# Risk-Based monitoring

# New concepts in clinical trial management and monitoring

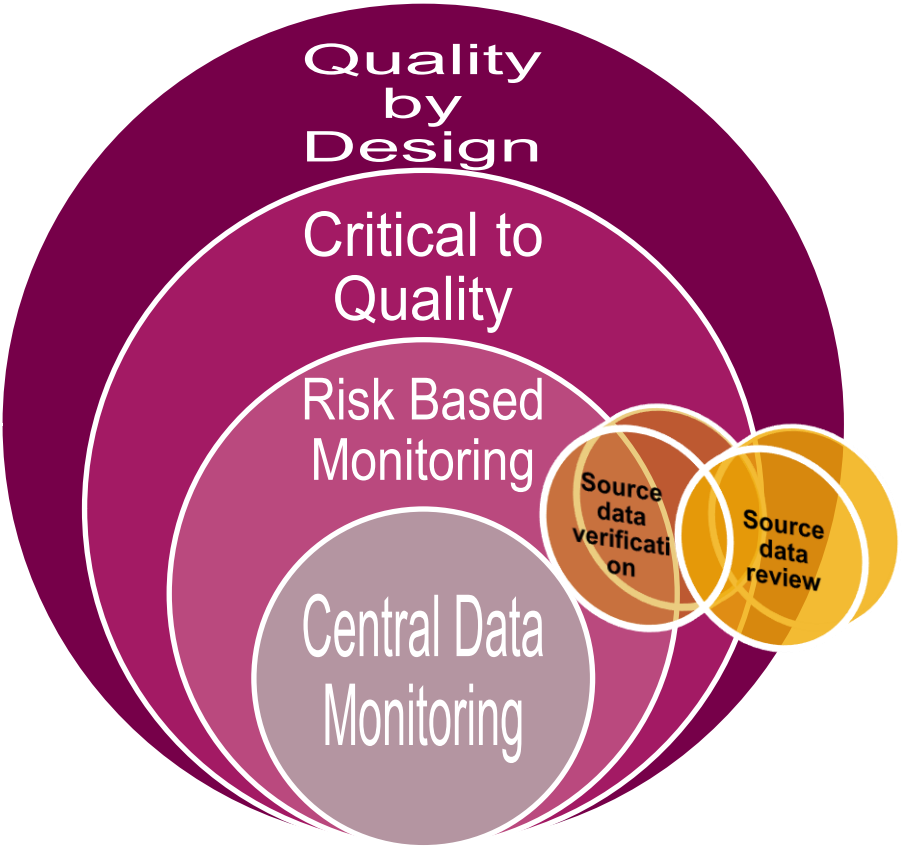
**Alina Pszczółkowska**
*Regional Director Site Management & Monitoring EMEA*
*Global Medicines Development, AstraZeneca*

20.05.2014

AstraZeneca

# Risk–based monitoring and its elements vs. QbD

## How they relate one to another?




- QbD - Methodical approach to ensure the output of a product or process delivers satisfaction to its customers on their most important factors (Critical-to-Quality) is applied and mandated by FDA in pharmaceutical development.

- Defining CtQ factors is a step in QbD approach and also a prerequisite for Risk Based Monitoring (RBM).

- RBM is directing monitor's focus and activities where they are needed most. Starts with trial risk assessment and definition of what is most important to secure trial's reliability safety and compliance (CTQs)

- Central Data Monitoring is, together with remote and onsite monitoring, an element of RBM and enabling monitoring of risks

- SDV and SDR are on site monitoring activities

# Rationale for RBM

TransCelerate BIOPHARMA INC.
ACCELERATING THE DEVELOPMENT OF NEW MEDICINES

| CTTI | FDA Guidance | EMA Reflections Paper |
|---|---|---|
| Quality by Design<br>• Change approach<br>• No single approach is appropriate<br>•Tailor monitoring approach<br>• Protocol quality impacts monitoring quality | Quality Clinical Trial Data<br>• Assess Risk<br>• Combination of monitoring activities<br>• Tailor Monitoring Plan | Risk Based Quality Management<br>• Plan<br>• Adapt<br>• Build on experience and advances |

**These three documents provide a framework for some of the concepts that are driving the industry to change away from the idea of "one size fits all".**

# Risk-Based Monitoring

## FDA recommendation that formed a base for this concept:

No single approach to monitoring is appropriate or necessary for every clinical trial. FDA recommends that each sponsor design a monitoring plan that is tailored to the specific human subject protection and data integrity risks of the trial. Ordinarily, such a risk-based plan would include a mix of centralized and on-site monitoring practices.

