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Defining a Central Monitoring Capability: Sharing the Experience of TransCelerate BioPharma's Approach, Part 1

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Abstract

Central monitoring, on-site monitoring, and off-site monitoring provide an integrated approach to clinical trial quality management. TransCelerate distinguishes central monitoring from other types of central data review activities and puts it in the context of an overall monitoring strategy. Any organization seeking to implement central monitoring will need people with the right skills, technology options that support a holistic review of study-related information, and adaptable processes. There are different approaches actively being used to implement central monitoring. This article provides a description of how companies are deploying central monitoring, as well as samples of the workflows that illustrate how some have implemented it. The desired outcomes include earlier, more predictive detection of quality issues. This paper describes the initial implementation steps designed to learn what organizational capabilities are necessary.

Keywords

risk-based monitoring, TransCelerate BioPharma, central monitoring, capabilities, implementation

Introduction

TransCelerate has set out to develop an alternative monitoring paradigm that will enable sponsors to move away from a monitoring model heavily focused on source data verification to a risk-based model that uses a combination of central, off-site, and on-site monitoring activities.[1] The appropriate balance of these 3 activities depends on several factors, such as the trial risks and the ability to identify those risks centrally. Critical enablers of effective implementation of risk-based monitoring (RBM) include the identification of critical data and critical processes; the identification of the risks within a study; and the assessment of the potential impact of the identified risks on subject rights and safety, data integrity, and good clinical practice compliance.[2] These planning steps start prior to the finalization of the protocol and continue with integrated monitoring strategies matched to the needs of the study.

Central monitoring as defined by the FDA is a "remote evaluation carried out by sponsor personnel or representatives (eg, Data Manager, Statistician, or Monitor)."[3] A remote evaluation can be accomplished in a number of ways. TransCelerate recognizes that central monitoring is a single component of a

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Table 1. Application of different types of monitoring.

Type of Monitoring	Focus	Typical Role Type	Primary Method
Site monitoring	• Protocol adherence • Process monitoring • GCP	Clinical research associate	In-person and remote interaction with the site
Central Monitoring	• Holistic review at Program, Protocol, Country and Site level that identifies issues and emerging risks more proactively • Trends • Outliers	Central role or roles with access to all clinical results data and operational data	Central review of all data for a trial (ideally including both clinical data and operational data) to find outliers and trends and poor-performing sites. Uses analytics/ visualizations to evaluate risk indicators/thresholds and triggers relevant activities.
Data management review	• Erroneous data • Illogical entries • Missing data • Query management	Data manager Data validator	Edit checks plus targeted, programmed reports
Medical review	• Consistency of data from a medical perspective (ie, is this compatible with medical science/practice) • Coding logic/consistency	Study physician	Targeted review of specific data, including safety and efficacy data, (listings/reports) using medical knowledge
Safety monitoring	• Patient/subject safety risks during participation in clinical trial	Safety physician	Targeted review of safety data (listings/reports) using medical knowledge
Statistical review	• Completeness of the data that may impact the validity and interpretability of the planned analyses	Statistician Statistical analyst	Programming of analyses for the study to find problematic/illogical data

monitoring strategy intended to identify and act on issues proactively.[1] Furthermore, resourcing for central monitoring activities can span from distribution of activities among existing roles to creation of a new central monitor role. With this understanding, TransCelerate is exploring the capability and sustainability of various central monitoring operational models. The intention of this paper is to provide an early look into those capability and organizational needs.

Many companies may have implemented aspects of monitoring that include a remote review of data (eg, safety physicians or medical monitors review safety data). Application of the RBM methodology as outlined by TransCelerate refocuses monitoring efforts to the identified risk indicators (RIs) and suggests a more integrated approach that distinguishes central monitoring as a new and unique activity. This strategy uses data analytics and visualization of integrated data from multiple sources to identify outliers, data trends, and potential site performance issues. The primary focus is the prediction and prevention of issues. It is important to note that the latest analytic tools alone cannot be effective without the proper planning outlined above. Experience with the various ways in which companies choose to implement central monitoring will inform a follow-up publication in which key lessons of the needed organizational and technical capabilities will be shared.

Methodology

When central monitoring is implemented, two key considerations have been identified: identification of what will be included in central monitoring activities (Table 1) and a description of the general prerequisites to be implemented for people, processes, and technology. This article describes what several TransCelerate member companies are implementing from an organizational perspective for the unique role of a central monitor.

