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Preparing for the ICH E6 (R2) Addendum

Nick Neri

The addendum is expected to increase quality risk management and centralized monitoring adoption.

The International Conference on Harmonization's (ICH) addendum to the ICH E6 Guideline for Good Clinical Practice has many implications for clinical trial sponsors and contract research organizations (CROs). The new E6 (R2) addendum to Good Clinical Practice has the potential to change the way clinical monitoring and trial management are conducted by making the adoption of centralized, quality risk management (QRM) throughout the trial lifecycle an integral part of their recommendations.

One of ICH's objectives with this addendum is to harmonize existing guidance from FDA and EMA, which they believe are not currently aligned. The resulting lack of harmonization has left much room for interpretation, which can be confusing for organizations striving to meet regulatory requirements on a global scale.

The addendum will require most biopharmaceutical companies and CROs to make significant changes to their risk culture and technology in order to be compliant, including the suggestion to implement a combination of on-site and centralized monitoring. The addendum is expected to increase adoption of quality-by-design and QRM principles and methodologies in clinical development, while driving the use of innovative strategies and technologies for risk monitoring. It further defines the scope of clinical trial oversight responsibilities, and the sponsor's responsibility to establish a risk-based quality management system, ensuring the tools and methods used are "proportionate to the risks inherent in the trial and the importance of the information collected." The addendum also specifically cites "evolutions in technology and risk management processes" as the reasoning behind the change, and encourages industry stakeholders to seek out new tools and processes that will help them take advantage of these efficiencies.

There are many advantages to implementing a centralized Quality Risk Management (QRM) system in addition to driving compliance with the new ICH standard. Centralization can also significantly cut the time and cost of clinical trials while helping to reduce risks. Yet most organizations are behind the curve when it comes to implementing the technology and processes needed to adhere to this new guideline change, and that may be putting them at risk.

Trial sponsors and CROs recognize real, measurable benefits from taking a centralized, technology-based approach to risk management. These include reduced on-site monitoring costs, real time identification of risk trends across all trial sites and access to trial-wide views that enable them to capture best practices for future trials.

This change is likely to go into effect by the end of 2016, which means organizations that haven't started transforming their risk monitoring process are already falling behind. To catch up, biopharma stakeholders need to take the time now to read the addendum in full, define the impact it will have on the way they conduct trials, and devise a plan to adapt their technology and risk management practices so they can meet coming regulations while

benefitting from a more centralized approach to managing clinical trial risk.

Six steps to compliance with ICH E6 (R2)

1. Read, assemble and plan. Before making any changes, sponsors and CROs should assemble an in-house working group of GCP experts to study the new addendum, determine its full implications to their organizations and make decisions about how to adapt their technology and practices to meet the new requirements.

2. Develop technology and process gap analysis. Once the GCP team defines what compliance looks like for their organization, they should evaluate their current processes and technologies to determine if/where they fall short of the new requirements. For example, they may need to define a more formal risk identification process, create or acquire a library of risk identifiers, and/or replace manual spreadsheets with a more robust, technology-driven solution for assessing risks. This gap analysis will help them define a strategy for change and the steps needed to get there.

3. Assess existing data systems. Most sponsors and CROs today rely on transactional study data drawn from numerous, diverse data capture systems like EDC, IVRS, Labs, etc. These data are often siloed and rely on unique codes and naming conventions. This lack of integration not only limits the sponsor's visibility, but also makes it difficult to proactively identify and react to risks. To overcome these shortcomings, organizations should first identify where silos occur, then look for technology solutions that can remove the silos and integrate these systems' data. This will provide a single operational view that supports real-time risk monitoring across the entire trial site network.

4. Study it. One of the biggest challenges companies will face is the culture transformation required to change the way risks are identified and managed in clinical research. To ease stakeholders into this new paradigm, organizations can roll out pilot projects with clearly defined metrics to demonstrate value and share case studies of other organizations that have already successfully made the switch. Studies show that a centralized approach reduces monitoring time and costs and often uncovers risks that on-site monitors miss. Demonstrating these benefits using real quantitative outcomes is the best way to engage stakeholders and increase their comfort with the change.

5. Evaluate your CRO. Regardless of whether a CRO is responsible for all clinical trial activities, the sponsor is still responsible for the quality, safety and efficacy of their processes and data. To ensure compliance with the addendum, sponsors should audit their CRO's technology and QRM approach to determine if it meets ICH requirements and if not, how the CRO plans to move toward compliance.

6. Join the discussions. The adoption of risk-based quality management has the potential to disrupt the industry and it has only just begun. To ensure compliance with the addendum and to achieve the greatest benefits, sponsors should look for opportunities to share learnings and participate in industry consortia, including TransCelerate BioPharma and the Clinical Trials Transformation Initiative, as they define standards and best practices for leveraging quality risk management strategies.

Conclusion

In 2012, the non-profit, TransCelerate BioPharma launched the Risk-Based Monitoring Initiative and partnered to launch the Quality Management System initiative to improve the quality and efficiency of RBM, and to describe a proactive approach for managing quality across the spectrum of clinical activities. This includes a framework for identifying risk indicators and performing consistent oversight of investigators throughout the trial lifecycle.

Yet the industry as a whole has been slow to update their technology or processes to take advantage of the efficiency and regulatory benefits of a QRM approach. In many cases, sponsors are still relying on on-site monitors capturing data in spreadsheets to monitor risks manually, or attempting to use their electronic data capture system as a reporting platform for monitoring—despite the fact that these tools don't have that capability. As a result they are missing opportunities to cut time and cost while improving overall quality across the trial process—a centralized approach to QRM has been shown to generate 15%-20% trial cost savings.

This addendum should be a wake-up call for sponsors and CROs that it is time to change the way they think about and address quality risk management in the planning and implementation of their clinical trials.

Nick Neri is Product Manager, Insights Cloud, ERT

Considerations in RBM Implementation

Ashok Ghone

A look at risk management principles that guide RBM from all angles.

