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Beyond SDV: Enabling Holistic, Strategic Risk-Based Monitoring

How Oracle Health Sciences Integrated Clinical R&D Cloud Platform Supports Risk-Based Monitoring Best Practices

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Table of Contents

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Executive Summary

Long discussed but rarely implemented, risk-based monitoring is coming into its own as an effective and pragmatic methodology to enhance patient safety while delivering significant efficiency benefits through reduced costs and better utilization of resources.

This white paper examines the current state of risk-based monitoring and builds on the extensive work done by TransCelerate BioPharma as well as regulatory authorities worldwide. It reviews the limitations of current eClinical technology to support the monitoring best practices called for, and why sponsors and CROs are shifting to comprehensive, real-time analytics – integrated with trial management, mobility, and data from any standards-based EDC system – as the technology backbone to effectively conduct a strategic risk-based monitoring program.

While we use the generally known industry term "risk-based monitoring" through this white paper, fundamentally what the industry is seeking to do is evaluate quality rather than risk. If the quality of the protocol, sites, eCRF, training, processes, tools, etc., is high, then you don't need to measure everything. So, in actual fact, we are not talking about risk-based monitoring so much as smart or reduced monitoring.

The Monitoring Landscape Today

Pharmaceutical and medical device companies inhabit a highly regulated landscape of protracted, complex product development that is dominated by the imperative for patient safety.

In recent years the complexity associated with clinical trials has increased dramatically, not least because of demands on sponsors to safeguard the well-being of clinical trial participants and the need to maintain the highest levels of data integrity. Other factors include the skyrocketing quantities of clinical data that must be managed and the necessity to plan for long-term trial follow up.

The industry has responded with a regime of frequent on-site monitoring where Clinical Research Associates (CRAs) verify data quality and monitor the trial against formal protocols for non-compliance. Such is the critical importance of data quality that the industry has widely adopted a mechanism of 100% source data verification (SDV) as part of the monitoring process.

Onsite monitoring, however, suffers a number of drawbacks. It is time-consuming and expensive, accounting for 25-30% of the cost of the clinical trial (Eisentein et al., 2005). Study costs escalate when sites begin to rely on monitoring for quality control. In today's multi-site, global trials environment, it is also difficult to determine a cross-site perspective. SDV is an intensely detailed method that is prone to human error and inaccuracies. Moreover, while source data verification assesses site attention to detail, it does not measure clinical competency.

"Increasing use of electronic systems, and improvements in statistical assessments, present opportunities for alternative monitoring approaches that can improve the quality and efficiency of sponsor oversight of clinical investigations."   *- FDA Guidance for Industry*

Regulatory agencies, however, have proven to be surprisingly open to new concepts made possible by advances in information technology and statistical practices. In its Guidance for Industry: Oversight of Clinical Investigations - a Risk-based Approach to Monitoring (August 2013) the FDA describes the growing consensus that use of risk-based approaches to monitoring are more likely to ensure subject protection and overall study quality than routine visits to all clinical sites and 100% data verification.

The FDA proposes risk-based monitoring (RBM) to build quality into the clinical trials system. The FDA encourages sponsors to leverage electronic systems to improve clinical oversight, prevent risks to data quality and safeguard critical processes that ensure patient safety and data integrity. While this guidance represents the FDA's current thinking, it makes it clear that the document contains non-binding recommendations and does not establish legally enforceable responsibilities.

The necessity of a more effective approach to monitoring clinical trials is acknowledged by international regulators. Along with FDA, Great Britain's Medicines and Healthcare Products Regulatory Agency (MHRA) and the European Medicines Agency (EMA) have each embraced the concept of risk based monitoring. The EMA adopted a similar stance in its Reflection Paper on risk-based quality management in clinical trials (August 2011).

