THE ULTIMATE STARTER KIT FOR RISK-BASED MONITORING

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Introduction

Clinical trials have evolved substantially since ICH adopted its original E6 Good Clinical Practice (GCP) guidelines in 1996. Trials have become more complex, clinical development is now a global operation and technological advancements are changing the ways sponsors want to conduct trials. In November 2016, ICH released its amended GCP guidelines in an effort to modernize the life science industry's approach towards these practices. The E6 amendment means to encourage sponsors to implement innovative approaches to their clinical development programs, rather than focus on trial processes that impede progress.

In an increasingly digital era, as the business of clinical trials evolves into a more complex, cloud-based realm, placing a high premium on monitoring is most crucial. ICH even specifically called out the industry's misguided focus on the "completeness and accuracy of every piece of data at the expense of critical aspects (e.g. carefully managing risks to the integrity of key outcome data). The paradigm has shifted, and trial leaders are asking, "How would a solid risk assessment plan help define endpoints, promote safety, and enrich overall trial quality?" "How does Centralized Monitoring enable more meaningful conversations between CRAs and sites?" "How are predictive analytics streamlining trial workflow?"

In this eBook, ponder and explore these questions — and many more — while sharpening your approach to risk-based monitoring.

Always (be thinking) about de-risking (your protocol)

Risk assessment is a very important first step in your overall monitoring efforts. Many sponsors look at risk assessment as a routine exercise as part of the trial and haven't necessarily made the connection to monitoring. However, risk assessment is a major driver for your monitoring efforts as detailed in the four requirements in the amended ICH E6 GCP guidelines on risk assessment.

Critical Process and Data Identification. ICH has made clear it expects sponsors to identify the processes and data that are critical to ensure patient safety and reliability of the trial data.

Risk Identification: Sponsors will be expected to identify the potential risks to the processes and data in the trial at both the program and the trial level. Program level risks apply to all protocols for which a compound is being tested.

Risk Evaluation: Sponsors should evaluate risks by:

- The **likelihood** of errors occurring
- The **impact** of these errors in patient safety and data integrity
- The **extent** to which errors will be detectable

Monitoring. ICH expects sponsors to develop a "systematic, prioritized, risk-based approach to monitoring clinical trials. A combination of on-site and centralized monitoring activities may be appropriate. The sponsor should document the rationale for the chosen monitoring strategy (e.g., in the monitoring plan).

There are a number of ways we can craft and maintain a more effective approach to risk assessment, contributing to a better and more streamlined Risk Assessment Plan. Consider the following below when thinking about your own approach to this process:

Cross-functional perspectives are crucial

Risk Assessment must go beyond the concerns of operations or monitoring teams and span the entire organization — because the conversation is no longer just about monitoring. That paradigm has shifted completely.

When we start thinking about central monitoring teams in relation to the IQRMP (Integrated Quality Risk Management Plan), or RACT (Risk Assessment Categorization Tool), we begin to understand how those responsible for monitoring a particular risk in a trial are identifying those risks, and gain insights from them. Since our industry historically uses the term 'monitoring' in relation to CRAs, the word became commonly associated, even synonymous, with CRAs and their duties. When we refer to monitoring, we must look beyond what a clinical research associate (CRA) does, as this is only one component. CRAs perform 100% source document verification (SDV), but this process does not allow them to compare subjects effectively.

When assembling a multi-functional team to develop a risk assessment — considering and discussing everything from chemical compounds to the objectives of that particular clinical trial — each member brings their own expertise, which helps define endpoints, promote safety, and enriches the overall trial quality. Some examples include:

- Supply chain management. Trial complexities can result from preserving a cold chain, or a temperature controlled supply chain. Nevertheless, its management and protection are most important, as it relates to trial end points.

- Statistician considerations. To reach the end point of the trial, we must ensure that we are looking for people from different "pockets," as endpoints are related to the exact right number of patients coming from various subgroups. We're not just including females aged 15-25, but we're also including men and women from other age brackets. This could be a statistician's risk associated with the trial.