Risk management principles are widely used in other industries like aviation, finance etc. with a five steps approach—Identify, Assess, Plan, Track and Control. When applying a risk-based approach to clinical trials, one needs to identify the risks to the critical data and processes that are very important to achieve the study objectives. Following are some examples of critical data and procedures:

Critical data (Examples)	Critical Processes (Examples)
• Subject eligibility • Data that support primary and secondary endpoints • SAE data andwtreatment discontinuation data • Randomization/ blinding and specific event • Adjudication data	• Informed consent process • Randomization process • Any protocol specific intervention or procedure • SAE reporting

Similarly, it is very important to identify the risks related to site performance variables to monitor them during the study. The key site performance variables are as follows:

Site Performance Variables	• Patient recruitment rates • Screening failures rates • Dropouts/ discontinuation rate • DCFs generation rate • Protocol non-compliance • eCRF entry rate • Number & frequency of monitoring visits per site

After identifying risks, we need to identify the sources or root causes of these risks and assess them further to see the probability of occurrence (likelihood), type of impact (consequence) on the study objectives, and to decide the risk level or risk score using 1 to 3 risk matrix or 1 to 5 risk matrix. The detectability is also used to assess the risk level. Based on this, risks can be categorized as low, medium and high. The risks falling in medium, high categories need to have close monitoring and strong action planning to take care of them if they occur during the study. Also, these risks are acceptable up to certain level, so it is necessary to decide threshold or tolerance limits

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beyond the deployments of "planned actions" for the risks. For example, the risks/KRIs and thresholds for eCRF completion rate could be '>20% CRFs pending for more than 30 days.' For patient recruitment, it could be '>20% of sites are below expected recruitment rate,' which means for patient recruitment risk during study conduct, when the threshold of '> 20% of sites are below expected recruitment rate' is reached, it gives an action alert to follow up on the sites for the planned strategies to be deployed to control this risk.

As far as the "Plan" part of risk management is concerned, there are generally four types of action planning , including Avoid, Transfer, Accept and Mitigate. Avoid, is self-explanatory--avoid the risk if it is real show stopper e.g. not including a country in clinical plan if there is no proper regulatory approval processes or uncertainties related to the study approval timelines. "Transfer" is any potential risk response outside of the sphere of influence of the team involved, it may be necessary to identify an alternative group to whom the risk could be transferred for action or decision-making. "Accept" is accepting the risk to a certain extent considering the benefits. 'Mitigate' response is very commonly used. Mitigation actions may have different objective, such as, eliminate the risk completely, minimize the impact of the risk, reduce the likelihood of the risk occurring, or increase the chances of the risk being detected if it occurs. An example of mitigation response could be keeping close tabs on an investigational site on a study with little or no GCP experience. This risk can be mitigated by close monitoring of the site or additional training to the site.

Risk-based monitoring plan

To ensure last two steps of risk management cycle i.e Track and Control, one needs to have a proper RBM plan in place to ensure proper tracking mechanisms of the risks identified in the beginning and to assess if there are new risks are arising during the conduct of the study. The risk based monitoring plan will have two distinct part—centralized monitoring and onsite/off-site monitoring. The following includes the key attributes of an RBM plan.

- Types of monitoring to be performed and identify the risk/s being managed by each type
- Centralized and On/Off-site
- Detail the criteria for determining the timing and frequency of monitoring activities—this also depends on the complexity of the study design, type of study population involved (e.g. seriously ill or vulnerable patients), geographic spread of the study and type of endpoint assessment etc.
- The actions comprising each type of monitoring
- Actions planned (in case risks occur)
- Documentations requirements to report central as well as on/off-site monitoring findings, escalations/resolutions done etc.
- Communication plan
- Events or results that should trigger changes in planned monitoring activity e.g. increased protocol deviations/violations, higher dropped rate etc.
- Roles , responsibilities and training—this includes role & responsibilities of central monitors, their training needs etc.
- Overall quality management and compliance- describing site specific training or audits planned

Centralized monitoring

Centralized monitoring is a remote evaluation carried out by sponsor personnel or representatives (e.g. data management personnel, statistical or clinical monitors) at a location other than the site(s) at which the clinical investigation is being conducted. Centralized monitoring offers many of the capabilities of on-site monitoring, as well as additional ones, and therefore FDA guidance document encourages the greater reliance on centralized monitoring practices wherever appropriate. It allows improved monitoring of critical data and processes for quality and patients safety using analytical and visualization tools. It helps early identification of risks/issues and keeps track of site performances with timely corrective actions. Centralized monitoring also increases the efficiencies of on-site monitors and they are more focused while they go for site visits. It reduces on-site monitoring visits and creates overall efficiencies in clinical trial management. Centralized monitoring offers a good option for oversight of study vendor/CRO or CRAs performances.

Central monitors

Due to introduction of centralized monitoring, the central monitor is emerging as an important role in RBM. The responsibilities of this role are to look at risk reports ongoing basis to identify the risks, trends and patterns and then escalate to the relevant stakeholders on a timely basis. It is helpful if they have the following attributes to support these new responsibilities:

- Good knowledge of overall clinical trial management, understanding of the protocol, study associated risks and their significance
- Clinical operations and data management knowledge to identify and provide insight into trends or outliers in data
- Critical thinking and analytical skills: define and analyze data from complex, overlapping domains to facilitate well-supported decisions
- Excellent communication and coordination skills
- Ability to use the available technologies effectively

Quality Metrics	Timelines Metrics	Budgetary Metrics
• Average number of protocol deviations / violations per site • Average Number of DCFs generated per site • Average number of major audit findings per site • Number of unreported SAEs / delay in reporting SAEs (safety)	• Average number of days from DCFs generation to resolution by sites • Average number of days from patient visits to eCRF data entry • Number of days from issue identification to resolution	• Average number of monitoring visits per site • Frequency of monitoring visits per site • Average on-site monitoring visit cost

Technology

Technology plays a critical role in implementation of RBM. The technology should support two important aspects in RBM implementation—one aspect is overall risk management part as risk management tool to identify, assess, plan and for tracking of risks and issues. The second aspect is analytical and visualization tool to support centralized monitoring.