The ability to provide a conclusion on the requirements for key capabilities will evolve over time as more experience is

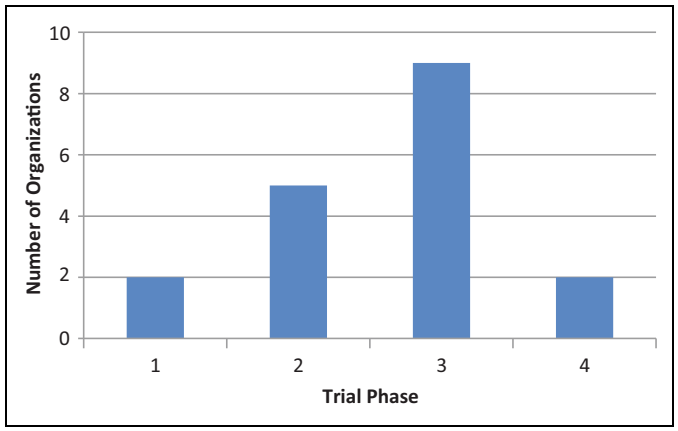

Figure 1. Organizational implementation of central monitoring by trial phase.

gained. It is assumed that all companies have site monitoring, data management, medical review, safety review, and statistical capabilities already in place. One of the biggest challenges of the TransCelerate methodology is defining the ideal structure of the central monitoring component.

In general, as molecules move into later phases of development, it is reasonable to expect an increasing trend to incorporate central monitoring into the set of monitoring tactics. This is evidenced in Figure 1, which provides an overview of central monitoring application to existing TransCelerate pilots, categorized by phase of study. Some companies are testing central monitoring techniques in small population studies, which could be useful in some phase I programs or in studies where there are low or slow enrolling sites. The benefits of the application of central monitoring in early-phase studies are not widely considered to be useful and are not a primary focus of the organizational descriptions in this article.

The organizational implementation of central monitoring can vary. When implemented, central monitoring should be part of an integrated set of capabilities and distinguishable from other types of review, where the goal is to ascertain when to act or conduct an intervention based on outliers and trends (Table 1).

To build an effective central monitoring capability, consideration should be given to the requirements around the people, process, and technology that are needed to be successful. Depending on a company's phase of implementation with respect to RBM, there may be different approaches to address these components. The first step is to decide whether the central monitor role is one that is a dedicated role or whether it reflects a collection of tasks that can be assigned to different roles. The second step involves a decision on whether to internally or externally source the model. Preexisting business practices may influence the manner in which these considerations are managed. Regardless of the model or the sourcing strategy, communication pathways must be clearly laid out.

The capabilities of people or systems that perform the central monitoring tasks are critical to the success of RBM. Failure to put the right people in place can seriously undermine the credibility of the output, as well as materially affect the success of the RBM program. As TransCelerate members have implemented central monitoring, several common competencies have emerged as critical to success:

- Clinical development expertise: comprehension of the protocol and the output from risk identification and assessment
- Critical thinking: define and analyze data from complex, overlapping domains to make well-supported decisions; see the bigger picture and target specific issues of importance for focused debate
- Data management and clinical operations knowledge: this allows for the ability to identify and provide insight into trends or outliers in data
- Communication skills (written and verbal)
- Ability to use the available technologies

From a process perspective, the use of statistical methods[4-6] is essential to identify data anomalies. Digit preferences, for example, can signal potential data integrity concerns. TransCelerate describes a series of RIs that need thresholds and statistical principles applied to make them meaningful and to allow for appropriate follow-up on emerging risks and identifiable issues. As such, the key focus of a central monitor is using data to provide a holistic review that identifies issues and emerging risks proactively. Earlier reviews may allow for the assessment of such elements as timely data entry and early protocol compliance. As more data emerge in a study, the central monitoring review can incorporate more sophisticated methods dependent on a certain volume of data.

TransCelerate recommends use of RIs[1] that could be applicable across multiple therapeutic areas or specific to a protocol or a therapeutic area. Questions regarding use, application, and definition of the RIs will be explored over the next few months as practical experience is gained. The most common questions about the use of RIs to date include the following:

- How are the RIs defined?
- Which RIs offer the most value?
- Are any of the RIs more predictive of serious good clinical practice misconduct issues?
- How reliable are individual RIs?
- How are thresholds applied?
- How often are the RIs assessed?
- Is there an optimal number of RIs to use?
- How does automation play a role in the assessment of RIs?

