Working Smarter with Data to Optimize Onsite Monitoring

Finally, a Dashboard Providing Dynamic Views across Patients, Sites, and Regions

Syneos® Health

Over the past several years, the life sciences industry began monitoring clinical trial data remotely through a centralized review process as part of a risk-based monitoring strategy. This practice reduces the frequency and nature of on-site monitoring performed by Clinical Research Associates (CRAs) – a practice that is costly, inefficient, impractical, and time consuming.

However, the various iterations of the tools available to support remote monitoring have not met all the needs of either Sponsors or Contract Research Organizations (CROs), hindering efforts to adopt Central Monitoring more completely and successfully. Here we review the evolution of Central Monitoring solutions and introduce a new Central Monitoring Clinical Review (CMCR) Dashboard that has the potential to dramatically change risk-based monitoring approaches and reduce costs related to bringing new therapies to market.

The Evolution of Clinical Data Monitoring

To appreciate the value of the latest available solution, which we discuss in detail later, it is helpful to understand the evolution of Central Monitoring technologies and capabilities...

Source Data Review/Source Data Verification

In this traditional method of monitoring clinical data (which is still in use to a limited extent)[1], CRAs travel to investigator sites on a pre-determined schedule to review 100 percent of all patient files. The purpose is to ensure that the site is complying with the protocol and that the data in the medical record was transcribed correctly when it was entered into the electronic case report form (eCRF). This approach, while thorough, has several drawbacks: it is costly, time consuming, and inefficient. And, because there can be a lag time of several weeks between the time the data are recorded at the site and when they are checked by monitors, errors at sites can be systematized and repeated many times over before they are caught and corrected. This can have serious implications for data integrity and patient safety.

Page-by-Page Remote EDC Review

In the last twenty years, with the advent of Electronic Data Capture (EDC) systems, monitors have been able to log into the system to examine the data entered for each patient. This is certainly more efficient than traveling to the site, and it provides a look at the data in real time, so that any errors can be found—and addressed—quickly. However, it is still a very time-consuming process with limited utility; the review can only be performed one patient at a time, one page at a time, over what could be hundreds of pages, per patient. As a result, it is difficult to spot trends even in one patient's history, and nearly impossible to notice trends across patients.

Patient Profiles Review

Patient Profiles are summaries of the available information about a clinical trial subject, generated by various commercially available tools. The output resembles a patient chart and can be used to review safety and efficacy data. It shows all of the relevant information for a single subject, including patient demographics, medical history, exam findings, laboratory results, treatments and procedure results, and Adverse Events (AEs) etc. This is typically presented as a single PDF per subject with multiple pages in that PDF covering the various categories of information. It is possible to use patient profiles to spot trends for individual patients. The system can also be programmed to flag potential issues such as entered values that are atypical or inconsistent.

However, these tools are static, and users must scroll back and forth between PDF pages to compare data in one table to another. This one-at-a-time review of individual patient profiles does not lend itself to identifying trends or making comparisons. So, it is not possible to see how one patient's data compares to that of other patients at the site, country, region or study level.

[1] Sixty-one percent of companies use Risk-Based Monitoring, and those that do may or may not also include 100 percent site data reviews and validations. https://www.acrohealth.org/wp-content/uploads/2019/10/ACRO-RBM-White-Paper-October-2019.pdf

Safety Database Review

Syneos Health has used a commercially available analytics platform, to create dashboards of safety data for the periodic use by medical monitors and safety teams. The platform is also capable of giving remote monitors access to safety data *across a study* as soon as data is entered into the EDC. In contrast to the more traditional Patient Profiles detailed above, the output allows for:

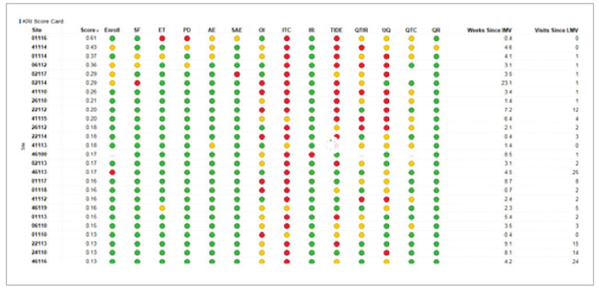
- Viewing data on multiple patients at once
- Analyses at multiple levels—on a single patient, patient groups, a single site or across sites, by region, and by study, for example