The key features of a risk management tool include,

- Provide list of the risk library relevant to clinical trials/ programs
- Effectively support risk identification, assessment and categorization process (with risk score or risk categorization)
- Support risk tracking–able to capture risk changes effectively
- Able to generate alerts/communication to relevant stakeholders when threshold/trigger is reached
- Provide the action plan as decided for mitigation/controlling
- Track issue management, including identification, escalation and resolution, categorization (risk scoring), risk level changes, escalation, communication, issue management etc.
- Generate audit trail

The key features of analytical and visualization tools are,

- Able to integrate with various data sources
- Collate and analyze the data from various sources like EDC, CTMS, ePRO, IRT etc.
- Produce graphical/visual representations of analyses and allow the export of the reports in PDF, excel etc.
- Identify trends, patterns, and outliers ongoing basis to assess performance at the trial, program, country, site, patient level
- Proactively generate alerts when risk indicator values meet predetermined thresholds
- Provide functionality to send alters to relevant system/ stakeholders
- Allow for dynamic redefinition and modifications to new risk indicators, thresholds, and alerts

RBM metrics

To assess the performance of RBM implementation, one can look into the above metrics indicators and their definitions.

Conclusion

RBM is an innovative and smart approach available to improve study conduct and management. It needs process change, new robust technology and resource alignment, training. Currently, industry is trying to get more confidence on the new processes, technology and new resource role requirements. However, it is the way to move forward as RBM helps to improve data quality, ensures better monitoring of patient safety. It also optimizes on-site monitoring visits and builds overall cost efficiencies in the operations.

Ashok Ghone, PhD, is Vice-President, Global Services at MakroCare, and a member of Applied Clinical Trials Editorial Advisory Board. He can be contacted at ashok.ghone@makrocare.com

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Four Tips on Writing an RBM Plan

Moe Alsumidaie

A comprehensive RBM plan is based on thorough risk-management preparation.

With recent changes in industry execution and increasing experiences with using RBM, many peers are inquiring about how to write an RBM plan. Hence, we thought it would be beneficial to provide a brief methodology on developing a risk management process to create an RBM plan. It is important to emphasize that RBM plans vary from one study to another, and the purpose of this article is to offer insights and tips.

Tip 1: Complete a Risk Assessment Categorization Tool (RACT)

Though, in a previous article, we've uncovered evidence that conducting the RACT exercise introduces subjectivity, the tool can be helpful in getting study teams to think about revealing and ranking study risks. Additionally, if study teams follow the suggestions provided in this analysis during the RACT exercise, they can improve the quality of risk assessment results, especially by involving other functions within an organization. Though study teams can conduct RACT and implement RBM anytime throughout a study, RACT is most effective when done during the protocol development phase, and can greatly mitigate study risks by enabling study teams to re-design the protocol, and study operations.

Tip 2: Identify Critical Study Risks

Study risks can be anything ranging from data collection and transfer all the way through enrollment. However, it is important to define and categorize your risks in a way that regulatory authorities consider important. Specifically, advice from a former regulatory member suggests that critical risks involve data related to (a) the study's endpoints, and (b) patient safety. For example, a critical risk could be ECOG score measurements in an oncology trial, changes in carotid stenosis in a cardiovascular trial, or adjudicating unexpected and unusual adverse events. The key is to identify critical study risks (which the RACT can help with), and it is important to note that critical risks are typically only a few data points. How do you categorize data that is not considered critical? Simply put them in the non-critical risk category.

Tip 3: Transform Critical Risks into Analytical Measurements

Once you've identified critical risks, you have to figure out how to measure them, and this is where key risk and performance indicators come in. According to the RBM Consortium, a Key Risk Indicator (KRI) is, "an objective measurement of a study-related parameter against a pre-set threshold providing a signal about the risk of a study process or any of its deliverables." A Key Performance Indicator (KPI) "measures the achievement of an operational or performance target." To elaborate, if your identified critical risk is ECOG score measurements, your KRI is ECOG score measurement, and your KPI is the analytical measurement of the ECOG score. In your monitoring plan, you have to (a) define risk pa-

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Addendum ICH E6(R2) potentially changes the way most sponsors and CROs will address clinical research oversight, including the adoption of quality-by-design, quality risk management (QRM) and risk-based monitoring (RBM) processes in every phase of development. There are many benefits to a QRM system beyond guidelines compliance: centralization can significantly reduce on-site monitoring costs, saving you 15-20% of overall costs per trial.

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rameters for deviation, and (b) delineate corrective actions, should there be a deviation.

According to the advice from the former regulatory member, you should QC 100% of any modification made to any data point impacting primary safety/efficacy endpoints. However, in my opinion, it is always a good idea to do 100% QC/SDV for data related to the study's primary safety/efficacy endpoint, and a random QC/SDV of a certain percentage for non-critical data (i.e., 10%-40% of randomly selected data).

Tip 4: Write the RBM Plan

Writing the RBM plan should be the easiest part, as most of the work has been done when you reach this point. Your task would involve structuring your RBM plan in a coherent way so that any auditor who is not familiar with the study can review the monitoring plan and easily grasp the rationale behind it. The monitoring plan should include (a) an introduction to the identified critical study risks (b) detailed sections on each critical risk, which involves an overview of why the risk is considered critical, the impact of deviations, and the monitoring activity associated with that particular KRI. It is important to define the KPIs (and what happens if there are deviations), and describe the function of centralized and on-site monitors, (c) monitoring activity for non-critical study risks (i.e., random data selection for QCing/SDVing 10%-40% of non-critical study data), and (d) RBM plan adjustments, which basically describes RBM plan change methodology as the study progresses.

Compliance expert Sharon Reinhard says, "It is important to outline the tasks that will be conducted centrally and on-site, and provide a description of how these activities will be documented. Usually these are important tasks, such as detecting and reviewing protocol deviations, ensuring data entry and query resolution is occurring in a timely manner, or complex cross checking of data between medical history, adverse events and concomitant medications; however, teams often don't realize they need to document these activities and ensure that documentation reaches the trial master file."