An Overview of Risk-Based Monitoring

Risk-based monitoring aims to more efficiently deploy resources across studies based on their specific levels of risk, with the goal of reducing total monitoring resource requirements while maintaining patient safety and data quality. Using a risk-based approach to monitoring clinical trials and verifying data could save companies an estimated $3- $5 billion each year.[1]

The recent FDA Guidance recommends a 'quality risk management' approach to managing clinical trials. Study monitoring is simply one aspect of ensuring clinical trial quality and subject safety. Study monitoring still follows ICH Good Clinical Practice (GCP) principles, which seek to protect the rights and

well-being of human subjects in clinical trials; confirm that reported trial data are accurate, complete, and verifiable from source documents; and ensure that the conduct of the trial is in compliance with the protocol, GCP, and applicable regulatory requirements. According to the FDA guidance, RBM could enhance patient safety, boost quality of clinical data collected, and improve efficiencies.

Risk-based monitoring shifts the focus away from intensive site-based scrutiny and 100% source data verification to centralized and off-site monitoring, with an emphasis on partial (or targeted) source data verification.

To accomplish this, risk-based monitoring uses centralized and offsite monitoring, rather than full on-site monitoring, and partial or targeted source data verification. RBM deploys predictive modeling techniques to assess levels of site risk, and allocate resources to areas of greatest need.

This risk-based approach to monitoring does not imply less vigilance. Rather, it focuses monitoring activities to prevent or mitigate risks to data quality, trial integrity or the well-being of participating subjects. Emerging technologies are making this demanding level of execution practical and cost-effective.

One interesting finding from the TransCelerate BioPharma consortium (a non-profit organization focused on advancing innovation in research and development) was that source data verification may be less critical to lowering risk than commonly thought. Member companies conducted a retrospective analysis to assess queries identified via SDV to find the percentage of SDV-generated queries in critical data. The total was only 2.4%, suggesting that SDV has little impact on the quality of the data.[2]

Since SDV is the most time-consuming activity for monitors on-site (in traditional 100% SDV), by using a risk-based approach to reducing SDV at sites, CRAs can more productively focus efforts on critical compliance activities such as patient-informed consent, completion of essential documents and site compliance with the study protocol and GCP.

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1 Getz, Ken. Low-hanging fruit in the fight against inefficiency, Applied Clinical Trials Online, March 2011

2 TransCelerate Position Paper, May 2013

Common Principles Underlying Risk-Based Monitoring

There are several core principles to risk-based monitoring, as identified by the FDA, TransCelerate BioPharma, and other experts:

» Early and ongoing risk assessment

» Building Quality by Design (QbD) into the study

» Identifying and tracking critical processes and critical data

» The use of risk indicators and thresholds

» Partial source data verification

» The use of centralized, off-site, and adaptive monitoring while the study is underway

Risk-based monitoring dynamically tracks, updates and analyzes data to facilitate continuous improvement programs in trial conduct and supervision. RBM provides flexibility, enabling organizations to shift gears in response to changing circumstances and to proactively plan for future needs. Sponsors and contract research organizations (CROs) have welcomed risk-based monitoring as a way to conduct clinical trials more efficiently and cost-effectively in the face of increased protocol complexities and CRA burden.

Risk-based monitoring can be used to verify assumptions as well, linking protocol objectives to endpoints to distinguish relevant information. RBM can help build quality into the protocol with an emphasis on fit for purpose and lean requirements, leverage analytics to adjust the monitoring plan based on issues and risks identified throughout the study, check for protocol compliance to ensure the adequacy of critical processes and source documentation, focus on conducting effective source data review, and vet reliability of study data and subject protection.

This convergence of regulatory guidance, industry support and emerging technology tools is paving the way for risk-based monitoring to achieve more efficient clinical trial management and safer, higher-quality clinical trials.

Risk-Based Monitoring Best Practices

It's important to keep in mind that risk-based monitoring is a methodology and not a standard, with common principles generally shared across regulatory authorities and industry. One of the main concerns now is how to best operationalize risk-based monitoring, since there is no standard definition or methodology.

The trend has accelerated with several recent developments. Beyond the regulatory guidance mentioned previously, the TransCelerate BioPharma consortium has published a position paper with extensive operational analysis, best practices, and practical tools for implementing risk-based monitoring.