When individuals responsible for trial safety, medical monitoring and operations are included in a cross-functional risk assessment, each can share what the trial looks like from their point of view, enhancing the discussion by accounting for and addressing all potential trial risks.

The combined approach of Central monitors, Site monitors, Medical monitors and Data managers is much stronger than review by a single CRA. Looking at trends across the study — at a patient and site level — means you are taking a much more thorough monitoring approach overall.

Change Starts From Within

Keep in mind these various skills needed to conduct a robust and meaningful risk assessment, including:

- Using the tools and resources at your disposal, without re-inventing the wheel

- Training individuals whose core competency is risk assessment, and who can help drive this process across all therapeutic areas
  - **Clinical Operations** professionals are good candidates, as they interact with all of the cross-functional members. They must, however, have a good understanding of the risk assessment goals and must be doing it on a continual basis
  - If not Clinical Operations, another key candidate is one who is **clinically oriented with a clinical background**. It can be difficult to facilitate this process without a clinical background, as these individuals understand when and why certain issues are raised
  - **Senior-level Study Managers or TAs,** or those who are well-versed in study operations. It becomes crucial to keep the "critical issues" list absolutely critical, as to elect someone who knows the difference.

Smaller companies may not have access to this level cross-functional support. At Medidata, our Professional Services team provides support across the board, and derives key insights and knowledge from each trial so managers don't have to start from scratch each time they begin a new trial.

Start Early

Start your assessment early, before you finalize your protocol, at the compound level. When you start researching a certain compound, you will understand certain things about it — its associated bench research, animal research, etc. — and you will therefore have certain hypotheses about risks and side effects. So you start building the risk associated with the compound early in the process, with the idea that all those risks can be floated down to a study level risk assessment so that you can take what you know, and apply it at a study level.

It's not unusual to see a protocol with 10-12 primary endpoints, which can lead to long and tedious trial enrollment. Studies are getting more complex, but using a Quality by Design (QbD is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management) approach allows you to find answers to your questions in the most efficient way possible.

- **Although De-Risking is Key, We're not Always Thinking About how to De-risk the Protocol.** This includes anything you can do to make your data more accessible remotely, from a central monitoring protocol, such as:
  - **Use of central vs local labs** — so you have access to a lab result without needing to visit a site
  - **Endpoint frequency** — your endpoint may require you to look at an image to assess tumor size, for example. If that endpoint is occurring frequently enough, you must review it often enough to draw conclusions early.

- **Better Late than No Risk Assessment.** In the event that you have waited to assess risk in your study, there is still a solid case for doing so. Not doing it at all can lead to costly and time-consuming protocol amendments, which you may not have the budget to manage mid-study.

  We have worked with customers who assessed risk later on in the cycle. Although not a best practice, it's never too late to track and document risks, as the process always helps with compliance. Be cautious to make sure you are not creating additional risks.

  Conducting risk assessment mid-stream may increase risk, because it may change monitoring plans and instantly make different individuals responsible for monitoring indicators of which they were unaware. While it might be difficult to get a central monitoring strategy underway, it is still worth conducting a risk assessment to stay in compliance.

Document, Document, Document

According to the FDA, if you didn't document it, it didn't happen. Regulators do not expect perfect data. They want you to focus on what's important, which, as mentioned, relates to trial endpoints, patient safety, and always ensuring adequate informed consent.

While assessing protocol risk is not a new process, documentation of these cross-functional risks in one consolidated place is new to many organizations. We now better understand what really helps from a monitoring perspective in a clinical trial; which is why we believe so strongly that it's important to do this now.

SDV is not the most cost effective or efficient way to monitor data, and we are learning more and more everyday about what machine learning brings to anomaly detection. Machines can analyze data much more effectively than the human eye and can categorize it much more efficiently.

