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How to Improve the Effectiveness of Site Monitoring Practices

# SMART Monitoring: Can new Approaches Make a Difference?

Depending on your role in the organization you may have been confronted with the topic of “Risk-based Monitoring”, “Fit for Purpose Monitoring”, “Targeted Monitoring” or some other permutations of the same basic theme in one context or another. You may be wondering what's all the fuss about or you may even have been tasked with the goal of setting up a new monitoring approach at your organization. In either case, this article has something of interest for you as it is a practical guide which explains how one can successfully improve the effectiveness of one's current site monitoring practices and ultimately the quality of work done at clinical trial sites. The article provides an overview of traditional monitoring practices and a new monitoring initiative in the pharmaceutical industry. Additionally it lays the foundation for a SMART Monitoring approach and provides advice on enabling technology.

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## Traditional Site Monitoring

Site monitoring during a clinical trial has traditionally been conducted in a rather rigid albeit comprehensive manner. The rigidity stems from the “one-size fits all” monitoring approach that has been frequently applied to sites contributing to a clinical trial. For example, a study monitoring plan consisting of visit frequency and a comprehensive visit activity plan once fixed is traditionally not systematically adapted based on events or particular problems that arise in the course of a study. Instead the monitoring plan tends to be strictly followed as it is believed that total quality control will result in better data quality. For site monitoring visits, this quality control activity has been typically dominated by Source Data Verification (SDV). As indicated in the TransCelerate Risk-Based Monitoring Methodology Position Paper [1] the traditional approach and the associated high level of SDV generally does not result in improved quality but nonetheless

retains its high level of cost without the anticipated benefits.

## New Monitoring Initiative

As a result, the pharmaceutical industry has begun to join forces and forged a new alliance under the umbrella of TransCelerate Biopharma Inc. in which a number of new initiatives “focused on the shared goals of increasing quality, patient safety and accelerating development timelines”

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*Simplicity is the ultimate  
sophistication.*

LEONARDO DA VINCI – POLYMATH (1452–1519)

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[2] have been started. In particular, there is an initiative focused on the improvement of site monitoring practices. This is their Risk-based Monitoring initiative that aims to develop a standard framework and approach to Risk-based Monitoring that is pi-

lotted within industry and vetted by regulators.

## SMART Monitoring

The term SMART is an acronym that encapsulates the key success factors which contribute to an effective clinical monitoring strategy. The acronym stands for:

1. Simplicity
2. Metrics
3. Adaptive
4. Risk-based
5. Technology

These factors underlie the SMART Monitoring approach and will be described in turn to illustrate their role in facilitating the overall approach.

However, before we turn to these success factors, let us consider the clinical trial landscape more broadly. The objective of improving the quality of clinical operations at the investigator sites is part of higher ordered operational goals of managing and con-



trolling the quality of patient safety and data integrity within clinical trials. These goals are paramount and are the light posts that should guide all clinical trial activities.

Given the clear focus on and illumination of the primary clinical objectives of patient safety and data integrity, the question arises as to how one achieves these objectives. This is the overall challenge and an effective response is by applying a systematic process for the assessment, control and communication of risks that may affect the quality of patient safety and data integrity. Such a systematic process is described in the International Conference on Harmonisation (ICH) guidance paper Quality Risk Management Q9 [3]. This Quality Risk Management (QRM) process is applicable to the entire clinical development process. As such a risk-based approach to clinical monitoring falls under its purview as well. Please bear this in mind as we turn our attention to SMART Monitoring and those factors that are key to its success.

### 1. Simplicity

Simplicity is often overlooked when one heads down the path of an initiative with grand goals and prospects. This is typically to the detriment of those individuals or teams that do not consider the merits of a simpler solution or approach over one that is more sophisticated and has perhaps more bells and whistles.

