White Paper

Risk-Based Monitoring and the Clinical Trial Management System

OnTheMove

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SUMMARY

- The original promise of Risk-Based Monitoring (RBM) was to reduce trial costs / improve trial quality.

  This was to be achieved by deciding in advance what types of problem might occur in a particular trial. Monitoring activity would then be focused on looking for instances of the problem types with the most severe consequences or that were expected to happen frequently. Simultaneously, less time would be spent on some traditional monitoring activities that in practice are proven to uncover few issues.

- Virtually every major trial sponsor has an RBM project. To date, these projects have invested in developing Risk Registers, Key Risk Indicators (KRIs) and centralized monitoring processes.

- However, to varying extents, these initiatives are all standalone from pre-existing core monitoring processes and systems. In particular, the amount and type of on-site monitoring activity is typically not being driven by the data generated from RBM.

  In other words, organizations have not yet truly embraced an RBM approach and, as a result, the promised benefits of reduced costs / improved quality are not being realized.

- In order to achieve these benefits, it will be necessary to change existing monitoring processes. In particular, the role of the Clinical Trial Management System (CTMS) needs to change from one that primarily is about capturing the results of monitoring activities to one that supports Trial Managers actively flexing the monitoring plan as issues arise.

  This whitepaper identifies the key process modifications and system capabilities required to support a true RBM deployment.

- OnTheMove Clinical is a suite of products that enable full RBM adoption without requiring organizations to completely replace their existing CTMS systems and processes. OnTheMove Clinical reduces the time, cost and risks of implementing RBM.

BACKGROUND

Risk-Based Monitoring (RBM) of Clinical Trials has for many years now been seen as having the potential to increase the value obtained from every dollar spent in the trial monitoring process.

In the largest pharmaceutical and biotechnology companies, this gain tends to be seen as a way of reducing the cost of a trial (same trial quality, less cost). In smaller organizations, the thinking is more typically that RBM should be used as a way of improving the quality of a trial without spending more money (better trial quality, same cost).

In either case, the thinking is the same:

- For each protocol, identify the problems that are most likely to occur in executing that protocol (the risks) and document them in one place, or "Risk Register". Risks could relate to the safety or efficacy of the trial substance or factors relating to the running of the trial. For example, the ability to recruit enough subjects.

- Focus monitoring activity on these risks. By using the generic term "monitoring", we mean both centralized monitoring and on-site monitoring. RBM, in and of itself, does not mandate the adoption of centralized monitoring. As an aside, what it does say is that organizations should adopt the most appropriate form of monitoring to manage a particular risk, which might be a centralized approach, might be an on-site approach, or might be a combination of the two.

- Simultaneously, reduce the amount of time spent on existing but low value monitoring activities that do not relate to risks on the register or only relate to risks where issues would have a low impact or be unlikely to occur.

  An important example of a low value monitoring activity, because it is often a significant driver of Clinical Research Associate (CRA) time and therefore monitoring cost, is Source Document Validation (SDV). We discuss this in more detail later.

- Based on issues found, modify the Risk Register and monitoring plan, both for the current protocol and for future protocols. In other words, RBM should be a dynamic, learning process.

DELIVERY TO DATE

Whatever an organization's standpoint on the target outcome, virtually everyone in the clinical trials industry has an RBM project and has been making substantial investments in processes and technology. To date, these investments have mainly fallen in two areas.

Risk Register Creation

Typically this has required aligning the thinking of different groups in the organization and defining a process, often using the Transcelerate Risk Assessment and Categorization Tool (the Transcelerate RACT) as a guide, that allows a meaningful set of risks for a specific protocol to be identified in a consistent and timely manner. IT expenditure is normally low although organizational effort is high.

Centralized Monitoring

We would contend that, strictly speaking, centralized monitoring is not part of RBM. However, a move from on-site to centralized monitoring does have the same underlying objective of improving the cost-effectiveness of trial monitoring activities. Furthermore because, quite correctly, an RBM approach has typically been used to inform the implementation of centralized monitoring, the two projects have a strong inter-relationship.

The core notion of centralized monitoring is that by analyzing various data collected in the trial process, issues or potential issues can be spotted without a CRA visiting a site.

The relationship to RBM is strengthened because by defining Key Risk Indicators (KRIs), i.e. numerical thresholds where breaching the threshold implies issues related to a particular risk might be occurring, it is possible to make a central monitoring review a structured process driven by the Risk Register.

In contrast to the small amount of IT investment involved in the creation of Risk Registers, centralized monitoring has normally required a heavy investment in data integration and analysis tools to allow monitors to analyze whether KRIs have been breached and, just as importantly, the trend in the KRI score over time.

THE CURRENT CHALLENGE

All of this investment has either been necessary as preparatory activity and / or of value in its own right, but it doesn't actually address the fundamental promise of RBM to refocus the complete monitoring process.

Although some would deny this, we believe to date RBM has been seen as separate to, rather than fundamentally changing, existing processes. In particular, site visits normally happen with the same cadence and with unchanged content.