What should you document?

- First and foremost, **what is the risk, how it is being measured**, and **who is responsible for tracking and mitigating the risk**. Of the tools available to document risk assessment, regulators are in general agreement that ***RACT*** works best, when used correctly.

- When **Transcelerate first developed its RACT Tool**, the feedback was that many people were overwhelmed about where to start. In the multiple iterations released since then, they tool has been simplified. The tool is readily available on their website, along with other directional information into what seems most successful for implementing risk assessment.

- **At Medidata**, we have built our Risk Assessment Categorization Tool based on guidance provided by Transcelerate and ICH E6 addendum. When combined with RACT Professional Services, it truly simplifies the process, keeping in mind the endpoints of the study. This, in turn, provides a blueprint for how to adequately monitor safety and to ensure that subjects are well consented.

Constantly Evolving, Constant Re-evaluation

The result of a proper risk assessment is a fluid document that must constantly evolve, be version controlled, and be re-evaluated. This may include:

- Setting up a cadence for document review
- Turning off certain KRIs when they don't apply anymore — for example: Closing risks associated with enrollment periods, and not trying to assess for them upon the end of the enrollment period
- Re-evaluate your risk plan when the protocol is complete, to ensure everything still applies, is de-risked appropriately, and nothing was missed before beginning enrollment

The Case for Centralized Monitoring

A Renewed Focus on Critical Data

With the rise of **Risk-Based Monitoring**, we must move away from a 100% SDV approach.

We shouldn't be worried about how many case report forms (CRFs) are collected or reviewed. Instead, going into the study, our **thinking should shift towards critical data and critical processes, and any major risks involved.**

With all the resources and money spent on a trial, **we have to use the CRAs in a more dynamic fashion.** The paradigm for the old method could be likened to auditors or fact-checkers checking a box along the path to a trial; now, we have realized there's a lot more we can do to ensure success along the way. If a trial doesn't work, for a patient subset or on the whole, we're finding out **why**.

Ever since reduced SDV has been all the rage, there's been a debate about whether or not sponsors should tell their sites which data points are being source data verified, and which ones are not. **Ideally, sponsors should make it clear to sites what critical data and what critical processes are being reviewed** throughout the study, to promote and ensure data quality.

This way, if errors occur, they can occur elsewhere. More importantly, sponsors should show sites they are partnering with them to achieve the desired outcome for their protocol.

A more targeted approach than simply reducing SDV...

Centralized Monitoring (CM) is ***not a checklist that looks the same at every site.*** It a *fit-for-purpose* — or targeted — approach to each monitoring visit, which goes beyond just reducing SDV. This type of an approach enables us to

- **Make decisions around site visits,** when issues are overlooked
- **Save time and resources** by prolonging time between visits
- **Obtain a more holistic view of the data** than we ever thought possible

In the previous section, we've seen how a Risk-Based Approach begins by de-risking your protocol. Every protocol is unique. Every site is unique. If you determine through your evaluation of protocol and through risk assessment that you don't need this component, and if you can justify this in your plan, then you can proceed.

*But remember: the more patients and sites you have, the longer the study, and thus greater potential for risk.

With CM, you can ask **what discussion CRAs should have with sites based on site** comparisons. Although the same results can be achieved with traditional monitoring, the process takes longer, as you are evaluating one subject at a time.

- **Example:** If a site has a higher-than-average screen fail rate, we may subsequently discover that Inclusion criteria #3 and #4 are exclusionary. Now, instead of blindly sending a CRA to the site, they have a specific conversation that involves a medical monitor.

With CM, you can pinpoint exactly what section of the protocol is causing problems earlier in the study, thereby allowing you to take the right action at the right time.