This is the first iteration of a monitoring tool that allows for dynamic views; meaning the analyst can filter the views for interactive data interrogation. Reviewers/users have the ability to filter or otherwise dynamically alter the pre-built visualizations to suit their needs according to their area of focus or to explore emergent information. Unfortunately, this database captures only safety information and does not include efficacy data.

KRI Dashboard

Syneos Health developed a dashboard of Key Risk Indicators (KRIs) for monitors' use in identifying site-level risks in the operations of a study. Some examples of these include: Rates of Adverse Events/Serious Adverse Events at a site, enrollment/screening/screen-failure rates across sites, rates of site issues, protocol deviations, data entry lag time, and aging on outstanding queries, etc.

Figure 1: Example of a Key Risk Indicator Dashboard



This dashboard has given monitors the ability to conduct comparisons across sites to determine if one site is a statistical outlier for the metrics under consideration. One site, for example, might show an unusually high rate of protocol deviations being reported compared to other sites in the study.

Figure 1 is an example KRI dashboard displaying the status (signified in Red, Amber, and Green) for each of the different site-level metrics.

This tool provides the operational team with site risk factors for mitigation, but has a limited amount of subject-level safety data available.

Central Monitoring Clinical Review Dashboard

Syneos Health has now developed a dashboard specifically to support clinical reviews by a Central Monitoring team. The tool uses a combination of 18 visualizations and multiple domain browsers so that data from different sources (EDC, electronic Patient-Reported Outcomes (ePRO), laboratory results, etc) can be integrated. The Central Monitoring Clinical Review (CMCR) Dashboard allows for near real-time reviews of data so issues can be identified and addressed quickly, before there is an opportunity for them to be repeated. The tool allows for dynamic views and the type of interactive data interrogations essential to Central Monitoring. With it, Central Monitors can:

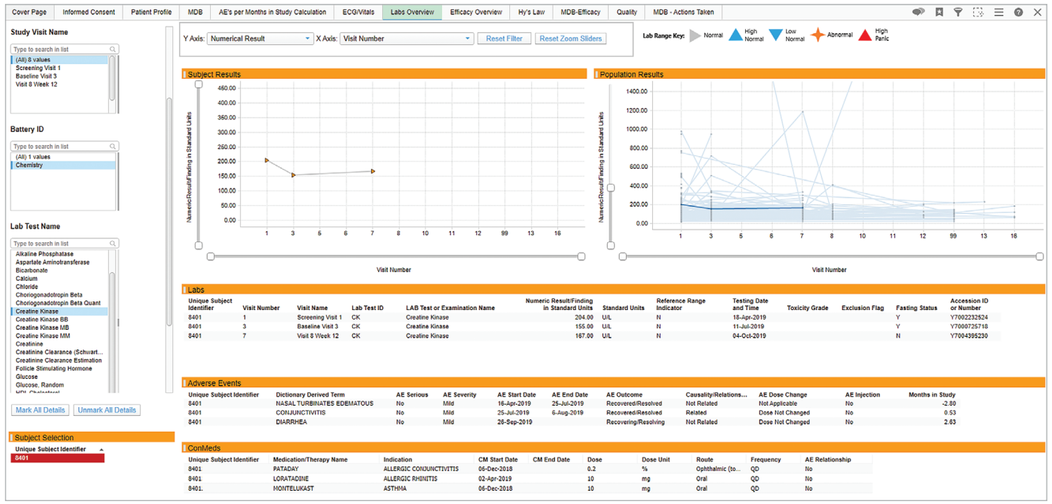
- Review both safety and efficacy data
- Identify trends and deviations within a patient—similar to patient profiles
- Compare a patient to other patients at the same site, country or region—similar to safety review dashboard
- Spot signals that might indicate data are being fabricated
- Monitor CMA productivity via metrics on how long they review each patient's data, how many queries they generate, how many action items they generate

Additional advantage – While KRI dashboards and other statistical tools that compare data across sites and subjects require a large amount of data to become relevant or useful. Often these require a minimum number of sites or subjects before the data can be analyzed/compared. The CMCR dashboard can provide significant benefits even in trials with a very small number of sites or subjects as data is trended within a subject. This makes RBM a reality for previously unsupported trials such as early phase, slow enrollers or rare disease trials.