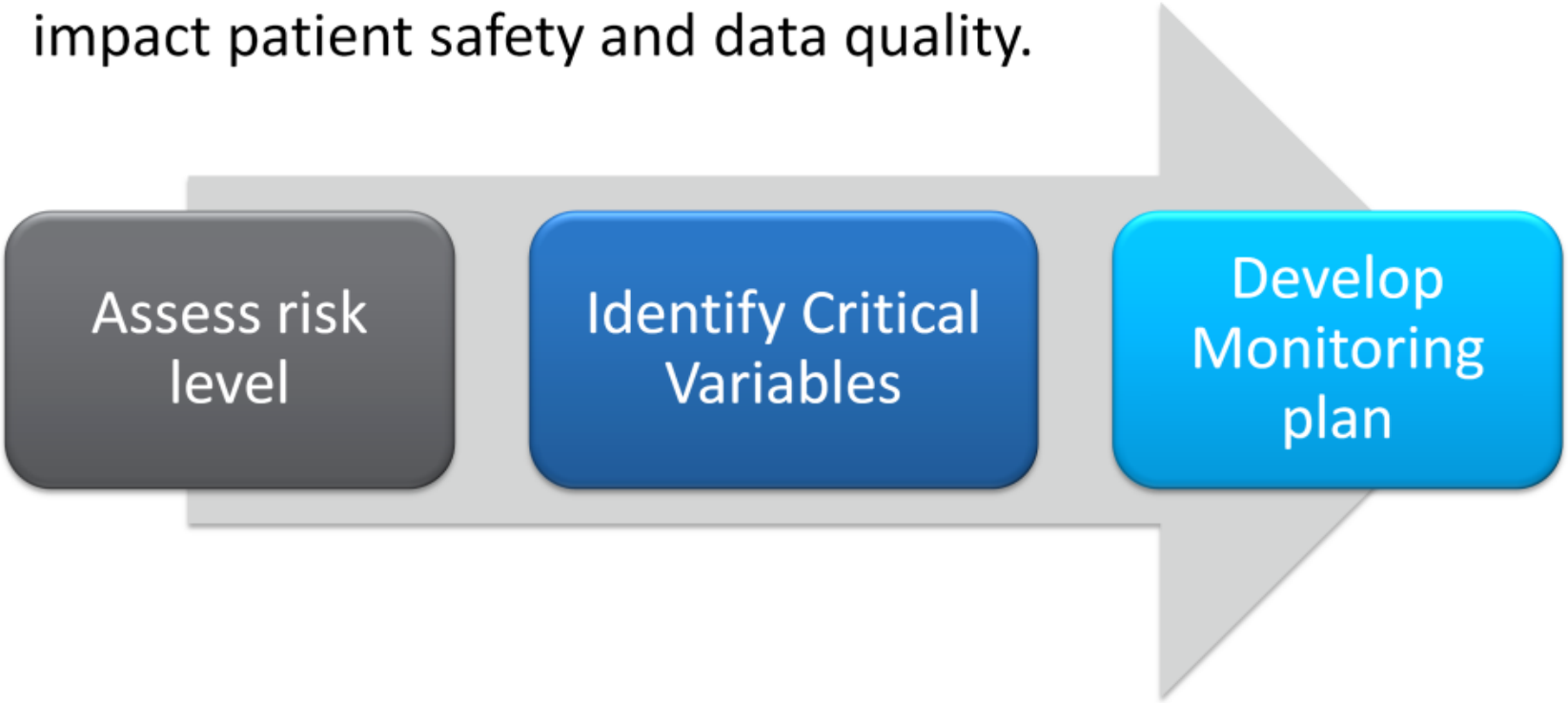
Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring
Final Guidance for Industry. U.S. FDA, August 2013





# Risk-Based Monitoring (RBM)

An adaptive approach to clinical trial monitoring that **directs monitoring focus** and activities to the evolving areas of greatest need which have the most potential to impact patient safety and data quality.