Summary

A comprehensive RBM plan is based on thorough risk-management preparation. Writing a good RBM plan not only enables you to focus resources on critical study areas, but also provides both auditors and regulators with a good impression of risk interpretation and monitoring proficiency. While setting up an RBM plan in the study's midst can be done, it is strongly advisable to create the monitoring plan during study design, as regulators say time and time again that a well-designed study is the blueprint for good quality.

Moe Alsumidaie is Chief Data Scientist at Annex Clinical and member of the Applied Clinical Trials Editorial Advisory Board.

The Core of RBM is Centralized Monitoring

Martin Giblin

Latest survey and research from QuintilesIMS shows gains in RBM awareness and implementation

Recent research indicates that the implementation of risk-based monitoring (RBM)—particularly using centralized monitoring as a core component of clinical trial execution—is impacting clinical trials of all sizes, indications and phases. Based on lessons learned from 150-plus trials involving this approach, and a recent survey of biopharma executives, this article will describe current awareness and usage of RBM, key drivers and considerations, an approach to central monitoring as well as implementation challenges.

Awareness and usage of RBM

Awareness of this innovative approach is now close to universal, at 93% for unaided respondents and 96% for aided ones in a recent survey from August 2015 conducted with clinical outsourcing key decisions makers and influences within the pharma industry. Top-of-mind RBM descriptions from survey respondents included:

Planning, with identification of key risk indicators (KRIs), and establishment of protocols for responding to KRI alerts

- Appropriate and efficient data monitoring: As one survey respondent explained, "It's actually using some of the technology that we have at our disposal like statistics and technology so that we can track quicker, have better feedback, diagnosis and actually fix the problem before it's too late."

Increasing data quality and actions through near real-time data monitoring: As another respondent noted, "It's the process of focusing on key data points for review and tracking of potential issues within a study. It's an overall view, ranking how important differencing data points are within a study and then assigning a strategic plan to monitor and clean those data points as the team agrees."

- Fewer planned site visits.

RBM use is increasing, from around 50% in 2013 to 63% in 2015, with sponsors and sites expressing growing satisfaction of RBM trials and planning to expand their use (Figure 1). Most current users plan to include RBM in future trials, and over half of non-users plan to implement RBM within the next two years over a wide range of therapeutic areas, led by dermatology (32%), oncology (32%), biologics (27%), immunology (23%), allergy/respiratory (18%) and CNS (18%). To date, RBM has been used most often in Phase II through Phase IV studies, but RBM usage is also cited being used in Phase I, including proof-of-concept, studies.

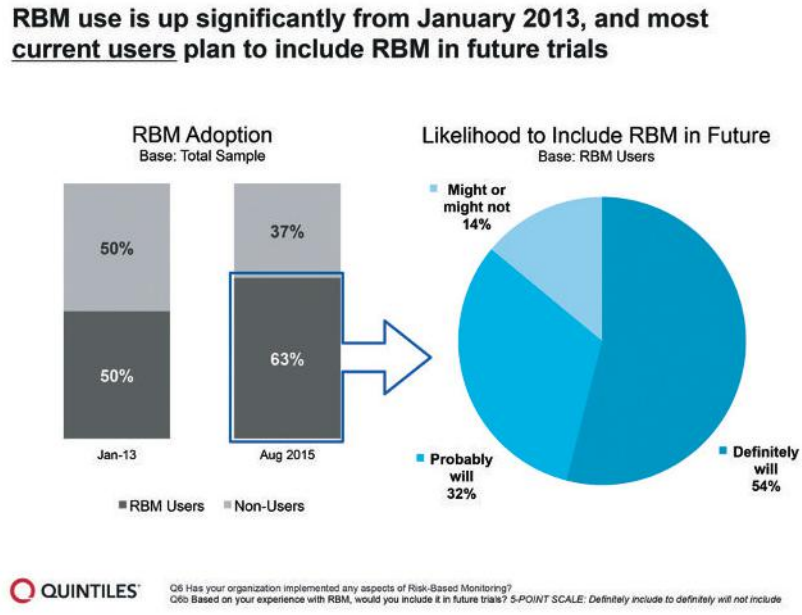
Key drivers and considerations

Key drivers for use of RBM are the potential to reduce monitoring costs (cited by 78% of respondents), mitigate risk (55%), enable data-driven decision-making (55%), improve data quality (54%), and use triggered monitoring to prompt an on-site CRA visit (54%; see Figure 2). For non-users, finding an appropriate trial is key, in addition to being made aware of CROs' RBM experience – including technology and process implementations to help in selecting a suitable partner.

Implementation

The most common new operational capability seen in successful implementation of RBM is

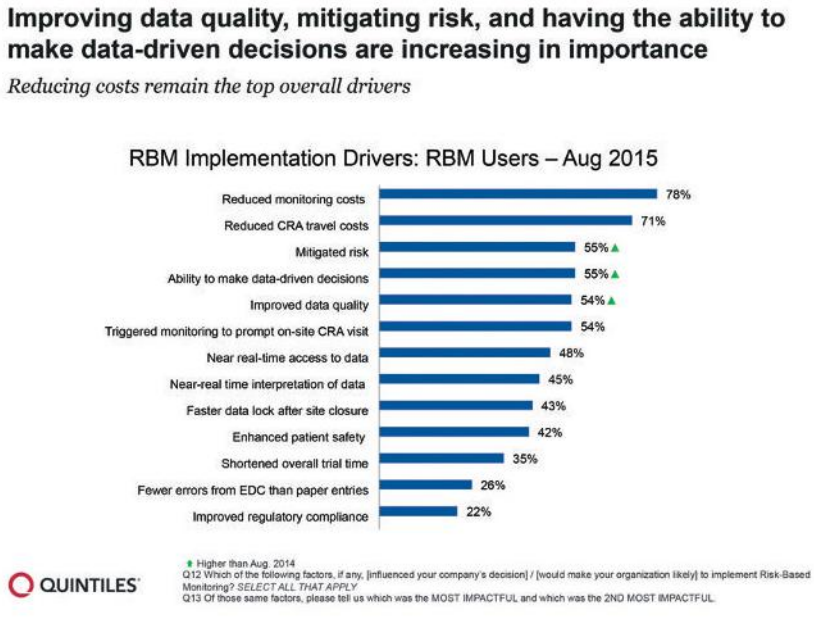
RBM Usage June 2013-August 2015



Source: Quintiles survey, 2015.