"Patient-level analytics performed using the CMCR Dashboard change how and when sites need to be monitored in person. Patient-level reviews can become a precursor to onsite monitoring."

The dashboard displayed in **Figure 2** shows the results of a lab test over time for a single subject as compared to the rest of the study population, along with the AEs and concomitant medications for that subject. This allows a reviewer to see if the lab results need further review and how the results compare to other subjects in the study. The AE and concomitant medication information is linked to add additional context in case the lab result should have an expected AE recorded.

Figure 2: Sample Central Monitoring Clinical Review Dashboard



"Central Monitors can assess patients' eligibility, identify protocol deviations, query illogical data and outliers, and evaluate trends and anomalies observed at the patient level."

Table 1 compares the features and capabilities of each of the technological innovations for clinical monitoring discussed here. Clearly, each iteration has been an improvement, and the new CMCR Dashboard in offers the broadest array of capabilities that are closely aligned with monitors' needs.

Table 1: Capabilities Comparison of Monitoring Systems through the Years

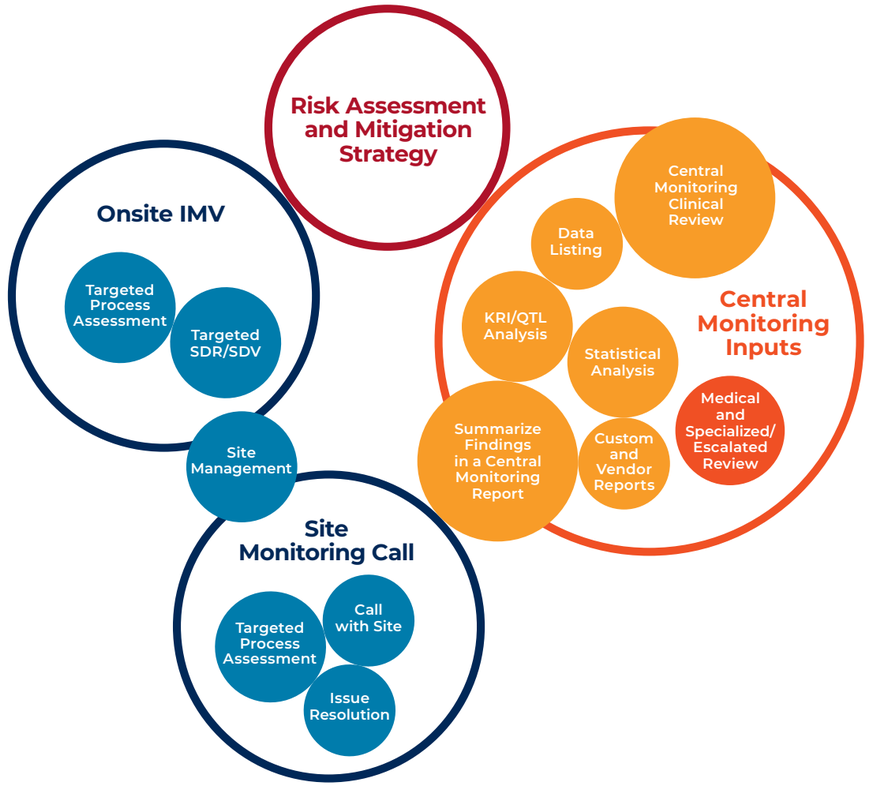
Evolutions in Monitoring

Type of Monitoring	Real Time	Trending	Dynamic Views	Safety Data	Efficacy Data	Operational Performance	Population Comparison
Traditional SDR/SDV				●	●	●	
Page by Page Remote EDC Review	●			●	●		
Patient Profiles				●	●		
Safety		●	●	●			
KRI Dashboard	●		●	● *limited*		●	● *site population*
NEW CMCR Dashboard	●	●	●	●	●	●	●