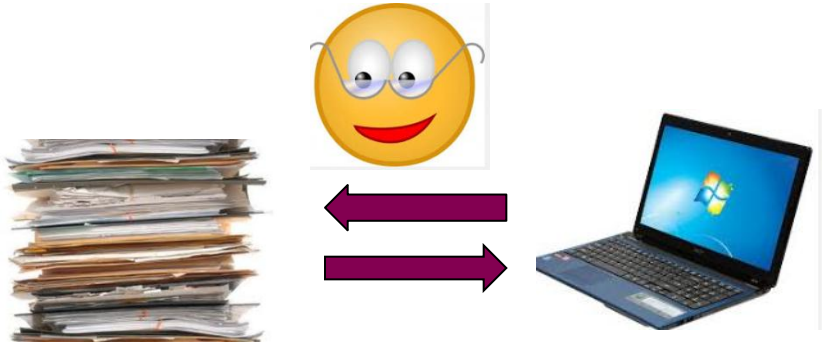


# Risk-Based Monitoring
## Key components of the methodology

- Focus on Critical Processes and Critical Data, identified already at CSP design stage
- Early and ongoing risk assessment
- Use of Risk Indicators and Thresholds
- Optimal “monitoring-mix” – central, remote, on-site
- Central Data Monitoring - early and continuous central oversight of data
- Adjustment of monitoring activities based on the issues and risks identified throughout the study
- Source data review

# SDV versus SDR

## Both are needed, but for various reasons



**Comparison of data between source documents and eCRF**

- Two way check
- Focused on selected data points (critical data)
- Focus on transcription errors or inconsistencies bewteen source & CRF
- Does not require very good knowledge of CSP
- Less likely to identify compliance issues, e.g.data may be the same in source and CRF but violating CSP criteria

**On site review of source documents**

- One way check of source for important areas without looking into CRF
- Reviewing source documents and other records in their entirety – like reading a book that tells the story of the subject's participation in the study
- Reading to assess CTQs e.g.protocol compliance, ICF process, investigator involvement and delegation
- Requires perfect understanding of CSP especially inclusion /exclusion criteria
- More likely to identify compliance issues

# Monitoring: What is the True Value of SDV?

TransCelerate Retrospective Analysis

- 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 was **2.4**%
- The rate of SDV-only discrepancies in Critical Data suggests that SDV has a negligible effect on data quality

**TransCelerate methodology proposes shifting the on-site monitoring focus away from 100% source data verification (SDV) to a risk-driven level of SDV and source data review (SDR)**

# Evolution of monitoring in AZ

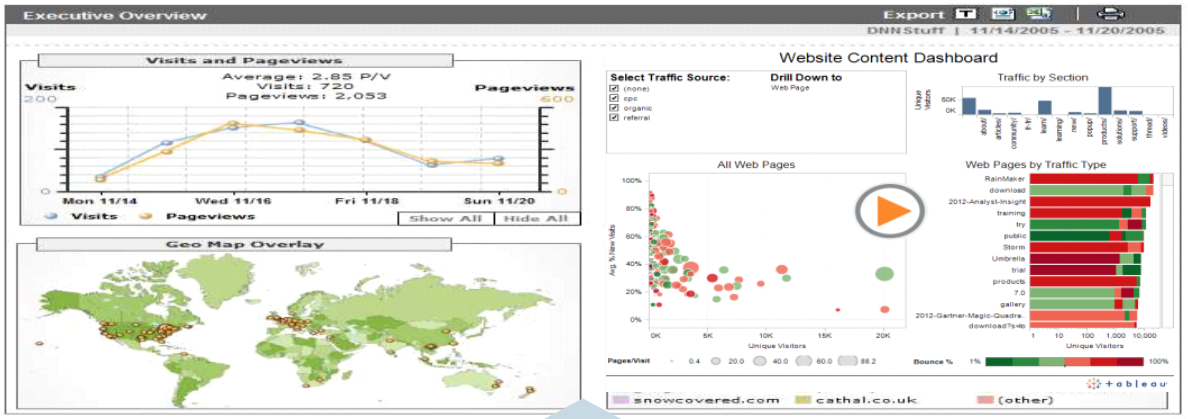
| | Traditional | AZ approach today<br>Targeted Monitoring | Future<br>Risk-based Monitoring |
|---|---|---|---|
| On-site visits frequency | Fixed | Volume and quality driven | Volume and quality driven |
| Study level risk-assessment | No | Yes: study assigned to high/medium or low risk category based on a list of standard criteria | Yes, identification of **CtQs** and detailed risk assessment , plus **ongoing monitoring of risks on study and site level** |
| SDV level | Usually 100% | ~30-100% | ~12-60% |
| Remote monitoring | No | Yes | Yes |
| Source Data Review | Yes, but only as starting point for SDV | Yes, but only as starting point for SDV | Yes, as a key, independent activity |
| Ongoing centralized data monitoring (CDM) | No | No | Yes |
| Assessment of need (trigger) for on-site and remote monitoring | NA | On local level, manual | On central and local level, data driven |