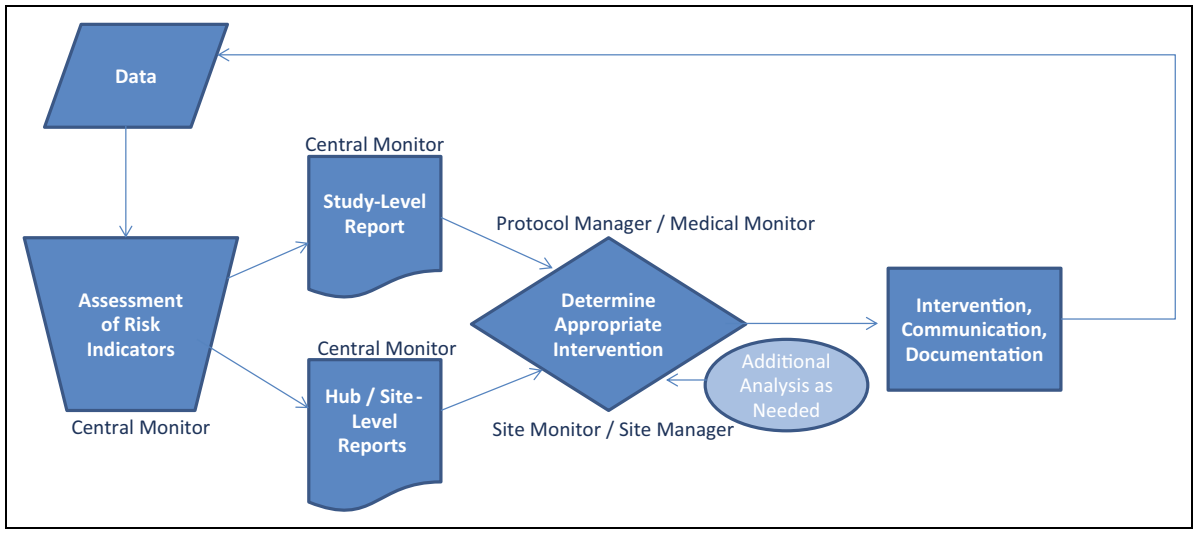

Figure 2. Company A utilization of a dedicated central monitor.

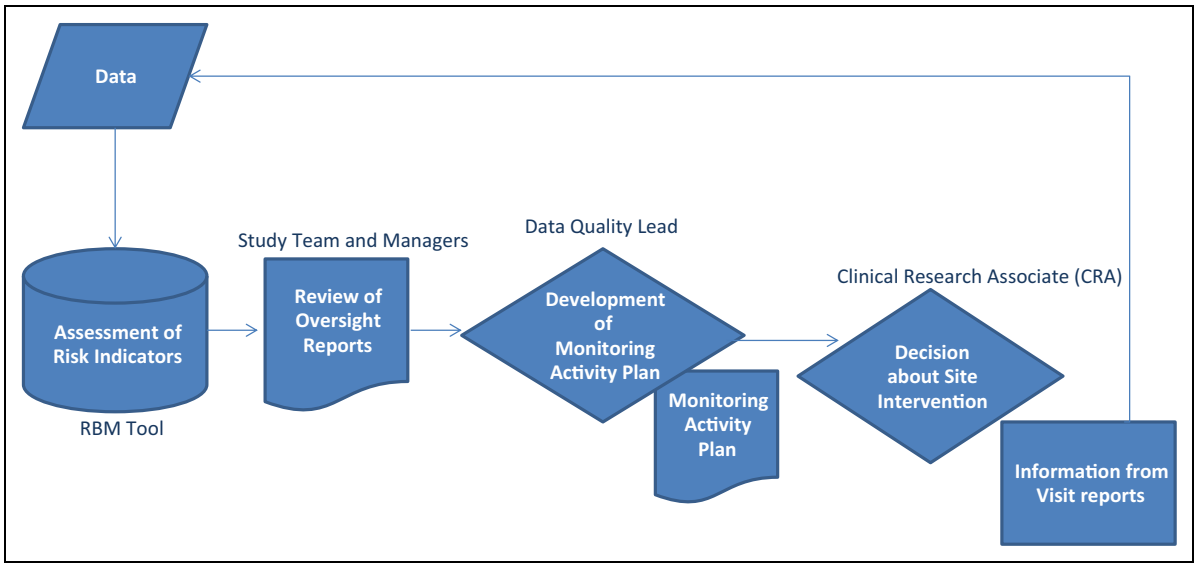

Figure 3. Company B distribution of central monitoring activities.