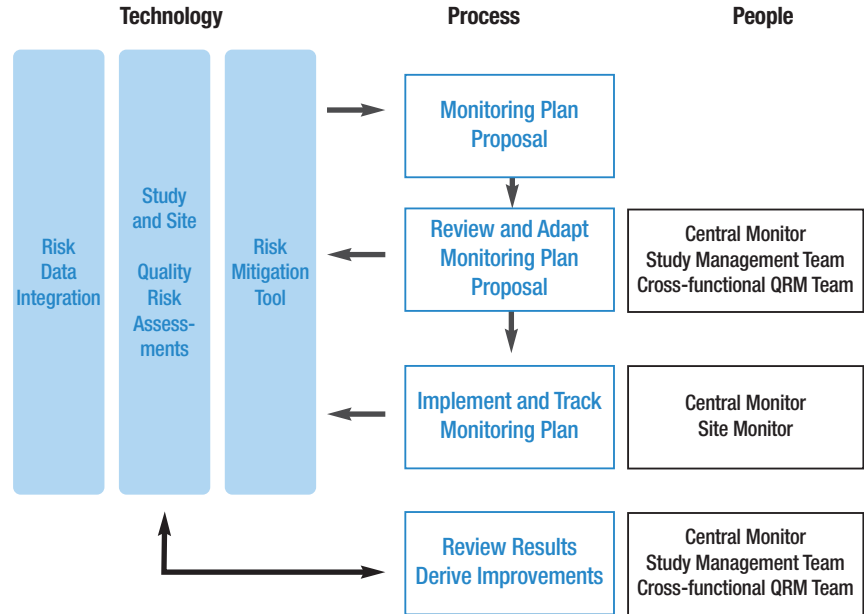


Figure 1: Adaptive Monitoring

As Leonardo da Vinci once said: "Simplicity is the ultimate sophistication." Leonardo being a genius in the fields of art and engineering has some words of wisdom that are worth heeding.

The daily work life of a study manager and Clinical Research Associate (CRA) within clinical operations is fast-paced, often geographically dispersed, multicultural, regulated from within and without, driven by deadlines, dependent on cooperation and in a word: complex. These realities coupled with the objective of delivering high quality study data and maintaining high patient safety standards are a

recipe for failure if quality management and control practices of the right kind are not executed. Given this inherent complexity and these ambitious goals, the study management team needs to execute simple but effective procedures while wielding specialized tools to address the issues that confront them.

### 2. Metrics

Monitoring is a control mechanism for assuring that certain quality levels are maintained. As described above, the primary objective for clinical trials is to maintain high quality regarding Patient Safety and Data Integrity. In

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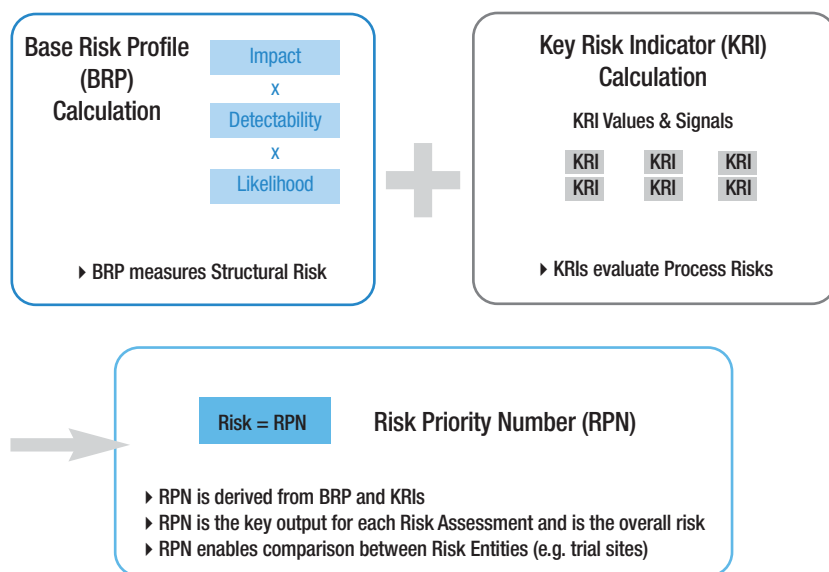


Figure 2: Risk Calculation Model

order for monitoring to be effective there must be a reliable means to systematically identify and measure threats to the quality as well as means to control these threats.