Source: TransCelerate BioPharma RBM group

# Centralised Data Monitoring

TransCelerate BIOPHARMA INC.
ACCELERATING THE DEVELOPMENT OF NEW MEDICINES

**ANALYTICS and visualisation**




**TRIGGERED INTERVENTIONS**

Technology enabling data integration, analytics, and visualization


**DIRECT, DIGITAL DATA CAPTURE**

# Challenges with RBM implementation

# RBM

## Successful transitioning to the RBM methodology requires

– Information to be provided to sites to help them understand and manage change

– Strategies to measure the impact of RBM

– Techniques to ensure efficiency

– Understanding and preparing for potential challenges

# Thank you





# QbD versus RBM in clinical trial process

## QbD approach in planning is base for RBM in execution


Build Quality into the scientific and operational design and conduct of clinical trials

- Focus on what matters
- Critical Data AND Critical Processes that impact on:
  - Patient safety or
  - Data Integrity
  - GCP / Regulatory Compliance

Identify risks at the program, study, and site level in order to employ the appropriate level of monitoring

- Map the risks to appropriate monitoring plans
- Employ mechanisms to monitor important parameters (inclusive of Central monitoring activity)
- Smarter use of Technologies that enable effective oversight
- Targeted on-site interventions

# Transcelerate RBM material

Check the transcelerate page, link below, to find:

- RBM position paper: describing  RBM methodology, terminology, recommended process and tools.
- RBM Update Volume 1
- Extensive, ready to use, RBM training materials including trainer's guide, course participants guide and many useful training modules

- http://www.transceleratebiopharmainc.com/rbm-resources/

# LINKS:

Note:
Links might be outdated soon if updated documents become available.