RIs, like all other measures, have the potential to create noise if there is too much information, while too few may prevent identification of issues that direct appropriate actions and escalations. The follow-up to this paper is expected to provide information that will include recommendations in response to the questions above based on practical experience and implementation. These recommendations will be the collective opinions of the TransCelerate companies that are working with different sourcing partners, different technology capabilities, and different RIs.

Technology is the third area of focus for central monitoring roles. In general, integration of clinical and operational data from disparate sources—for example, electronic data capture and interactive voice response systems—is necessary to enable the activities of central monitoring. The visualization of the data that are created using a robust data warehouse enables effectiveness and decision making. It should be emphasized that the technological solution that supports RBM is only a part of the RBM framework. TransCelerate has created documentation that describes the fundamental technology needs of RBM in more detail.[7]

Results

A few representative samples of work flows that depict central monitoring models have been selected and are displayed in Figures 2 through 5. The common elements that should be

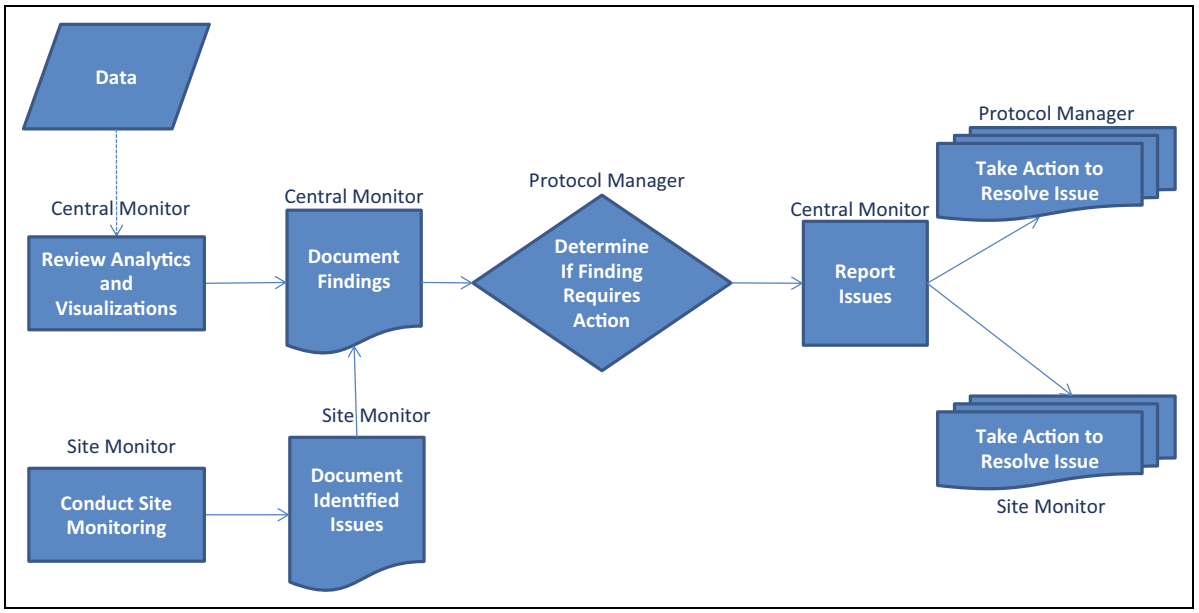

Figure 4. Company C utilization of a dedicated central monitor.