- **Example:** In a metabolism study, drug efficacy in shown via a lowered HBA1C. A holistic look at the data reveals that patients are getting excluded because of differences in 1 decimal point, and sites are therefore losing half of the patients because of Inclusion/Exclusion criteria. Statisticians can then amend the protocol, expanding the I/E criteria to a wider range of HBA1C values, and thereby allowing more patients into the study while still showing efficacy. If this happened at just one site, you might check the lab equipment, or perhaps look into whether the coordinator was only screening patients whose HBA1C levels were high.

Centralized Monitoring for Smaller Studies

It's natural for a sponsor to consider forgoing CM for a 4-site trial, because it won't cause a huge resource burden on the CRA to visit all 4 sites. This would be a completely acceptable rationale to include in a Risk Assessment Plan for why there is no CM component.

However, a lack of CM — even for smaller trials — increases the risk of misused resources, data anomalies, and chasing operational metrics (SAE rate, time for data entry, etc.). Best practices dictate using CM, even on a 4-site study, to ensure we adhere to the study protocol and look at data across patients from a centralized location.

When discussing your monitoring plan, it can be as simple as looking at electronic data capture (EDC) data to see who has the most outstanding queries and workload based on operational metrics. This is still considered a CM approach, because it changes the way the CRA interacts with the site based on newly acquired information. Historically, the CRA knew when they had to visit the sites (every 8 weeks or so). Therefore, everyone stands to benefit from a targeted monitoring approach that is paired with CM.

Regulation and Centralized Monitoring

While ICH E6 R2 addendum has helped many adopt CM, the FDA is more concerned about seeing protocols and data submitted with errors and trends that could have been avoided; errors identified via a simple analytic tool. Regulatory agencies need sponsors to do a better job of analyzing their own data before it reaches the FDA. ICH E6 is exactly that.

Even if sponsors find issues they can't fix, but have addressed them proactively in the initial FDA submission, they can ultimately save time by eliminating multiple cycle reviews. *You won't be able to fix all the anomalies you're finding, but you are aware of them, and here's the analysis ...* is essentially the purpose ICH E6 is serving.
Therefore, CM has become a rallying cry: "Let's not wait until study end to prepare for FDA submissions; let's do it all during the course of the study, **so we can fix errors in real time and avoid loss to data**, or avoid subjects being dismissed in a data analysis set.

Regulatory guidance dictates that everyone evaluate their protocol; evaluate their study (risk assessment). If after RA you determine you don't need CM, you must document the rationale for why your study did not need such an approach.

Common misconceptions about Centralized Monitoring

The key to a proper CM approach is clearly defining expectations on what it can deliver. This is not about moving from one EDC system to another, or switching between CTMS systems. At best, there are biostats and programmers who build reports and hand off to CRAs and Clinical Operations teams, but no one is sharing the plan, bringing it together, or delegating across different functional teams without stepping on each others toes.

Here are a few common misconceptions about Centralized Monitoring:

Centralized Monitoring is a one-person function. You won't be able to move things for CM until you get buy-in from other groups. CM requires an internal advocate, and experienced vendors like Medidata can help enable sponsors and partners to realize this. It's best to gauge where your organization is in respect to CM: how much interest is there, how many other parties you can bring to the table, etc. You just can't do CM in a silo.

A Central Monitor is a lower cost resource than a CRA. A qualified Central Monitor won't necessarily cost less than a CRA just because they are traveling less. Not just anyone can look at a box plot generated by a statistical tool and determine whether it's a serious concern or a real outlier, and plan a course of action. We must ensure a Central Monitor has the right expertise, is clinically oriented, understands the protocol, and truly grasps what is relevant throughout a trial.

Doubling the CRA as a Central Monitor. We have seen examples where the Centralized Monitoring function was performed by the same CRA who performs on-site monitoring. If you really want to do CM right and leverage statistical tools for advanced analytics, you can't expect the CRA to monitor sites and be able to provide interesting cross-study insights into other sites while on visits to one singular site.

