Risk Based Monitoring: A Future State Vision Driven by Analytical Maturity

In 2007, the FDA released “Guidance for Industry Computerized Systems Used in Clinical Investigations” as EMR and eDC usage became more common. The presence of data in electronic format created an obvious opportunity and a few years later, draft guidance was released that included a brief and general idea that technology could complement existing oversight procedures of clinical trials. In 2011, the term “risk-based monitoring” appeared in a draft document called “Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring.”

Since release of these early guidance and draft documents, the industry has heterogeneously pursued various flavors of risk-based monitoring, with some organizations fully embracing the push to evolve while others have chosen to maintain traditional oversight techniques or outsource those capabilities via CROs, FSPs and consultant entities. Early guidance also saw rise to industry specific organizations such as TransCelerate. Founded in 2012, TransCelerate’s current mission statement is to “identify, prioritize, design and facilitate implementation of solutions designed to drive the efficient, effective and high-quality delivery of new medicines.” The organization has sought to drive harmonization of design and execution within the industry, but like early FDA guidance, adoption has been mixed.

The FDA has since released multiple evolving guidance on the topic, and more recently we have seen a significant industry-modernizing shift when a risk-based approach to study execution became formalized in the ICH/GCP E6 R2 guidelines.

Early risk-based models saw a rise in efforts to both improve data review and cleaning as well as reduce high operational costs that were typically associated with 1:1 source data review. Focus was placed on better ways to “monitor” the data as a complement to work performed by clinical research associates. Industry adopters moved to create a competitive advantage through analytics where focus was on improving data quality, using varied degree-of-intelligence methods, but typically standard and ad-hoc reporting, querying, and alerts. Data from the study maintenance phase that needed to be “cleaned,” or suggested protocol compliance or safety concerns was high priority target. Planning period analytics targeting feasibility and site selection efforts eventually became more common as well.

Within this period, it has been exciting to see innovation by some of RBM model industry leaders. Monte Carlo Analysis and other simulation techniques have been applied to complement feasibility and site selection decisions for years. The Infosario platform was an impressive tool designed to leverage visualization, standardize displays, and overcome system silos, developed shortly after the 2011 Risk Based Monitoring guidance document was released. Companies developed centralized data review process to improve review time gaps of critical data. Sophisticated statistical KPIs, that broke the traditional “metric” mold can be found. In one example, when a major pharmaceutical company applied their KPIs to retrospective data, some were found to be predictive. Robust risk-based monitoring policies were being developed to define approaches and create audit ready documentation of findings, decisions, and why decisions were made. Advanced data management and remote monitoring processes using rule-based programming allowed for better data cleaning and identification of safety and protocol deviation issues. The industry saw increased usage of visualization software like Spotfire and Tableau and topics on how to use Python and R to support risk-based monitoring have recently gained attention at industry conferences.

There are many examples and given new evolution with telehealth, wearables, and virtual trials, its

Telehealth, electronic ICFs, wearables, virtual trials, etc

The future state of risk-based monitoring will transcend its existing scope and apply to all phases of trial execution from pre-protocol to close-out. To accomplish this effectively, RBM model design must include efforts to increase analytical maturity within the organization and be driven by a multi-pronged solutions to RBM that include all appropriate levels of business intelligence, technology applications (example: single eTMF platform), process improvement methodologies (ie: lean, six-sigma, agile/scrum), and a pervasive analytic mindset across all human resources operating within the RBM model.

**Analytical Maturity**

*Business intelligence and analytics:*

At a high level, the future state of risk-based monitoring can be viewed as an adaptation of the SAS Institute’s relationship between intelligence and competitive advantage, an often-cited indicator of analytical maturity:

Figure A:

Machine generated alternative text:
Business intelligence and analytics 
8 
Optinization 
Predictive modeling 
Forecasfing/extrapolation 
Statistical analysis 
Alerts 
Qiery/ dom 
Standard 
o 
O 
o 
o 
Whats the best that can happen? 
What WII happen next? 
What if these trends continue? 
WIV is happening? 
What acfions are needed? 
Where exactly is the problem? 
1---bw many, how often, where? 
What happened? 
Analytics 
Access 
and 
reporting 
Degree of intelligence 

However, in an interesting towardsdatascience.com piece, Jason Widjaja, an AI developer with experience in pharma, suggests graphics like this incorrectly imply that prescriptive and predictive analytics are both higher in value and also a sequential output of methods with lower degrees of intelligence. Within an RBM space, Widjaja’s assessment is especially relevant because of the diversity in scope we see across stakeholders and end-user roles within the industry.

Instead, a flattened version of the model is proposed in which competitive advantage is gained by possessing the appropriate capabilities across the varied degree of intelligence spectrum:

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Procedure | Standard Report | Ad hoc Reports | Query / drill down | Alerts | Statistical Analysis | Forecasting / Extrapolation | Predictive Modeling | Optimization |
| Procedure Type | Access and Reporting | | | | Analytics | | | |

Conceptualizing analytical maturity in this manner for an RBM model implies that while the degree of intelligence gained from each procedure varies according to the hierarchy in the SAS graphic, each is still reflected to be a potential necessary contributor within a robust RBM strategy. Also removed is the impression that business intelligence is a linear development method. Instead, an agile mindset can more easily be envisioned: parallel development where value is defined by whether appropriate functionality is delivered to the stakeholders who need it.

*Information as a Strategic Resource:*

Design must include a process to obtain stakeholder feedback so that may be incorporated into product improvement. For example, KPIs are commonplace within the industry. However, often, time is spent developing KPIs and providing these to stakeholders where action is not taken on the finding. RBM leaders need to understand when actions are not taken and a process as simple as requiring a stakeholder to enter what action was taken, and if none, before a KPI can be closed.

It will be applied to multiple phases within a clinical project.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Pre-protocol | Planning | Start-up | Maintenance | Close-out |
| Protocol design | eDC design | Site selection | Retention | Data completion |
| Lessons learned | KPIs | Site training | Monitoring | Vendor data |
| PD planning | Protocol extraction | Recruitment | Control | Lock procedures |
|  |  |  | Protocol compliance | Operational data |
|  |  |  | Safety |  |

Inputs:

Data:

Clinical

Operational

Real world data

Stakeholders:

Capabilities:

Existing procedures

Existing tools (ie: software, platforms)

Personnel

Workflows

Outputs:

Functionality based on user needs

Stakeholders:

Project

Clinical teams

Sponsors

Study participants

Silos: we break down platform or database silos but leave in place functional and capability silos (or unintentionally create new ones)

Clustering risk, probability of events occurring (at a site, for a subject, in a country, etc), KRIs (predictive, not simply metrics)

Discuss resampling techniques ie: bootstrap to complement or reduce reliance on sample distributions which require a lot of work to aggregate data across disparate study databases.

RBM considered during EDC design

Analytical Maturity: analytics cannot be limited to a small group within an organization: must be pervasive

Are there differences in study phase, TA, target countries that would benefit from having a tailored analytic approach (set of tools and processes) to better support those studies

If you think you’re ever going to get to a steady state, think again!

References:

1: ‘Guidance for Industry Computerized Systems Used in Clinical Investigations’, <https://www.fda.gov/files/drugs/published/Guidance-for-Industry--Computerized-Systems-Used-in-Clinical-Investigations.pdf>

2: Widjaja, Jason 28 Jan 2020, ‘How analytics maturity models are stunting data science teams’, <https://towardsdatascience.com/how-analytics-maturity-models-are-stunting-data-science-teams-962e3c62d749>