Data Management) workshop meeting

2nd September 2013 – Leiderdop, The Netherlands

Risk-Based Monitoring: *a unique opportunity*

Frederic Hlavac, Global Studies Manager
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RBM: Why a unique opportunity

Data Quality: (Re-)defining the definitions

Impact on Data Monitoring

What's next

A unique opportunity

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.

Quality in Clinical Development

"Maximally efficient, agile clinical development programs that reliably produce high quality data and protect trial participants without extensive regulatory oversight[1]"*

"Quality in clinical trials may be defined by the absence of errors that matter[2]'"

Data that are **fit for purpose, that are sufficiently accurate to support regulatory decisions and/or sponsor claims about a product/labeling equivalent to those derived from a error-free database.*

[1]Meeker-O'Connell a, Ball L., Current trends in FDA inspections March/April 2011
[2]Clinical Trial Transformation Initiative (CTTI) - Quality by Design Workshops Project. Jan 2012

RBM at Roche – Fit for Purpose Monitoring
A Smart Risk Approach

- Evolution over time
  - 2009:
    - *focus on improving monitoring efficiency for* Long Term Follow-Up studies
  - 2011:
    - *Implementation of key concepts on all types of studies supported by*
      - Monitoring and Site Oversight SOP
      - Trial Monitoring Plan (TMP)
  - 2012 onwards:
    - *Exploration of different monitoring models*
      - *Remote monitoring (triggered on-site visits only)*
      - *'Partnered' monitoring (remote monitors and on-site monitors).*
    - *Evolution towards Centralized Monitoring*
      - *remote monitoring with on-site monitoring only if major quality and safety findings*

RBM at Roche

A Smart Risk Approach for Monitoring is supported by Retrospective Data Analysis

"*Less than 3% of eCRF data is updated after the initial capture session. …over 97% of all data provided in the study eCRF is in its final form—ready for analysis, reporting, and submission—before any site monitor or data manager reviews the data.*"

Industry Metric Indicates Low ROI with Full Source Document Verification, Medidata Solutions, Apr 2012

"*Nine sample studies from 6 Transcelerate member companies were analyzed [Retrospective Analysis of Monitoring and SDV]. (...) The average percentage of SDV queries generated was 7.8% of the total number of queries generated. The average percentage of SDV queries that were generated in Critical Data as represented as a part of the total number of queries was 2.4%.*"

Transcelerate Position Paper: Risk-Based Monitoring Methodology – 30 May 2013

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RBM and Data Quality

Fact: We have deviated from initial fit for purpose data monitoring because of outdated perceptions and urban myths around the meaning of Data Quality and of Monitoring...and a well intended goal to reach perfection!?

RBM and Data Quality

The Definitions*

- **Critical Data**

Data that are critical to the reliability of the study findings, especially those data that supports primary and secondary endpoints (...)

- **Risk-Based Monitoring**

An adaptive approach (...) that directs monitoring focus and activities to the evolving areas of greatest need which have the most potential to impact subject safety and data quality

- **Source Data Verification (SDV)**

(...) Transcription checking (...)

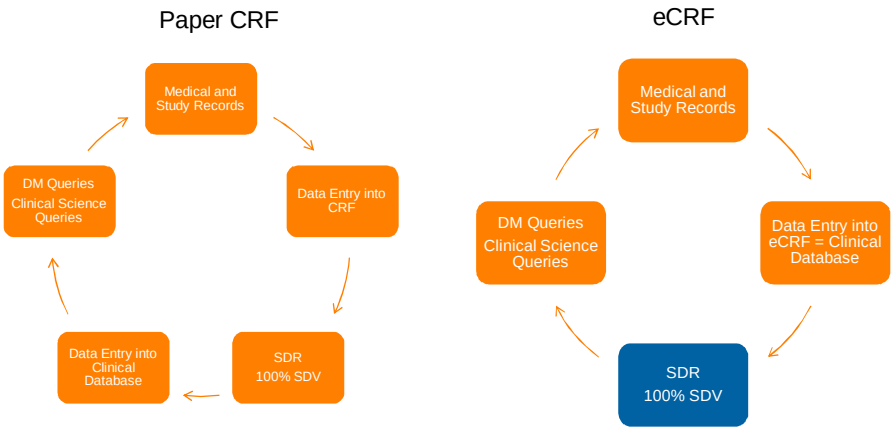
- **Source Data Review (SDR)**

Review of source documentation to check quality of source, review protocol compliance, (...) and source documentation (...) are adequate (...)

