Paper AR05

What does Risk Based Monitoring mean for Data Management?

Swapna Pothula, ICON Clinical Research, Netherlands

ABSTRACT

Following the FDA and EMA guidance, and the requirement to be compliant with ICH-GCP E6(R2), implementation of Risk Based Monitoring has become a norm today. While the idea of RBM is to have a customized monitoring plan for each trial, how, when and where Data Management comes into play is something that has not been discussed much.

In practice, creation and implementation of a RBM plan requires input from various roles and departments to help identify critical data and critical processes. Being part of this process allows DM to understand data that matters and focus on 'absence of errors that matter'; leading to improved data cleaning, querying and validation processes resulting in cost and time efficiencies.

In this paper, we will discuss the role of DM while implementing RBM; the challenges faced and the best practices to achieve analytic ready quality data, that enables timely decision-making leading to overall patient safety.

INTRODUCTION

Risk Based Monitoring has been used as a standard for clinical trials in the recent past. The basic concept of RBM is to focus on the data and processes that are critical to ensure data quality and ensure patient safety. Once critical data and processes are identified, the risks associated with these data and processes are assessed and categorized to define a strategy to enable detection of these risks and act on them when needed.

There are quite a lot of diverse tools, methodologies, practices and services available in the market today that can be used to implement RBM. While technology is the key to implementation of the RBM, what makes it a success is the holistic team approach where monitors, data managers, statisticians and medical reviewers are all part of the risk assessment and mitigation process.

It has been proven that RBM implementation improves data quality and at the same time reduces the overall monitoring costs. But, what does RBM mean to Data Management? Can Data Management benefit from RBM?

ROLE OF DATA MANAGEMENT

Data management is an important stake holder in the holistic team approach to RBM implementation process. Being part of the RBM implementation in the capacity of a Data Manager makes one wonder if Data Management can benefit from RBM.

While we are all aware of the improved data quality benefit with RBM, can Data Management benefit in other ways from this RBM process? Well yes, If Data Management emphasize and prioritize some of the data management activities around the critical data and processes identified as part of the RBM, Data Management can benefit in terms of cost and time.

DATA MANAGEMENT ACTIVITIES IN SCOPE

RBM implementation requires a customized plan for each study based on the specificity of the study design, processes and data that matter. Certain sets of data management activities/deliverables remain unchanged, as these are independent of the RBM implementation. Examples of such deliverables/activities are: Data Management Plans, CRF development, Database set and SDTM mappings, Database freeze/lock/archival etc.

There is another set of data management activities/deliverables that can be fine-tuned to benefit from the RBM implementation. Examples of such deliverables/activities are: CRF design, Data Review/Validation Plan (Edit Checks, Offline Checks and Listings), Data Cleaning, Data Querying and Reconciliation of external data.

CRF DESIGN

Data points which require Source Data Verification (SDV) are identified during the CRF design process. Earlier all the data points on the CRF were specified to be SDV'd (Source Data Verified). However, having identified the critical data points and process as part of the RBM implementation plan changes the SDV requirement and specification thereof. The process is simple and straight forward. Each of the identified critical data points and the data points that correspond to a critical process (when part on the CRF) must be SDV'd.

Below are two examples of critical processes identified during RBM implementation (Fig.1).
ICF (Informed Consent Form) completion Process: ICF is a critical process as it is part of GCP (Good Clinical Practice) compliance. The Central and Local monitoring methods have been defined (specific to sponsor/CRO), the data point that is part of the ICF process in this case, the ICF date will be SDV'd

Eligibility Criteria: Eligibility is again a critical process as it falls under GCP compliance. The corresponding data points for this process are the Date of birth (Demography screen) and Eligibility Check form (Inclusion/Exclusion screen) and will therefore be SDV'd.

Another important document that can be helpful in identifying the critical data points is the Clinical Trial Protocol. All the Primary, Secondary and Tertiary end points which are part of the analysis could be candidates for SDV.

Focus should be on capturing data that matters. For example, it is OK to not capture data that will not be part of analysis. For Example, all the assessments that are part of the eligibility criteria and will not be used as baseline assessment during analysis, need not be captured. If an ECG assessment is done as part of eligibility criteria, at VISIT 1(pre-dose), and later at VISIT2 and so on, and if the VISIT 1, PRE-DOSE assessment will be the baseline assessment, it is OK to not capture the ECG assessment results from the SCREENING VISIT.

If the ECG at SCREENING showed abnormal results, the subject would be a screening failure and not all screening failure data needs to be collected and cleaned. Decisions about not capturing data must be made at a study level based on what matters the most to the study team while keeping in mind the primary objective of the study.

Decisions as such are made dependent on the study design and in agreement with all the study stake holders.

ID number	Critical data & processes		Risk ID (if applicable)	Key Risk Indicator(s) used for risk detection (if applicable)	RBM strategy		
					CENTRAL MONITORING	LOCAL MONITORING	
	List the Critical data and Critical processes	Provide Rationale				SDV Critical data to be verified	SDR Clarify what needs to be reviewed
1	ICF	GCP compliance	NA	NA	Trial Monitoring report PD report, Standard listing	Inform consent screen: Informed consent date	Ensure original signed and dated ICF is present for each subject & correct version is used. Ensure evidence of consenting process (in compliance with ICH-GCP and relevant SOPs)
2	Eligibility Criteria	GCP compliance	NA	NA	PD report Standard Listing	Demography screen: Date of birth Eligibility check form: Inclusion and exclusion criteria	Review source to ensure protocol compliance with inclusion/ exclusion criteria Ensure PI review of screening sample lab reports and review of the lab values

Fig.1

DATA REVIEW / VALIDATION PLAN

After the SDV items have been identified during the CRF design, the data review / validation plan can be built around the SDV items. Many CRF pages are standard and therefore come with their own set of standard edit checks, offline

checks and listings. The standard edit checks, offline checks and listings can be copied as is from the standard library to the study as these do not require any programming and validation overheads.