Figure 1. Sponsors and sites express growing satisfaction of RBM trials and plan to expand their use.

Drivers of RBM Implementation



Source: Quintiles survey, 2015.

Figure 2. Non-users are looking to try RBM in the right trial, as well as find providers that have technology and implementation experience.

some form of centralized monitoring. It's increasingly clear that this capability is a core driver that is improving efficiencies, decision support and unlocking real value by fundamentally changing the way clinical monitoring is performed.

Successful implementation also requires data integration, enabling data from disparate sources to drive actionable insights using integrated IT services (Figure 4). Enhanced decision making based on data insights also clearly depends on sophisticated capabilities in data curation and technology platform management.

As shown in Figure 3, elements of centralized monitoring include:

- Key Risk Indicators (KRIs) and trigger management, is the most common element of a centralized monitoring solution, reviewing pre-defined triggers and alerts based on agreed thresholds to drive subsequent actions. This is very useful for driving elements like data flow, but have some limitations when it comes to identifying relative site risk or designing appropriate actions for multi trigger events.
- Predictive and advanced analytics, designed to identify where risks are and where they are likely to be at both the site and patient level. As shown in the green area of Figure 3, these combined inputs across multiple variables, including operational performance and study data to provide unprecedented insights for study monitoring. These analytics are the first such model-based capabilities fully integrated into an RBM approach and represent a major step forward in improving quality and productivity in the next generation of risk-based clinical research execution.
- Targeted site support, enabling improved protocol compliance, clinical data flow and site visit preparation as represented in the light blue area of Figure 3. Specific site performance metrics and information are provided to CRAs, identifying key actions to execute—optimizing each site visit and making site interactions more effective and efficient from all three perspectives of cost, quality and time.

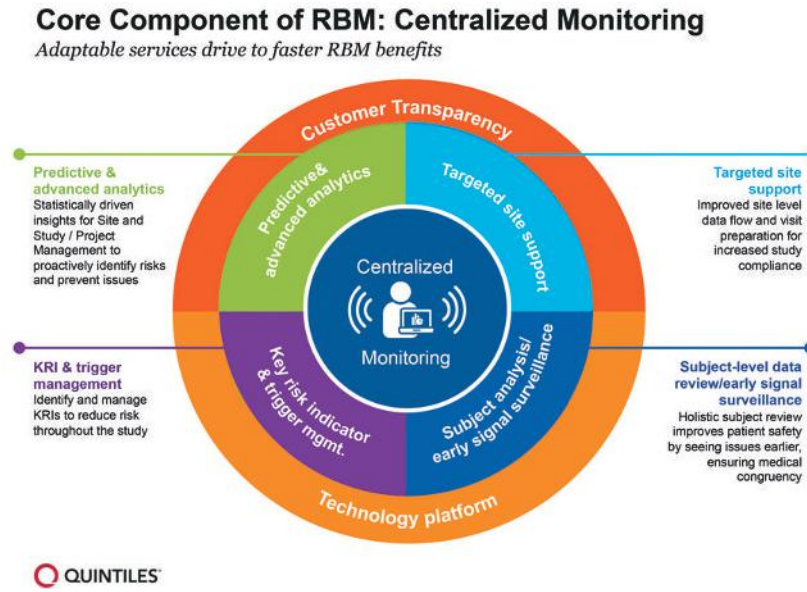
- Subject-level data review/early signal surveillance, provides holistic review of critical subject data by medically-trained staff, and identifies clinical incongruences earlier to resolve potential eligibility and safety issues. The process—illustrated in dark blue in Figure 3—also helps detect protocol compliance and subject retention issues.

Demonstrating improved data quality and shorter time to make data-driven, key decisions has helped some biopharma companies overcome their initial lack of comfort surrounding reduced verification of all source data – a key component of RBM. Around half of companies surveyed plan to develop their own internal RBM solution: however, these companies will face new challenges with adapting roles, systems, and processes to implement and maximize RBM rather than working with a partner that has those systems, roles and processes in place already. Here, change management is a core consideration, and buy-in needs to be driven from executive levels.

Conclusion

There's no doubt that awareness and usage of RBM is increasing. Sponsors and sites are broadly satisfied with this approach and expect to expand its use to include all phases of clinical research and all therapeutic areas. Cost savings are key; however, mitigating risk, improving data quality, and enabling data-driven decisions are increasingly important drivers for RBM adoption. As technology continues to drive change, centralized monitoring has the promise to further improve efficiencies to change the way clinical monitoring is performed. New analytics capabilities can help clinical researchers assess the probability of a future event occurring—for example, a protocol deviation that may require on-site action. The ability to cut through noise and predict potential risks before they occur means teams can optimally allocate current and future site management resources, as well as achieve enhanced patient safety and data quality at greater speed and lesser cost.

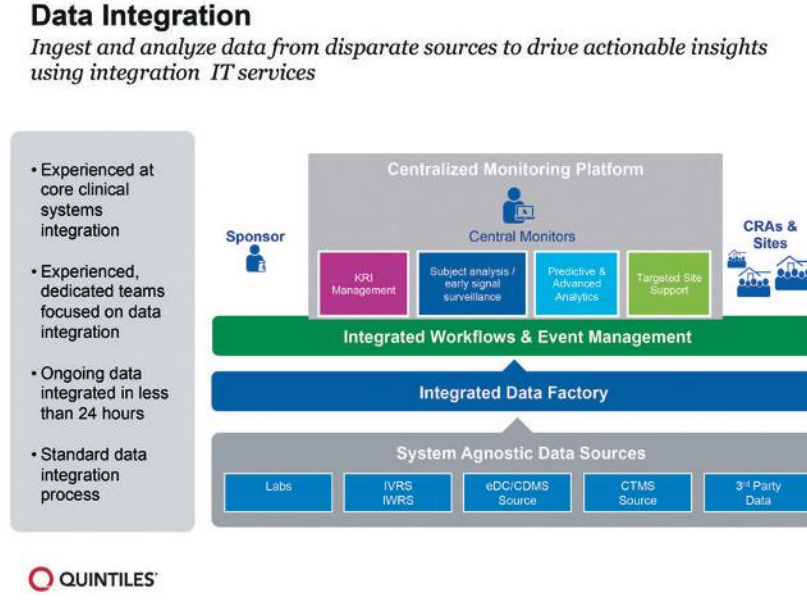
Elements of Centralized Monitoring



Source: Quintiles, 2016.