Technology for Centralized Monitoring

Historically, CRAs cross-reference EDC data with CRFs before a site visit, but this view is limited in that

- it only shows data on a patient by patient basis
- it is difficult to see trends and/or draw conclusions from the data
- It limits access to patient or study-wide data, so we can learn from it in real-time

However, in today's world, advanced analytics have made it possible to employ a smarter strategy for analyzing data. By aggregating data that's available through any source: mHealth, wearables, EDC, patient questionnaires, lab data, etc., and formatting it to help identify trends and consistencies/inconsistencies, we can realize a more holistic approach to the data.

FDA and EMEA regulatory bodies decree that we must evaluate every protocol. Medidata asks, "Now that you realize that you have to do it for every study, can you handle the volume and is it actually giving you what you want?" The focus is less on fancy tools, but rather are you looking at data holistically?

Advanced Data Analytics is replacing predetermined SAS reports and J-Review reports that programmers were building to ask specific questions, expecting specific answers for almost anyone (eg: KRI dashboard). You don't necessarily know what you're going get back from these advanced analytics tools, because they can find both known as well as unknown risks.

This is new data that our industry has never worked with before. Biostats may have seen it, but making decisions and course corrections in real-time is new. Not everyone knows where this data and tool and work should land within the organization. Medidata has worked with a number of customers — both partners and sponsor companies — to help build skillsets, job descriptions, and show how CM could fit in their organization.

It is important to choose a vendor that has experience with many customers, has failed fast, and knows what success looks like; someone who has the expertise and time to work with the customer to ensure their organization is ready to use advanced analytic tools, and understand the infrastructure and unique workflows.

We're working with partners on this, as well and helping to build out their organizations with such talent — than when sponsors tell us that they're unable to find such skillsets, we can recommend partner orgs that have these capabilities, have already gone through the accreditation process and have the skillsets, if you'd like to work with them.

Impact of RBM on Site Monitors

As this risk-based monitoring approach gathers momentum, we will start to see monitoring teams evolve from box-checkers to partners, advocates and strategists: developing relationships with sites and jointly deciding how to increase efficiency for the sponsor and site. The important question to ask now is, "Can site monitors impact data quality?"

From a regulatory perspective, both ICH E6 R2 guidance, as well as the Transcelerate definitions of a risk-based monitoring approach are mainly emphasizing the ***maintenance of quality*** throughout the clinical trial. As a result, it is no longer an option to exclude data quality from a site monitor's roles and responsibilities.

The more we focus on data quality, the greater the impact on the site, sponsor and trial overall. Targeted communications and interactions with study sites also leads to increased efficiency, performance, and ultimately data quality. Examples of such high-value activities include:

- Lead early and informed discussions on the protocol
- Understand root cause of an issue at the site to reduce protocol deviations
- Understand the implication to data quality when queries are closed incorrectly
- Demonstrate how a study site's performance compares to others in the trial
- Ensure regulatory compliance through ongoing source data review (SDR) of study site process

Technology to promote efficiency and data quality

Technologies that site monitors use can help improve data quality if efficiencies and adoption are integrated, and three main criteria that ensure this are:

- **User-friendly technology:** saves the monitor hours when learning and using the new system.

- **Automation within technology:** for example, pull CRF data directly into an MVR, or roll issues and resolutions from visit to visit without consulting multiple systems. Monitors who efficiently write and complete Monitoring Visit Reports (MVR) and follow-up activities can spend more time on quality.

- **Structured data approach to producing an MVR:** ensures consistency in reporting. MS Word, or another word processing software, is, at best, an electronic typewriter without a structured data approach. Using structured data has multiple benefits, including:
  - Data is stored in databases that can be shared anywhere in the world and reused everywhere in the organization
  - Saves time and resources by enabling data flow in, out, and in-between MVRs, allowing monitors to follow-up remotely

Technologies available today, when used correctly, help make the site monitor more efficient and thus enable them to focus on data quality. What's missing ***is the intelligence or the interconnectivity*** between the risk planning technology, and that used for operationalizing these plans.