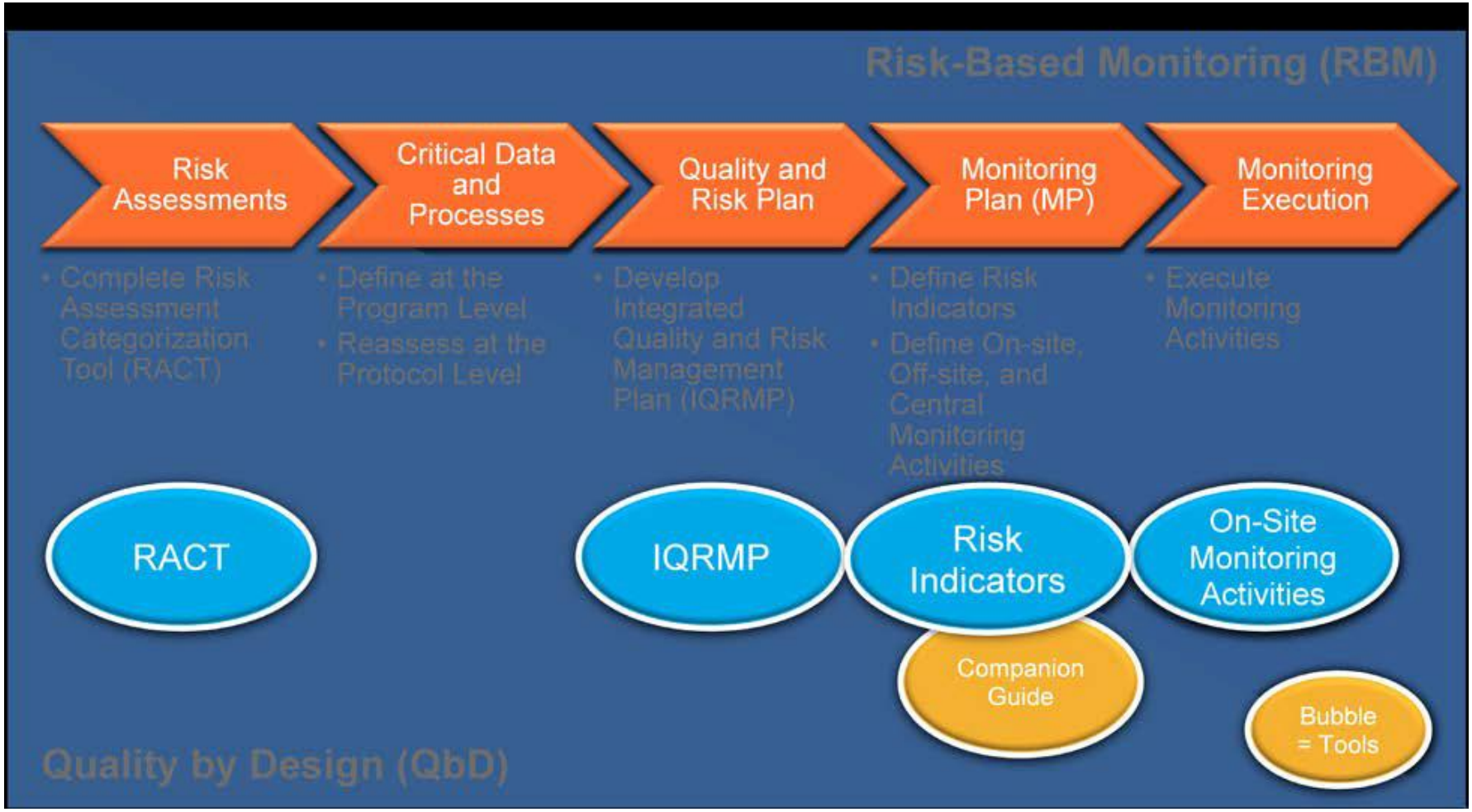
- TransCelerate Home Page
  http://www.transceleratebiopharmainc.org
- FDA Guidance for Industry Oversight of Clinical Investigations - A Risk-Based Approach to Monitoring [Final].
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269919.pdf.
EMA Reflection Paper on Risk Based Quality Management in Clinical Trials (EMA/INS/GCP/394194/2011).
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/08/WC500110059.pdf
Clinical Trials Transformation Initiative. Effective and efficient monitoring as a component of quality.
https://www.ctti-clinicaltrials.org/project-topics/study-quality/effective-and-efficient-monitoring-as-a-component-of-quality

# Risk-based monitoring
# Summary:

## Sponsor/Patients/Investigator

- Focus on important factors
- Early detection of risks
- Misstatements prevention
- Intelligent resorces utilization

# TransCelerate Methodology for Risk-Based Monitoring – High Level Process and Associated Tools



# Risk based monitoring, background External Factors and Influences:

## Direction from Regulators

- 2011-2013 FDA guidance for Industry: Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring.
- *"FDA encourages greater reliance on centralized monitoring practices than has been the case historically, with correspondingly less emphasis on on-site monitoring"*
- 2013 EMA: Reflection paper on risk based quality management in clinical trials

## Industry Focus

- 'TransCelerate' consortium focus on Risk-Based Monitoring, with Centralized Data Monitoring as a key component
- 2013 TransCelerate publish RBM position paper on RBM, setting common standard for terminology and methodology. RBM pilots
- Other companies already have elements of CDM and continue its development to enable fully effective RBM

## Evolution of TransCelerate Methodology for Risk-Based Monitoring