Figure 3. Key Risk Indicators (KRIs) and trigger management, is the most common element of a centralized monitoring solution.

Data Integration in RBM



Source: Quintiles, 2016.

Figure 4. Successful implementation also requires data integration, enabling data from disparate sources to drive actionable insights using integrated IT services.

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Standardized Metrics for Better Risk Management

Linda B. Sullivan

Metrics form the foundation for continuous feedback and strategy in clinical development.

The proliferation of cloud-based technologies has made it easier for stakeholders to collect and share performance data that flow into data analytic tools. To access these data, sponsors and contract research organizations (CROs) have invested heavily in electronic data capture (EDC), eSource, and other solutions since data from these systems can be aggregated into a single database to run data analytic reports. Metrics found in these reports provide the foundation upon which emerging clinical trial strategies, namely risk-based management (RBM) and quality by design, can be implemented, with an eye toward better performance. In keeping with this effort, organizations such as TransCelerate[1] and Metrics Champion Consortium (MCC)[2] have been developing proactive methods and tools around risk assessment and management to improve clinical trial quality while increasing patient safety.

But just because information can be gathered and shared more quickly among stakeholders does not mean that the data contained in the reports, or the resulting metrics can identify risk. And are they actionable, meaning can they help stakeholders make decisions about when to take action and when to monitor? Specifically, when organizations attempt to integrate data across studies—from multiple vendors and systems—they discover that some data fields are not defined consistently. Moreover, if study teams are utilizing customized metrics, it becomes even more difficult to determine which data to use, undermining the validity of the analysis.

Clinical trials is all about proper planning and risk mitigation, determining what needs to be measured, and when to take action. For every measure that is defined, what is the key performance question it is trying to answer?

This article describes the need for the industry to adopt fully-vetted, standardized operational-level time, cost and quality performance metrics as critical tools for tracking and predicting performance. Standardized performance metrics have standard definitions of key terms and study milestones, along with performance targets to ensure that metrics are measuring the right factors in the right way. Driven by competitive and regulatory pressures,[3,4] and the notion that "you can't improve what you don't measure," the goal of standardized metrics is to plan and predict performance by identifying known risks, followed by a proactive stance on risk management, including upfront assessment and mitigation and ongoing risk monitoring.

Becoming strategic

More than 15 years ago, the Tufts Center for the Study of Drug Development (CSDD) reported on the importance of using standardized performance metrics to evaluate clinical development across the industry.[5] Embracing this concept, the Metrics Champion Consortium (MCC) was created several years later to bring stakeholders together to define standardized performance

Table 1: Some Standard Definitions

Site Activation Date: The data that the site is ready to receive patients/subjects–it has received investigational product and completed site initiation activities.
Database Lock Date: The date of final database lock, which some organizations call "hard lock". Datasets are available after this lock for statistics to complete their final tables, listings, and graphs, and statistical analysis. If the database is reopened, the database lock date is reset to the last lock date.

Source: Metrics Champion Consortium, 2015.

Table 2: Benefits of Adopting Standardized Definitions of Performance Metrics

Establish clear, consistent performance expectations for internal and external operations
Facilitate adoption of best practices across sponsors and service providers
Ensure consistent measures–reduces "garbage-in/garbage-out" problem
Avoid cost of customized IT programming
Support comparison of performance across all studies within an organization, including across multiple vendors
Decrease time spent trying to understand what is being measured, and focus on achieving meaningful process improvement

Source: Metrics Champion Consortium 2015

metrics that organizations could use to drive process improvement. MCC members have established clear definitions of the performance metrics, including key terms and data elements, such as site activation date and database lock date (Table 1). Defining key terms is essential for apples-to-apples comparisons of current versus past performance. In addition, organizations report other benefits such as establishing expectations and facilitating adoption of best practices (Table 2).

This industry is a latecomer to standardized definitions for performance metrics, but the sharp focus on improving productivity while reining in costs is now driving demand for detailed analytics.[6] Yet, simply collecting analytics is not enough. They need to be actionable, providing sufficient information for users to make decisions about adding resources or conducting a root cause analysis to determine how to fix an issue. When possible, metrics should be leading indicators providing results that help identify opportunities to impact the direction of the study.[7] For example, if a number of sites have only enrolled one or two subjects months after initiation, this may be a leading indicator that factors are present that may cause future delays.

An insightful article by Rick Piazza notes that reports generated by analytic tools are informative as they indicate the overall status of a project, and the metrics they generate may focus attention on outliers or trends at the study level.[6] Rarely, however, do these reports provide enough actionable information to make an impact at the organizational level.[6] To be actionable, operational metrics should be data-driven, standardized across studies, indication, and therapeutic areas, and be timely.

Closing the gap between collecting information from disparate systems and making that information actionable is the purpose of MCC and research conducted by industry consultant Margaret Fay. She explains, "Well-defined metrics form the foundation for a continuous feedback loop known as 'Plan, Do, Check, Act,' an established business framework dating back to the 1950s.[8] It can be applied to the formation of risk management and mitigation plans to limit risk upfront in clinical trials, instead of reacting after the fact."

