WHITE PAPER

How To Design A Risk-Based Medical Data Review Plan

In a clinical trial involving human subjects, safety is a two-pronged concern: there's the need to protect those subjects, and the need to protect data integrity.

The role of the medical monitor, a mainstay of the clinical trial team, evolved to address these twin objectives. Modern medical monitors offer a contemporary update on the traditional role, bringing with them a new practice of ongoing medical data review throughout a study's life-cycle, not just at its conclusion. With this update comes improved software designed to help medical monitors quickly identify outliers, patterns and trends through data visualizations. This means a faster road from insight to action, giving the clinical trial team more opportunities to address study integrity in-flight.

Throughout this pattern of continuous improvement, one important factor in guarding patient safety and data integrity has been often overlooked: the medical data review plan (MDRP). Without one, or with one that's insufficient, medical review software struggles to find its usefulness (because it's designed too broadly, without a specific use case) and medical monitors themselves struggle to balance productivity with quality (because they're spending hours manually scouring data, leaving little time for clinical analysis of the data they're reviewing).

In order to empower a new generation of productive medical monitors, we need to agree on the elements of a strong MDRP. Then we need to put that MDRP to work using software designed with those elements in mind.

Anatomy of a Strong Medical Data Review Plan

a) In the Past: Quality by Vigilance

The International Conference on Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) issued is first Good Clinical Practice (GCP) document in 1996. At that time, most source data was reviewed manually. Sponsors paid for clinical research associates (CRAs) to work on-site, verifying the source data in a meticulous, paper-based process. Even with the introduction of Electronic Data Capture (EDC), peace of mind remained an expensive commodity for sponsors, and an elusive one. Like sailors on nightwatch, medical monitors spent hours groping through EDC-generated listings one line at a time, trying to navigate the study towards a safe conclusion.

History shows us what happens when the nightwatch fails to spot that iceberg in the darkness. For medical monitors and (moreover) for study sponsors, the consequences can be equally titanic.

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"For the last quarter-century, medical monitors have been trying to identify signals and draw conclusions from thousands of lines of data in spreadsheets and PDFs," explains Dr. Anthony T. Everhart, owner of Aequanimitas, LLC, a firm that consults on medical monitoring and medical data analysis. "It was expensive, time-consuming, and not particularly well-suited to identifying problem areas."

To be sure, there was help available. Data managers (DMs), for example, supplemented programmable database checks with a level of necessary human oversight. The program could automatically flag data that was grossly out of sync with acceptable thresholds, like a recorded birthdate that pinned a study subject at 1,000 years old. DMs with good clinical knowledge, meanwhile, could notice and query more nuanced aberrations, like a blood pressure value that appeared conspicuously low. Borrowing from their efforts, medical monitors could draw conclusions from data that they knew was relatively clean and reliable.

Things changed as the pharmaceutical industry grew, leading to an increase in the number of clinical trials underway at any given time. Demand for DMs with clinical experience surged, creating a shortage of that particular confluence of skills. As a result, study teams began hiring DMs with strong data management skills but less clinical experience. This has left much of the responsibility for both cleaning and assessing the data on the shoulders of the medical monitor.

The nightwatch sailor comes to mind again, perched alone in his eagle's nest, scanning the ocean. In order to relieve the medical monitor from this difficult and inefficient task, the industry needed a new approach to managing data quality.

b) Today: Quality by Design

The contemporary clinical study environment is rapidly adopting the principle of risk-based planning. This principle introduces an era in which medical safety review, statistical analysis, data management and clinical assessment operate together, identifying and removing risk and enabling quality from a study's genesis to its conclusion.

"The risk-based approach has repositioned data review as a team sport," explains Dr. Everhart. "It puts the sponsor and the clinical trial team at the same table with the shared objective of 'designing out' as much risk as possible at the planning stage, then dealing with whatever risks are left in a strategic and statistically-sound way throughout the study."

In its 2016 update to GCP guidelines, the ICH acknowledges what Dr. Everhart calls a "team sport," and says that this team's objective should be to "decide which risks to reduce and/or which risks to accept." This, says Dr. Everhart, is the essence of quality by design.

"To build a modern data review plan, medical monitors work with the sponsor and statistical analysts to identify the data that's critical," he explains. "They work with the sponsor to design the protocol based on pre-identified risks. They also work with data managers and the data management plan to fill any gaps, reduce any duplication, and develop a strong data review strategy. Finally, they work with the data itself, using all of that planning to monitor for evidence of risks to subject safety or study integrity."