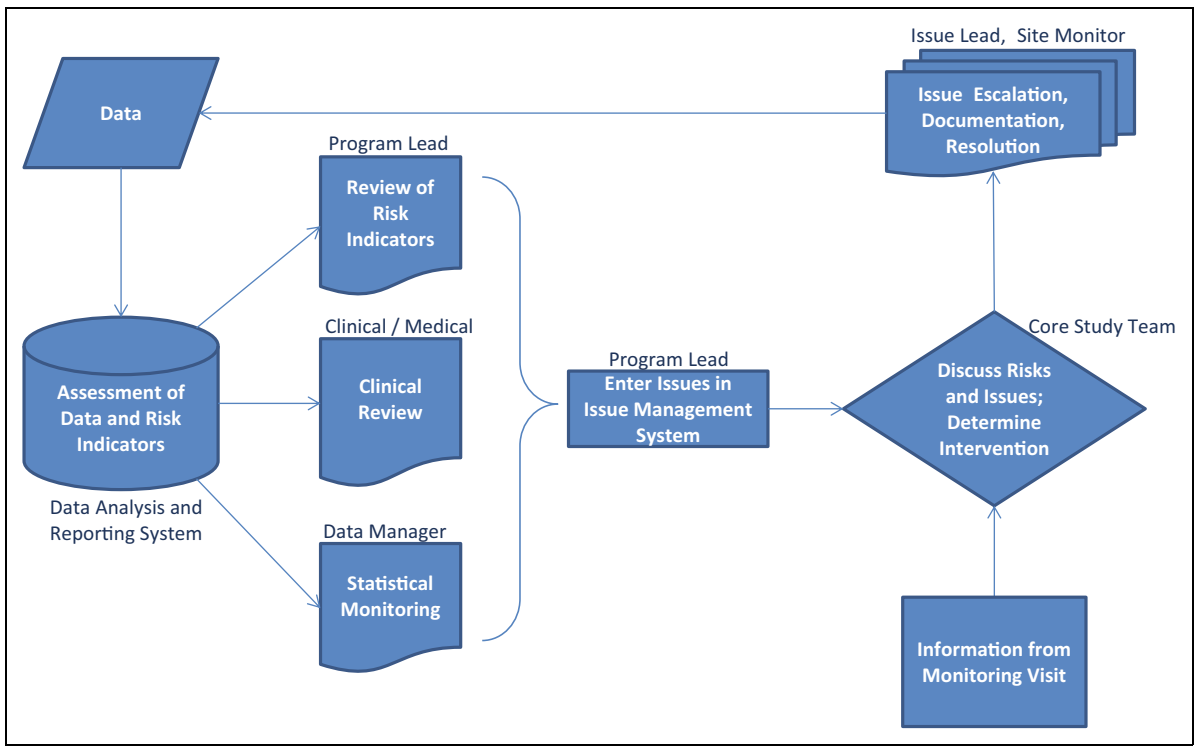

Figure 5. Company D distribution of central monitoring activities.

identifiable in the work flow include the illustration of inputs and outputs for the various models. Inputs include source systems, and outputs include documentation, communication, and escalation paths for risks and issues. A continuous cycle of review is a common element of the methodology, including identification of actual roles within companies.

Discussion

The desired outcomes when applying RBM is improved quality and patient safety, with a more effective and efficient focus of monitoring resources on the critical data. This does not always imply less monitoring but rather a shift to the most appropriate

Table 2. Metrics indicator and definition.

Indicator	Metric Definition
Quality	Average number of major/critical audit findings per audited site
Quality	Percentage per site of unreported, confirmed SAEs as compared to total SAEs as discovered through any method
Quality	Number of significant protocol deviations per site
Efficiency	Average monitoring (all types) cost per site
Efficiency	Average interval between on-site monitoring visits per site
Cycle Time	Average number of days from data entry to initial monitoring (central, off-site or on-site)
Cycle Time	Median number of days from patient visit to eCRF data entry
Cycle Time	Median number of days from query open to close
Cycle Time	Median days from issue open to close

SAE, serious adverse event; eCRF, electronic case report form.

monitoring, with a combination of centralized, off-site, and on-site activities providing the optimal level of oversight based on identified risks. There should be minimal impact on the site regardless of how a company chooses to implement.

This integrated approach makes use of various monitoring methods that expand the scope of monitoring beyond the site and beyond the role of the typical monitor. Use of central monitoring allows more time on-site to be focused on patient safety, data, and processes most critical to the given trial or program. In addition, broader exposure to the aggregated data for functions such as data management, medical, and safety provides greater opportunity to identify performance trends before significant issues arise. This provides the opportunity to leverage the diversity of skills and experience within the study team to detect, predict, and address emerging issues before they become significant.

Success of central monitoring depends on a number of factors. Quantitative measures (Table 2) described by TransCelerate provide an overall view of how well the models work as they relate to RBM success. In addition, qualitative feedback provides insight into the pros and cons of the various models. Additional experience will be gained over time, and the follow-up to this paper will share the different experiences of TransCelerate that will help to inform the capabilities needed to create an effective central monitoring capacity.

Conclusion

Regardless of the model and the status of implementation for central monitoring, confidence is high that the approaches outlined in this article allow for thinking to evolve and for the entire industry ecosystem to benefit. As part of this evolution, TransCelerate continues to be committed to sharing what it learns through its application of the RBM methodology.

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Declaration of Conflicting Interests

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