*Transcelerate Position Paper - http://transceleratebiopharmainc.com/

Monitoring the Data Quality

The eCRF: a missed opportunity for RBM ?



RBM and Data Quality

The Impact of (Re-)Definitions: Changing the Mindset

- Awareness about RBM
- Desire and Motivation for RBM: Fear of the Unknown, Benefit, Comfort Zone
- RBM Implementation: Trainings, Increased Workload, Processes and Procedures
- Myth busting

And if you think smart people are by default open minded: "*There is no reason anyone would want a computer in their home*."

Ken Olsen, founder of Digital Equipment Corporation, 1977

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RBM and Data Quality

The Impact of Definitions on Data Monitoring

For an individual study what do we need to define?

- What Data Quality means
- The Critical Data (Quality by Design and Data Standards)
- The Key Risk Indicators and acceptable level of risk
- Who, what, when and how risk will be managed/monitored
- Clear accountabilities for cross-functional “monitoring”
- SDR and SDV levels based on overall risk level

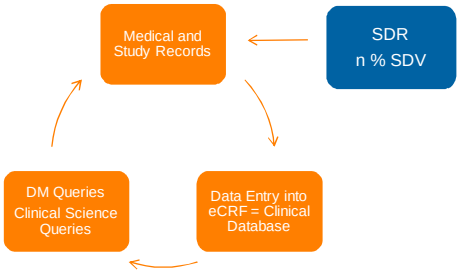
Quality by Design

Ability to effectively and efficiently answer the intended question about benefits and risks, while assuring subject safety.

Reminder: “Quality in clinical trials may be defined by the absence of errors that matter

RBM and the CRA activities

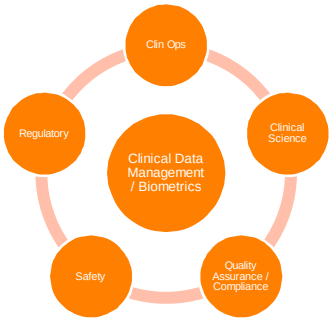
- eCRF – RBM



- 100% SDV does not equal quality data
- For the Critical Data, CRA monitoring activities will be performed remotely wherever possible. The underlying assumption is if there is no related data field in the eCRF, then the data is probably not a Critical Data.
- Targeted on-site data review (both SDR and SDV) will be done based on the overall risk score and focusing on critical data **and underlying processes**

Data Review Tracking and Reporting

- Integrated, Cross Functional Data Review Plans
- Risk Indicators and associated thresholds monitored by all functions
- SDR/ SDV are understood and not one size fits all
- Trends and Outliers in Data
- Clinical Data Management / Biometrics have a central role to play



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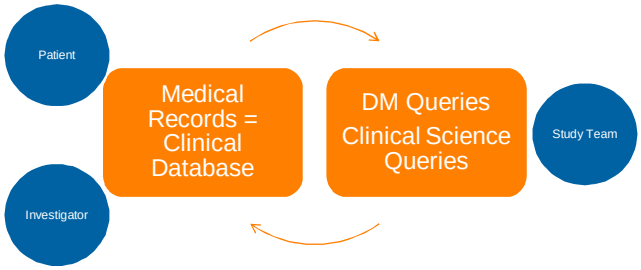
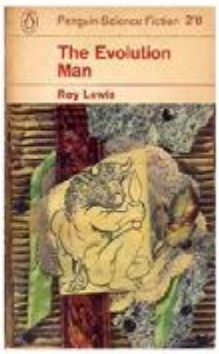
And Tomorrow ?

- Full Centralized Monitoring
- Data Standards





Or How I Ate My Father

Q&A

Doing now what patients need next