This effort represents a paradigm shift toward statistical modeling that uses built-in risk indicators to trigger action.[9] This starts with identifying known risks upfront, based on past performance, knowing which key performance questions need to be answered, not using a metric in isolation,[10] and making certain that enough usable data are collected to make a proactive analysis.

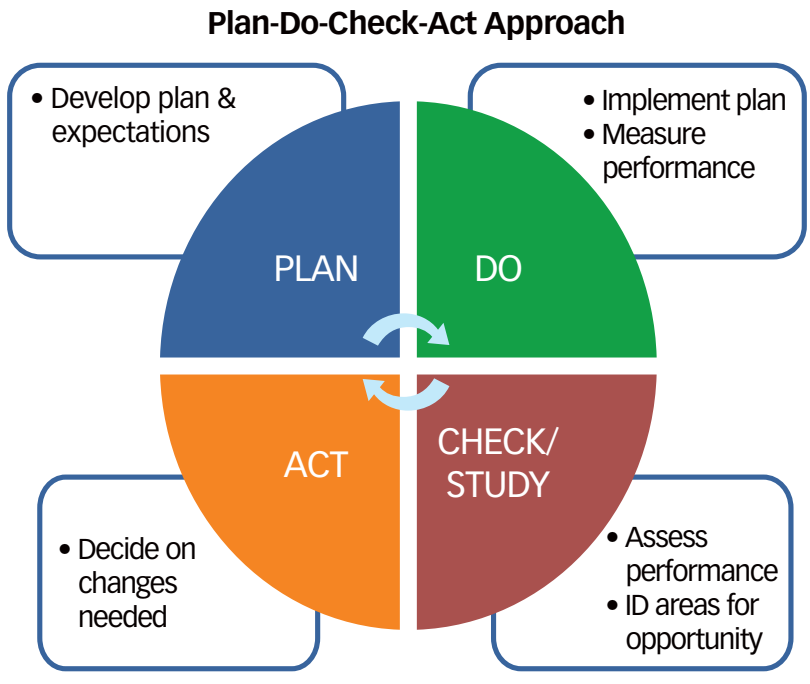
Taking this approach helps stakeholders perform surveillance to assess the likelihood and severity of potential problems. Consider the two families driving across the desert. Does each family's car provide information about whether a potential risk is becoming an issue? If yes, do they know how to interpret the data and when and how to take action?

Too much data

When performing risk assessment, the issue of collecting "enough data" is critical, but collecting too much data, has emerged as problematic as technology adoption accelerates.[11] A recent survey of technology adoption suggests that electronic solutions are in heavy use, with EDC topping the list.[12]

With reliable technology, collecting data is far easier than the paper-driven methods of yesteryear, but this has resulted in excessive data flowing into analytic tools, much of it irrelevant for conducting surveillance. Applying this situation to the drive-through-the desert metaphor, collecting data on the number of fast-food outlets along the route, or ability to receive satellite radio signals, while interesting, is not meaningful for achieving the goal of making it across the desert without mishap. Similarly, the clinical trials industry continues to collect the same data for every trial, mostly in check-box fashion, disregarding its relevance to the risk and performance areas of the study.

Plan Do Check Act Approach



Source: Balanced Scorecard Institute.

Figure 1. Using a risk-based "Plan, Do, Check, Act" model, Medtronic reviewers reduced non-core data elements by 1,360 data points (42%).

Table 3: Too Much Unusable Data

"A company's measurement systems typically deliver a blizzard of nearly meaningless data that quantifies practically everything in sight, no matter how unimportant; that is so voluminous as to be unusable; that is delivered so late as to be virtually useless; and that then languishes in printouts and briefing books, without being put to any significant purpose... In short, measurement is a mess."

Source: Hammer.M. 2001

This morass of information weighs down the risk assessment process, much as it does in other industries. In 2001, Michael Hammer, a management consultant, confronted this issue[13] by honing in on the importance of defining, measuring, and improving processes. He reported that a company's measurement systems typically deliver a blizzard of meaningless data (Table 3). Keith Dorricott made a similar finding and reported that only a small number of items—key performance indicators—need to be measured."[14]

According to a study conducted by the Tufts CSDD, 24.7% procedures performed in Phase III protocols and 17.7% of Phase II procedures per protocol have been deemed "non-core," resulting in the collection of data that do not support primary endpoints, but rather supplemental secondary, tertiary, and exploratory ones.[15] The notion holds true in the performance-metric arena as well, as many organizations collect and report numerous time-related performance metrics, but few quality metrics.

A published Medtronic case study depicts the value of limiting the amount of data collected to what is needed to support primary and secondary endpoints.[16] Medtronic was interested in accelerating closeout of a study with 1,500 subjects conducted at 45 sites. Given Medtronic's monitoring methodologies at that time, Fay, charged with overseeing the clinical trial, estimated it would cost in excess of $21 million to monitor the data and address risk factors, such as substantial numbers of unresolved queries, and a lengthy timeline. Using a risk-based "Plan, Do, Check, Act" model, the reviewers reduced non-core data elements by 1,360 data points (42%), and monitoring efforts focused on 1,556 critical data elements essential for a regulatory filing. Protocol optimization, risk identification, and analysis of case report form data fields resulted in a $19 million cost avoidance for the pivotal trial with savings linked to fewer on-site visits, translating into reduced travel costs and resource demand.

As this case study illustrates, reducing the volume of data collected and defining performance metrics to monitor performance are pivotal to improving processes, lowering costs, and providing the groundwork for risk-based management.

Foundation for risk management and assessment

Competitive and regulatory pressures are pushing risk and compliance to the forefront of operations, forcing stakeholders to expand use of metrics to benchmark their performance. In 2013, both the European Medicines Agency (EMA), and the Food and Drug Administration (FDA) released documents on greater acceptance of risk-based approaches to monitoring, starting from the beginning of a trial.[3,4] The EMA Reflection Paper states that the identification of priorities and potential risks should start at a very early stage, as part of the basic trial design process.

Similarly, the FDA guidance notes that sponsors should be prospective about identifying critical data and processes, and understanding the risks that could affect data collection and performance of critical processes. (Table 4).