In order to determine the extent to which quality is threatened, a systematic evaluation of the underlying process, with respect to risk, needs to be carried out.

Failure Mode Effects Analysis (FMEA) is a methodology that is well suited for this task as it provides a standardized method to derive ways in which a process can fail, determine the impact of each such failure as well as its likelihood and how well the threat of failure can be detected. Impact, Likelihood and Detectability are factors that contribute to the determination of the overall quality threat exposure for each potential failure mode. In order to determine the level of threat, in the course of a Failure Mode Effects Analysis as it is applied in QRM, corresponding metrics are defined and their relative contributions are mapped to the Impact, Likelihood and Detectability factors. Additionally, the failure modes are mapped to Patient Safety and Data Integrity.

The most effective way to assess the threat to quality is to define metrics that are data driven and as such are objectively determined. For example, an indicator of a threat to patient safety is the Early Patient Ter-

mination rate as this is an indicator for possible inadequate site management, safety management, lack of protocol adherence and investigator oversight. In order to evaluate the level of threat to patient safety, data would have to be collected, such as number of patients enrolled at a site and number of early terminations at site among other data.

Naturally, in order to determine the actual extent of quality threat exposure a set of metrics is required.

### 3. Adaptive

“Intelligence is the ability to adapt to change.” This insight, made by the cosmologist Stephen Hawking, is fitting to the concept of SMART Monitoring as the monitoring approach earns its name primarily due to its adaptive nature.

SMART Monitoring is smart as it provides dynamic decision support for the allocation of monitoring re-

*Intelligence is the ability to adapt to change.*

STEVEN HAWKING – COSMOLOGIST (\*1942)

sources that facilitates an adaptive data-driven approach to monitoring. As the input data for the calculation of metrics vary over time, then the output of the calculation is a dynamic

quality threat assessment that provides the study management team with decision support whose advice varies, i.e. is adapted with each threat assessment. With this type of input the study management team is empowered with the information it requires in order to adapt the monitoring plan according to the current assessment. Moreover, the specificity of the metrics enables the study management team to direct resources to particular sites and focus on particular concerns that are indicated by the individual metrics that happen to exceed their corresponding quality threshold.

When assessments of quality threats are carried out regularly, then identification of temporal trends becomes possible and can be used as evidence to validate that actions taken have yielded particular results such as improvements in protocol compliance or patient retention. It is the maintenance of this type of communication feedback loop in the context of an interdisciplinary QRM core-team that enables a study management team to achieve local study-specific improvements and a central monitoring team to achieve program-wide, regional and more globally beneficial adaptations.

The diagram in figure 1 illustrates the adaptive monitoring process. It highlights how technology supports the process by generating a monitoring plan proposal that is reviewed by the cross-functional QRM team which carries out root cause analyses of risk signals, considers appropriate responses and then adapts the monitoring plan and other functional plans as appropriate. These adjustments to the plan are recorded in the risk mitigation tool and then the workflow continues by having the central and site monitors implement the adapted plan.

### 4. Risk-based

A risk-based approach to monitoring is key to successful monitoring as it provides clinical development the means to allocate its limited personnel resources in an optimal way. The risk signals are like torches that illuminate the various threats to clinical trial quality. They help clinical development

staff successfully navigate the vast and rough seas on the way to dossier submission of the patient data at the end of the long and arduous journey during a clinical trial.

As the investigator sites are the islands of productivity that power the drive toward a successful market approval of an Investigational Medicinal Product (IMP), they need sufficient protection from the threats to patient safety and data integrity. The investigator sites are usually geographically dispersed throughout the globe within various countries with various regulations.