Enabling a New, Streamlined Monitoring Process

Central Monitoring, as illustrated in **Figure 3**, is one component of an overall Risk-Based Monitoring approach that begins with a Risk Assessment and Mitigation Strategy and includes Onsite, Interim Monitoring Visits and Site Monitoring calls, as needed. The great advantage of the CMCR Dashboard is that the Interim Monitoring Visits and Site Monitoring calls are needed far less often. Patient-level analytics performed using the CMCR Dashboard change how and when sites need to be monitored in person. Patient-level reviews can become a precursor to onsite monitoring and may replace the need for routine onsite monitoring where the majority of time onsite is spent performing source data review (SDR) and source data verification (SDV) activities. When the CMCR Dashboard is used, Onsite SDR and SDV can be limited to only subject visits where eligibility is confirmed, when an SAE has been reported, or a sampling of subject visits where the primary endpoint is captured. The routine subject visit SDR/SDV review strategy can be supplemented by subject visit specific action items and/or queries generated by the Central Monitors in CTMS or EDC and addressed by site staff or CRAs.

Figure 3: Central Monitoring Is One Component of a Risk-Based Monitoring Strategy



Challenges

Adopting the CMCR Dashboard and our subsequent Central Monitoring approach has not been without some challenges, which are worth noting.

Technical Challenges

The hurdles we encountered from a technical standpoint were:

- Obtaining or collecting adequate test data in place to ensure that study-specific elements of the custom output can be produced and tested in advance of when they are needed for review.
- Standardizing output across multiple therapeutic areas and indications. This entailed arriving at a “best fit” or sufficient compromise to enable us to produce output quickly and efficiently that works for the majority of our studies.
- Synching data delivery with review frequency. Typical models involve transactional vendor data (such as labs, ePRO) delivered on a monthly basis, which doesn’t align with the timing of data delivered from an EDC nor with our expectations for review frequency.

Process Challenges

Adopting a new review process involves integrating new Standard Operating Procedures (SOPs) with old ones, and there is always a “chicken and the egg problem” of which ones to implement first. Changes must also be made to the CTMS to accommodate additional tracking and reporting.

Personnel Challenges

Moving from a paper-based process to an electronic process necessitates employing all of the best practices in change management. And, it will be necessary to review various tasks to ensure that there is no duplication of effort. Traditional review of data listings by data management and clinical may need to be reviewed and in some cases may no longer be required.

Anticipated Benefits

While using the CMCR Dashboard to support centralized monitoring is too new to have produced concrete results, we have modeled the impact and generated estimates of the savings. We foresee that changing our monitoring strategy and tactics in this way will result in:

- Decrease in clinical monitoring costs
- Reduction in travel costs
- Drop in time to identify protocol deviations
- Cut in IMVs/site visits
- Reduction in the time to the initial review of subject data
- Decrease in critical and major audit findings

In our initial implementation of the dashboard, we hypothesize that up to 25% of standard programmed listings might be replaced by the more “real time” dashboard reviews.

We are confident that the process will work equally well with small and large studies in all indications and disease types, including early-phase trials and trials focused on rare disease indications.

Conclusion

It is clear that clinical development must become more efficient, and Central Monitoring can be key to cutting both time and costs, *while ensuring patient safety and data integrity.* Strategic use of centralized data reviews to monitor patient safety, protocol compliance, and data integrity are now possible with dashboards. With real-time access to patient data, Central Monitors can assess eligibility, identify protocol deviations, query illogical data and data outliers, evaluate trends and anomalies as a precursor to other monitoring activities. This approach requires companies to rethink their risk-based monitoring processes and procedures, but all indications are that the effort will be well worth it.

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