For medical monitors, this approach is liberating. It means they can use visualizations of real-time study data to draw conclusions quickly and accurately, with less time spent reviewing normal, non-critical data. Instead, they're free to devote their time—their scarcest and most valuable resource—to the clinical insights that matter.

c) What Does a Modern MDRP Look Like?

According to Dr. Everhart, a good, modern MDRP has three qualities to which he's assigned a memorable acronym. Build these three qualities into your MDRP, he says, and you'll be S-E-T.

Sufficient. Drop the word "exhaustive" from your lexicon, advises Dr. Everhart. Modern medical monitors should strive for sufficiency instead. This means using risk assessment methodologies to focus the monitor's attention on the data that matters most.

Efficient. Modern data visualization technology, if designed for the medical reviewer's needs, will add efficiency to a sufficient plan. Rather than searching through data line by line (recall the sailor, scanning the vast ocean), visualizations liberate the medical monitor to hone in on what matters—the outliers, the patterns, the trends.

Timely. Historically, medical monitors have been last in the workflow. If the data management process runs long, or the clinical research associates use more time than anticipated, medical reviewers could find themselves squeezed into a white-knuckled 48-hour sprint. A good MDRP prevents this hazard. It establishes a cadence for in-flight medical data review that keeps monitors involved from the start, providing timely advice on the study's safety and integrity.

How To Operationalize Your MDRP

a) First, Visualize Your "Options."

Once your MDRP is "set," you need a software solution that will put it to work. The best of these solutions allows the medical monitor to toggle between perspectives, from a macro view of the study population as a whole to a particular study subject's individual metrics.

And herein lies another useful acronym from the desk of Dr. Everhart. Giving the medical monitor a "zoom" button—that is, providing the means to zoom out to a wide-angle view of the study's data, and zoom in to view an individual subject—is about giving the monitor the O-P-T-I-O-N to reduce data "noise" and reveal insights that matter. That is to say, advanced medical monitoring software uses visualizations to help medical monitors quickly identify:

Outliers. Some outliers indicate a data error, like a blood pressure value inconsistent with life for a subject very much alive. Others are the canaries in the coalmine—the medical monitor's critical safety signal. Moving between the macro and micro view is especially useful for a medical monitor determined to understand what's going on with the population at large and with individual subjects of interest.

Patterns *and* **Trends.** Some of the study's best insights emerge first as a visual pattern in the population data, indicating either opportunity (like a positive response to a drug) or risk (like seeing multiple subjects' white blood cell counts decrease after the eighth day of treatment).

Inconsistencies. With visualizations, medical monitors can quickly identify data that is discordant with the study's details, such as a treatment-emergent adverse event (AE) that is reported to have started two weeks before the study medication was administered.

Omissions. Missing data is a problem for data management. Omitted data, on the other hand, is the medical monitor's baton. This is data that you would expect to see but don't, like a missing AE record for a patient with a very high set of liver function tests.

Non-compliance. Maybe the data reveals an 80-year-old study subject in a study with a cutoff age of 70. Or maybe subjects with a history of diabetes are disqualified, yet somehow three diabetics are in the study. With the right software, the medical monitor can find these violations and proactively ensure that the study itself is saved from noncompliance.

b) Next, Document the Review.

The marriage of purpose-built visualization software and a strong, team-driven MDRP means the arrival of a safer, more quality-focused clinical study. There's just one thing missing to put the sponsor's mind at ease: a way to capture review activities. How can a medical monitor prove that the MDRP, so carefully crafted in the study's design phase, netted a thorough and ongoing review of the data throughout the study's lifecycle?

Queries would help. A query is, after all, an indication that a medical reviewer was there, asking questions. But what if no queries are required? What if the combined strategic advantage of an airtight MDRP and a data visualization dashboard reveals that everything in the study is just right for the moment?

That's where the best medical review software makes another kind of difference. It allows the medical monitor to leave a breadcrumb trail, giving sponsors the documentation they need to feel confident in the safety of human subjects and the integrity of the data.

It works like this: a medical monitor, reviewing the study data from that "macro" view, notices an outlier in the population scatterplot. The medical monitor drills down to that patient's record and discovers that all is well; the data was reported and captured correctly. Using software developed for this purpose, the medical monitor can leave a marker indicating that the data was reviewed, even though (and especially when) it did not reveal anything of concern.

For Dr. Everhart, this documentation stage is the final benefit of a perfect union between modern medical monitors, their purpose-built software solution, and strong, risk-based MDRPs.

"Although the word is in its title, a medical data review plan is more than simply a 'plan,'" he says. "It's a mindset. It's about helping medical monitors perform their job productively and expertly, with a supportive team and well-designed technology. By shifting to this mindset, we'll all benefit from the emergence of more credible, more cost-effective, and, above all, safer clinical studies."

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