Bringing it all together

Monitoring in the larger sense, as covered in the first section (**where monitoring is more than just "monitoring"**), requires thinking broadly about various stakeholders now involved and the need help them manage their findings.

Once a problem is detected, we must ensure that it is documented, along with its associated actions and resolutions. Findings must not be confused with tasks-lists that could result from a site visit. It is very important to have a centralized solution in place that can provide appropriate workflows, creating a reproducible and consistent way of creating and resolving findings. This also helps auditors see an issue's entire lifecycle.

In our many years of experience, we have found some common mistakes study teams have made in managing issues and their workflows. Here are the top 3, and why we think there is a better way to handle them.

Using word-processing documents or spreadsheets. These do not provide the same level of global visibility, the ability to categorize issues, or the ability to build out-of-the-box workflows. Also, since a human is required to capture issues and actions, there's always a possibility for error when using a spreadsheet tracker.

Lack of efficient processes or adequate training. Not creating a repeating, reproducible, consistent process for creating issues — like how to automate and review escalation of issues, etc. — can result in delay in documentation or resolution. Similarly, not training the central or site monitor what "an issue" is — and what it is not — results in documenting all findings that do not necessarily impact study outcomes.

Keeping it siloed. The best reporting s done by the individual who reported it, because they're best suited to describe why it is an issue. Not enforcing other roles within study teams to use these issue management systems can result in a lack of detail, or worse; erroneous reporting. If 4 different roles are working on a study, this could result in 4 different types of issue listings that haven't been reviewed by certain crucial parties.

Efficient, centralized management of issues and workflow

The right kind of technology for managing issues and related workflows is a technology that helps get your study inspection-ready. Our industry must be thinking about integrated, cloud-based technologies that can seamlessly interconnect the **Risk Assessment Plan** *with* **Advanced Data Analytics** systems: finding signals, patterns, anomalies or trends *with* **Monitoring Visit Reports.**

This enables workflow visibility — for anyone connected to any/all of these systems — from *create to close* in a centralized fashion. Ultimately, it all boils down to improving data quality, because quicker issue resolution helps achieve faster study outcomes.

Machine-learning is an important component of such a technology. But it is important to think about machine-learning as being beyond the system that makes recommendations based on past behavior around issue resolutions (like Amazon buying history recommending future purchases). What these technologies need to be capable of is **predictive analytics** that can recommend based on the number of times a certain issue occurred and the action that was taken that drove the quickest resolution or even better, the ideal resolution.

This end-to-end technology that provides a centralized repository to manage issues and their workflows is the leap we need to make from today's technology to tomorrow's to support the next generation of clinical trials to ensure high quality, inspection-ready clinical trial data.

In our always developing, ever-changing clinical trial landscape — where new access to more data increases risk and even %100 SDV is not enough — a quality-based approach is vital. A robust risk assessment plan, a more strategic centralized monitoring solution, and newer and more efficient technology are at the heart of this approach, which is helping redefine the clinical trial and ultimately deliver expedited treatment to patients worldwide.

About Medidata

Medidata is reinventing global drug and medical device development by creating the industry's leading cloud-based solutions for clinical research. Through our advanced applications and intelligent data analytics, Medidata helps advance the scientific goals of life sciences customers worldwide, including nearly 850 global pharmaceutical companies, biotech, diagnostic and device firms, leading academic medical centers, and contract research organizations.

The Medidata Clinical Cloud® brings a new level of quality and efficiency to clinical trials that empower our customers to make more informed decisions earlier and faster. Our unparalleled clinical trial data assets provide deep insights that pave the way for future growth. The Medidata Clinical Cloud is the primary technology solution powering clinical trials for 17 of the world's top 25 global pharmaceutical companies and is used by 16 of the top 20 medical device developers—from study design and planning through execution, management and reporting.

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