However, when building the data review / validation plan for the study specific pages, the critical data points and processes identified during the RBM process can be used as a guideline. Study specific Edit checks, Offline Checks and Listings should be considered for all the SDV'd items on the CRF.

During the CRF design the focus was on SDV and capturing the data that matters. During the data review / validation the focus will be on the review of the data that matters in the scope of the study. The CRF design step brings critical data in focus, which can be used during the data review step to develop the data review plan

Again, the decision to have an offline check programmed versus a listing programmed should be made at study level based on parameters such as subject size, number of sites etc. If the study subject size is not big (less than 100), programming of listings should be considered instead of programming offline checks. Offline checks programming tends to have large overheads in comparison to programming of listings. Use of Manual Checks could be considered when the subject size is small (less than 60), followed by a QC depending upon the company policies and sponsor needs.

Focusing on critical data and processes leads to a leaner data review / validation plan with reduced overheads. Reduced overheads imply quicker turnaround times making instream cleaning from First Subject First Visit (FSFV) possible. This means, critical data issues can be identified from FSFV onwards.

DATA CLEANING AND DATA QUERYING

It has been a common practice to clean all the data that is collected. But, does it make sense to clean data that will not be part of the analysis? This is a question that needs to be answered before the cleaning activities start. This question can be addressed during the CRF design. Should we collect the data that will not be part of the analysis? Having these questions addressed helps us target the cleaning activities towards data that matters.

Data Cleaning and Query resolution plan should be set up to identify data that matters at different milestones (Interim Analysis, Safety review meetings, Database Freeze/Lock) to have these data cleaned and the corresponding queries resolved in time.

Data reviewers should be trained to issue queries that matter, queries should not be issued without thinking. There must be a thought process and strong rationale behind it. The team should discuss and agree on the Data Cleaning and Querying strategy in the scope of the study and within the context of a study milestone.

RECONCILIATION OF EXTERNAL DATA

External data can be varied: Lab, eDiaries, ECGs, drug accountability, randomization etc. This data could be provided by multiple sources. For ex: Lab data can be provided by multiple labs based on the type of tests performed. External data reconciliation plan and approach should be fine-tuned around the critical data and processes identified during the RBM implementation.
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5	Blood sampling process for hematology and biochemistry	Primary Objective: safety	6	NA	PD report Trial Monotoring report Reconciliation listings to flag issues Standard listing	Blood sampling screen: All fields	Samples has been taken according to study procedures. Sample labelling is done as described in SPM. Samples has been taken at the correct timepoint Safety samples are shipped daily

Fig.2

Above is an example of safety lab data (Fig.2), a primary endpoint and therefore identified as a critical data point during the RBM implementation. As part of the RBM implementation these data will be SDV'd and standard listings run to clean and reconcile safety data as and when data is transferred.

But then, what would you do with other type of external data or source of external data that is not critical? For example, the blood samples collected for future research and routed to labs for storage. The reconciliation plan in such cases, which involve non-critical data, should be specific to type and source of data. Not all external data should be reconciled in the same way, resources should be spared when not needed.

CHALLENGES

Challenges remain, what should be the approach towards the data that has not been identified as critical (Non-Critical) but collected? Non-critical data needs to be cleaned but how should we invest in terms of time and resources is something that needs to be discussed and agreed upon. Sample size permitting, would manual cleaning suffice to address the cleaning of non-critical data? Something that needs to be discussed and agreed upon between the sponsor and CRO.

It has been a general practice to have all the items on the CRF SDV'd. This must change. It might seem like we are doing less and it makes one wonder how doing less can lead to high-quality. It takes time to change processes and convince people that focusing on what is important can indeed lead to quality and save time and resources.

BEST PRACTICES

Team work is the key, we should aim to achieve seamless integration of processes and people.

Different stake holders within a clinical study tend to work in silos. RBM attempts to be break these silos and if data management is to benefit from the RBM approach, continuous conscious efforts should be made to bring together all stake holders and work closely not just until the RBM strategy is developed but, till the very end of the study.

Each study is different, requiring different strategies for capture and cleaning of data. A customized approach towards review of critical data and processes and non-critical data should be created to enable access to quality data at various study milestones, with the end goal being able to make decisions in the best interest of the patient safety.

The Sponsor and CRO should share the same mindset and vision of the 'Data that Matters' and have a clear agreement on the approach to data capture, handling and cleaning. A lot of standard processes change when we focus on the data that matters, It is strongly recommended to have a well-documented agreement on the approach specific to each of the study and have this approved by all the stake holders with Sponsor and CRO organizations.

CONCLUSION

Each study is different and needs a different approach to improve data quality while being compliant and not compromising patient quality. While RBM focuses on data that matters, Data Management should focus on the absence of errors that matter. Having this shift in the mindset enables us to target and prioritize resources towards data that matters leading to high quality data and economic efficiencies.

We need to think before we act and not just follow processes because that was how it has been done all these years. It might seem like we are doing less, but, it is not the case. We are doing it differently. We are focusing on what matters. This mindset shift is should drive our actions.

With a shift in mindset, the right strategy and good team collaboration, Data Management can achieve high-quality databases while being efficient with time and resources.

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CONTACT INFORMATION

Your comments and questions are valued and encouraged.
Contact the author at:
Swapna Pothula
Icon plc Clinical Research
Boeing Avenue 62-68
1119 PE
Schiphol-Rijk
Netherlands
Email: swapna.pothula@iconplc.com