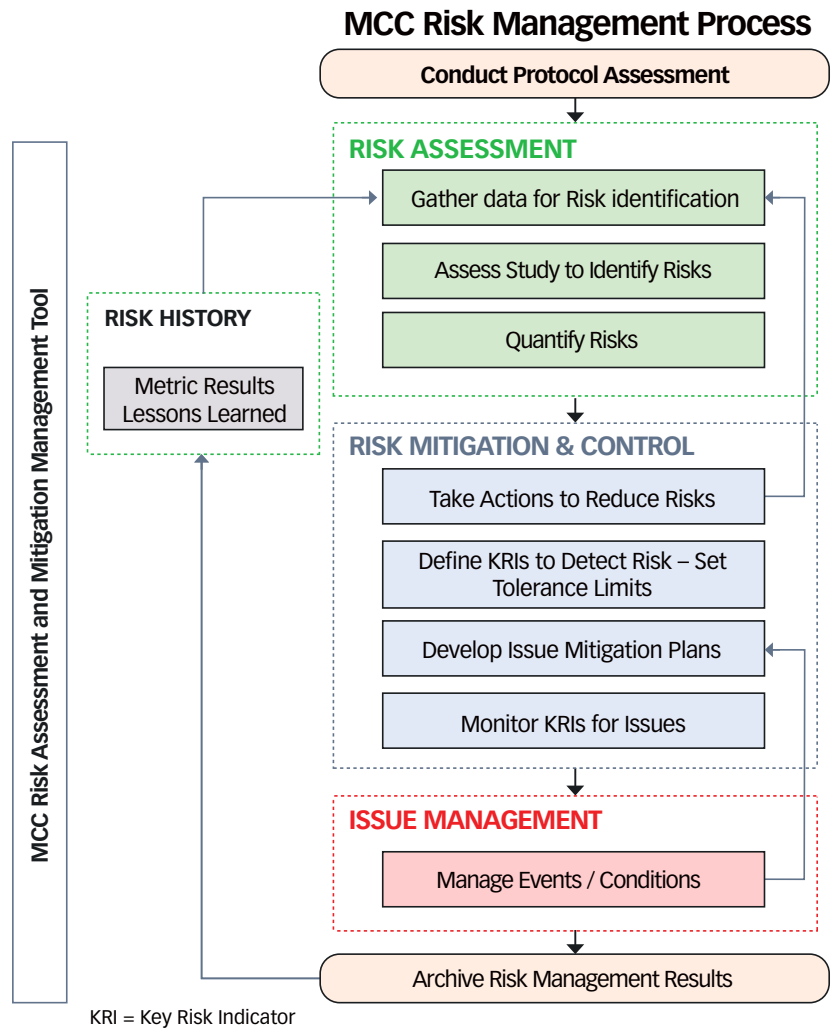
Both regulatory documents comment that the degree of risk is predictable, and, therefore, should be anticipated. Resources should be devoted to mitigating those risks to better protect the well-being of study volunteers.

Consultant Fay concurs that there is a known degree of potential risk. "There are things we encounter in every trial, namely issues related to informed consent, site performance, compliance, time to data entry. Other factors are unanticipated, and the key is to design a risk management plan that addresses risk indicators as they arise over the life cycle of the study. The idea is to identify and prevent likely sources of risks that are critical, particularly the ones that could sideline the research," she remarks. For example, if a site contracted to enroll 10 patients, but after three months, it has not enrolled a single patient, whereas other sites are on track, something is clearly wrong. Did the site lack the correct study population? Was the site unprepared to perform the protocol?

A formalized approach to risk management and assessment aligns with processes developed by MCC. The industry group has worked with sponsors, CROs, central labs, and electrocardiogram and imaging core labs to define an array of performance and operational metrics that serve as the underpinning of risk assessment, mitigation, and management planning. Specifically, MCC has established a peer-vetted set of standardized performance metrics—time, cost, and quality measures—that measure performance throughout study start-up, conduct, and close-out. This approach can lead to establishing industry benchmarks from which organizations can compare their performance.

- MCC proposes starting early with the following:
- Assessing protocol risks during protocol development to mitigate protocol design-related risks
- Conducting a risk assessment of the study plans and near final protocol prior to study conduct to identify risks, mitigate and/or assign appropriate levels of resources to high priority risks

MCC Recommended Risk Management Process



Source: Adapted from EMA Reflection paper on risk based quality management in clinical trials EMA/269011/2013.

Figure 2. Metrics Champion Consortium Risk Assessment and Management Tool, 2015.

Table 4: FDA Comments on Prospective Risk Assessment

Sponsors should prospectively identify critical data and processes, then perform a risk assessment to identify and understand the risks that could affect the collection of critical data or the performance of critical processes, and then develop a monitoring plan that focuses on the important and likely risks to critical data and processes.

Source: FDA Guidance: A risk-based approach to monitoring, 2013

- Establishing plans for responding to risks, and using results to continuously improve the quality of future studies

Moving toward a risk-based approach

In considering why performance metrics should be standardized, Fay observes, "As technology has moved forward, everyone has been looking at dashboards to spot information such as delayed enrollment, inconsistent data compared to other sites, and issues of non-compliance. But, this information alone is hardly sufficient to help stakeholders be proactive about planning for mitigation and resolution. It's more effective to establish a process to identify the drivers of performance for each study, and measure performance in a standardized way," she explains. This predictive methodology is a major departure from the traditional methods of checking all the same boxes, study after study, without regard to the relationship of those boxes to a particular study, or how they work together to flag and mitigate risk. Specifically, all of the drivers of performance need to be identified and weighed for their contribution to performance.[9]

With regulatory pressures for improved monitoring and better risk assessment, stakeholders are scrambling to comply and are doing so by expanding use of technology. Fortunately, electronic solutions are facilitating the flow of data and performance metrics into analytic reporting tools that help answer important questions about trial risk, study progression, and vendor and site performance. Industry is looking at standardization to optimize efficiencies in clinical trial management while making better utilization of resources. The ability to measure these changes and take early action go to the heart of where the industry is heading.

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