Potential issues uncovered in centralized monitoring are often logged in separate systems and managed through separate workflows to issues raised elsewhere. There is rarely a holistic view of all risks and issues at protocol, region and site levels to inform where attention should be focused. Often issues raised in centralized monitoring do not seamlessly flow through to CRAs preparing for visits. Effectively, there is often a significant disconnect with two independent teams monitoring each site and only limited interaction between the two.

Site visits still normally follow a "one size fits all" structure. In particular, there is often a culture of 100% SDV, i.e. verifying that all data has been correctly entered into the Electronic Data Capture (EDC) system. This is despite the fact that it is widely recognized that SDV is a time consuming, and therefore expensive, task that normally raises few significant issues. An RBM mindset would suggest de-emphasizing a low value activity.

Finally, the lack of holistic view of issues raised in centralized and on-site monitoring, and elsewhere, makes it very difficult to "close the RBM loop", refining the risk register and adjusting future monitoring plans as a trial evolves.

PROCESS AND SYSTEM CHANGES TO FULLY IMPLEMENT RBM

Figure 1: The Full RBM Cycle

So, given the desired outcome is clear, what needs to change to achieve it? Clearly, this will vary based on an organization's existing systems, but we believe that in a complete implementation of RBM, organizations need to deliver the following capabilities.

- A central structured repository for the Risk Register and KRIs so that the risks can be linked to other entities; in particular, issues. Whilst a shared spreadsheet may well be a suitable, low cost method of documenting risks at the start of a trial, it is not adequate when those risks need to be exposed through multiple core processes.

- A defined repeatable process by which Central Monitors can execute a structured review of a site, or higher level entity such as a region or protocol, and raise issues.

- A single view of all issues relating to a protocol accessible to all interested parties including Trial Managers, Central Monitors and CRAs. In an ideal world, all issues would be stored in a single location. However, many organizations have multiple validated issue management systems with complex integration to other systems. Consequently, replacing these might be difficult. A good, more quickly achievable second best, is to have the capability to view issues stored in multiple systems through a common portal.

  The single view means that Central Monitors can ask additional questions of the data that might not have occurred to them if a CRA had not spotted something on site, a Trial Manager can prioritize and de-prioritize monitoring activity based on what is happening at particular sites, or a CRA easily follow up on something spotted by a Central Monitor before it has become a serious problem.

- In a more advanced state, the capability to group issues (at a site, across multiple sites for a protocol or even across protocols). Groups should have their own resolution and escalation lifecycle. Issues should be able to belong to more than one group.

- The capability for Trial Managers to dynamically maintain a monitoring schedule (both centralized and on-site) and to define the activities to be performed in a particular monitoring event. For example, if a site is performing well, it may still be appropriate to visit them but do so less frequently or with an abbreviated checklist of items to review.

- A particular but key aspect of defining the activities to be performed is the ability to define what SDV and higher value, Source Document Review (SDR), should be performed. It should be possible to:
  - Specify thresholds (e.g. 10% of subject visits are to subjected to SDV and 25% to SDR) and then have the system randomly allocate which subject visits will be used to achieve that level;
  - Increase that level, potentially to 100%, for a particular subject or for a particular visit or for a particular review type (e.g. concomitant medications), perhaps in response to a group of issues arising.

- Guiding Central Monitors / CRAs through the pre-defined activities for a monitoring event, but also allow them to use their initiative to act on potential problems outside of the pre-defined monitoring event scope. When issues are raised, Central Monitors / CRAs need the ability to link them back to risks on the Protocol Risk Register and add them to groups.

- A feedback loop, probably predominantly manual / ad-hoc activity, informed by the single issue management view allows managers to determine whether issues raised in the course of a trial might: i) have a wider impact; ii) require a change to the Protocol Risk Register (which of course ought to be dynamic); iii) require a change to the overall monitoring plan, or; iv) trigger visits to other sites or new centralized monitoring activity to verify the problem is not wider than currently reported.

ABOUT ONTHEMOVE CLINICAL

OnTheMove Clinical is comprised of a number of modules that: i) support implementing RBM through the complete monitoring process, and; ii) simplify CTMSs for users. It can be implemented standalone or as a layer over the top of your existing CTMS (so all your existing integrations to other systems are unchanged). We have particular specialisms in Veeva CTMS and Oracle Siebel.

OnTheMove Clinical Issue Management

- Protocol and site level views of issues
    - All issue types and issue sources shown in single integrated view
    - Multiple source systems supported with no data duplication and no need to change existing systems
- Risk register to issue mapping
- Issue grouping: Related issues within a site & Thematic grouping across sites
- Flexible issue and issue group resolution and escalation processes
- Works in conjunction with existing issue management systems
- Closes the RBM loop

OnTheMove Clinical Monitoring

- Extremely simple and productive workflow for CRAs to complete visit reports and Central Monitors to complete central monitoring reports
- Prompts users to only perform activities and SDV / SDR requested by Trial Managers in the Visit Planning Workbench
- Optional disconnected mode means that CRAs can continue to work on reports when on sites with no connection back to corporate systems, or whilst travelling
- Improves user productivity
- Works in conjunction with existing CTMS

Find out more at www.onthemovesw.com/onthemove-clinical.

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