A successful study manager is the captain who leads his crew of central and site monitors such that threats to investigator site operations are kept at bay to avoid the onset of site quality degradation or at least minimizes the impact of these threats by judicious allocation of monitors and associated task assignments.

The risk assessment is the instrument that provides the study manager with

regular threat forecasts throughout the population of investigator sites. The risk assessment is both a compass and a seismograph providing the study manager with both coordinates and magnitude of expected seismic activity within the island complex of investigator sites. With this information, the study manager is able to give the command and launch monitoring visits with site monitors or provide remote support to the investigator sites with a crew of central monitors.

The risk assessment provides the study manager with an assessment of both structural and process risks.

Structural risks are the risks of an entity that are inherent in it. For example, in the case of an investigator site, its experience level in a particular therapeutic area or knowledge and skills executing GCP studies are examples of structural risks that should be considered when engaging in Risk-based Monitoring as it is imperative to understand the baseline of risk

that one is exposed to before selecting or working with a site.

Process risks are those risks that one is exposed to when clinical operations are under way. Examples of these are: the number of protocol violations and number of early patient terminations. During the course of the study these types of events take place and the extent that they occur and the context in which they occur determine their contribution to the overall risk exposure.

The overall risk of an entity is derived from both the structural and process risk factors. The overall risk is also referred to as the Risk Priority Number as it provides a risk-based means to prioritize resources. The diagram in figure 2 illustrates the three primary risk metrics that should be included and calculated in all risk assessments.

The particular risk factors and their respective contribution to the overall risk of an entity such as a trial site are derived in a standardized and reliable

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way by applying a risk evaluation methodology such as Failure Modes Effects Analysis (FMEA). This standardized method empowers clinical operations personnel with the techniques to systematically identify and quantify risks and thereby enable them to effectively keep patients safe during a clinical trial and ensure that study data integrity is maintained at a high level of quality.

**5. Technology**

An integrated technology is essential to the overall success of an effective monitoring approach as SMART Monitoring is data driven and the data that needs to be leveraged is stored throughout the globe, in multiple databases both within the sponsor organization as well as external to it – for example, at the various investigator sites, central labs and at the CROs.

In general, technology is needed in order to automate the Quality Risk Management process described in the ICH Quality Risk Management (Q9)

guideline [3]. In other words, the technology needed for SMART Monitoring will be required to support and automate the five activities depicted in the following diagram of figure 3.

Please note that the ICH Q9 process as illustrated above is both an iterative and adaptive process. After each risk assessment, results are reported so that they can be analyzed by a cross-functional team and the risk signals

*Quality is not an act,  
it is a habit.*

ARISTOTLE – PHILOSOPHER (348–322 V. CHR.)

are considered in the context of the various functional areas. The conclusions of these analyses drive the adaptations of the various functional plans. These plans and their corresponding interventions are implemented and tracked. This process is repeated with each successive risk assessment. Peri-

odically the results of the risk assessments and risk control measures are reviewed from multiple perspectives in order to derive new opportunities to improve the underlying business processes that are not necessarily study specific but perhaps geographic or therapeutic area specific.

**Data Integration**

Due to the broad number and types of risk data sources (Clinical Trials Management System – CTMS, Electronic Data Capture – EDC, Safety Systems etc.) and the quantity of data, a suitable technology is needed to integrate these data in a scalable, efficient and reliable manner. This is typically done with so-called ETL systems that Extract data (E) from source systems, Transform (T) the extracted data and then Load (L) (ETL – Extract Transform Load) it usually into some central repository such as a clinical data warehouse. After the data is integrated in a central repository new application opportunities arise such as risk assessments. These are generally executed according to a predefined schedule.

An alternative data integration approach is to implement a Service Oriented Architecture (SOA) in which web services are published within a network to facilitate the transport of data from source to target systems. A push-mechanism is recommended in which the source systems push, i.e. send their data to a web service which is able to transport the data either to the central data repository or directly to the SMART Monitoring technology. In either case, there is a decoupling of heterogeneous source systems from the target system. One benefit of the SOA approach is its wide applicability. The data source systems can change but the gateway into the target system remains stable in terms of structure as well as technology independence.

**Risk Calculation**

If monitoring is considered in a broad sense, for example in the sense of quality control of risk entities, then one needs a risk calculation model that is generic but can be flexibly applied to the various risk areas within clinical development. Given this starting point an important requirement



Figure 3: Essential Activities of SMART Monitoring

on the risk calculation technology is to provide functionality to configure the risk algorithms. This configurability requirement would typically include risk metric weightings, thresholds and activation/deactivation switches e.g. for enrollment Key Risk Indicators (KRIs) to name a few. These configuration functionalities should be available within the user interface.

### Risk Reporting

Once the risk assessment has completed, the technology should be able to automatically generate standard reports and dashboards to enable the members of the cross-functional team to analyze the results in an efficient manner. The risk reporting should be done consistently across all the risk areas within the organization in order to facilitate effective communication across the functional teams.

The importance of a common risk language cannot be underestimated. The fundamental elements of the common risk language should be communicated consistently throughout the risk reporting process. Specifically one should readily receive information about a risk entity's Base Risk Profile, its KRI signals and its Risk Priority Number. When discussing results of a risk assessment these quantities should always be included.

The reports should be readily available and hence should be available within an internet browser. They should also be readily transferrable, for example they should be available in PDF format and risk assessment results should be downloadable from the SMART Monitoring system into CSV or Excel file format to enable further analysis of the risk signals.

### Plan Adaptation

In order to support the cross-functional team in determining the appropriate focus, type and amount of monitoring, the technology should be able to automate the generation of risk mitigation plans that target the identified areas of high or unacceptable levels of risk. Furthermore it should be possible to generate these plans based on a dynamic intervention model. Such a model contains the conditions that need to be

met before the technology automates the generation of a corresponding risk mitigation task. Thresholds associated with these conditions are optimally parameterized so that parameters can be configured according to the organization's monitoring intervention model.

### Risk Control

After the risk mitigation plan is adapted, the SMART Monitoring technology should also provide functionality to enable the tracking and reporting of risk control actions. Consistent with the principles of knowledge management, we also recommend that the technology provides a means to readily reuse and thereby benefit from past experiences. For example, if certain monitoring interventions were consistently effective at mitigating certain types of risk, then the technology should inform the user of this and recommend the reapplication of these interventions should the same risk arise in a similar context.

### Conclusion

The question posed in the title of this article is: Can new approaches make a difference? provides an apt starting point for the conclusion. This article depicted a historical perspective on trial site monitoring as well as current trends and initiatives within the pharmaceutical industry concerning the practice of monitoring. The concept of SMART Monitoring was developed and concretized according to the factors: Simplicity, Metrics, Adaptive, Risk-based and Technology.

In summary, the SMART Monitoring approach as described in this article can and does make a difference and in particular a positive one when clinical operations personnel ensure that the SMART Monitoring key success factors continue to inform and influence monitoring planning and execution.

As Aristotle once wrote: "Quality is not an act, it is a habit." So in the spirit of this and the objective of maintaining the utmost quality re-

garding patient safety and data integrity, it is recommended to make a habit of applying a SMART Monitoring approach. |

### References

- [1] Position Paper: Risk-Based Monitoring Methodology by TransCelerate Biopharma Inc., published 30 May 2013.
- [2] TransCelerate Biopharma Inc. website, web page: <http://www.transceleratebiopharmainc.com/our-initiatives/>
- [3] ICH Harmonised Tripartite Guideline, Quality Risk Management Q9, by ICH Expert Working Group, published 9 November 2005.

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