TransCelerate's methodology focuses on building quality and risk management approaches into the scientific design and operational conduct of clinical trials to mitigate risk and detect issues early – or even prevent them from occurring in the first place. Their approach also shifts monitoring processes from an excessive concentration on Source Data Verification to comprehensive risk-driven monitoring

Figure 1. Determining the appropriate critical data items and critical processes to track is key to effective risk-based monitoring

Key risk-based monitoring best practices include:

» Identifying critical data and processes to be monitored (e.g., verification that informed consent was obtained appropriately)

» Conducting a risk assessment to identify potential causes of risks that could affect the collection of critical data or the performance of critical processes, such as evaluating the results of site audits

» Considering key factors such as complexity of the study design, types of study endpoints, and clinical complexity of the study population; geography and other factors such as the experience of partners working with each other, use of electronic data capture systems, the stage of the trial and the quantity of data

» Creating a well-designed and articulated protocol as well as a case report form (CRF) that captures data accurately and facilitates consistent data collection across investigator sites.

A more efficient monitoring process can produce a number of benefits, including faster and better data analysis, lower study costs and increased productivity. In addition, other studies suggest that data anomalies and fraud such as non-random data distributions and fabrication of data may be more easily detected by centralized monitoring techniques than by on-site monitoring.[3,4,5] Above all, more effective oversight reinforces participant and patient protection.

Often overlooked – since they are more difficult to measure – are the qualitative aspects of monitoring. For example, the overall impression a monitor has of a site's quality and preparedness can be a critical indicator in determining that site's future success.

3 Usher, R. PhRMA BioResearch Monitoring Committee Perspective on Acceptable Approaches for Clinical Trial Monitoring. Drug Inf J. 44: 477-483 (2010).

4 Baigent et al. Ensuring Trial Validity by Data Quality Assurance and Diversification of Monitoring Methods. ClinTrials. 5: 49-55 (2008).

5 Buyse et al. The Role of Biostatistics in the Prevention, Detection and Treatment of Fraud in Clinical Trials.Statistics in Medicine. 18: 3435-51 (1999).

One way to address this challenge is to add quantitative data points as yes/no questions to a CRA questionnaire that derive from qualitative measures. For example: Do the site personnel seem to have sufficient understanding of the protocol? Are the source documents readily available and clearly assembled before a site visit?

Risk-Based Monitoring: Enabling Technologies

Putting RBM into practice requires enabling technologies that can provide centralized control and visibility, yet a flexible and immediate response. Technology already plays a central role in the conduct of clinical trials, ranging from electronic data capture (EDC) to wider clinical trials management systems (CTMS), from randomization to interactive voice response systems (IVRS), electronic patient diaries and mobile technologies. It is not unusual for organizations to be using disparate proprietary systems, possibly linked but not integrated. However, few make extensive use of real-time data, and monthly or bimonthly data transfer is still commonplace.

Depending upon a single system such as electronic data capture to conduct risk-based monitoring is insufficient to monitor clinical trials. The evolution towards targeted source data verification and centralized, off-site, and adaptive monitoring has given rise to a new eClinical 'footprint' for a flexible, holistic, integrated cloud-based platform supporting RBM.

This platform enables the building of quality measures into real-time reporting systems; a systematic and proactive risk assessment early on in a trial to predict what can go wrong; the evaluation of study objectives, timelines and enrollment targets to estimate what could impact study subjects' safety; and supports review factors like critical data variables, what labs and procedures need monitoring, and expected adverse events. It would also help delineate how staff should be trained on study procedures, and what could impact the reliability of study results. Critically, this platform also provides the ability to define thresholds for performance as well as triggering events to ensure prompt notification, tracking and follow-up.

The core clinical application areas remain much the same but are now overlaid with a requirement for clinical data management, trial management, and safety – all this integrated into a single overall system that can provide levels of detail upon demand.

The linchpin is a single source of comprehensive operational analytics to inform better design and monitoring of studies. For example, the ability to view detailed and real-time analytics that are pulling data from a CTMS, any standards-based EDC, and mobile monitoring applications can enable an automated workflow where risk indicators are paired with thresholds in the analytics system according to a holistic risk assessment. If a threshold is reached, it triggers an action from the CTMS such as a phone call, a site visit or possibly additional tasks to take place at the next site visit. This is received by the CRA from a mobile app in the field, which can increase responsiveness. Monitors and study managers can follow activities, ensuring that actions are completed and the monitoring plan is followed.
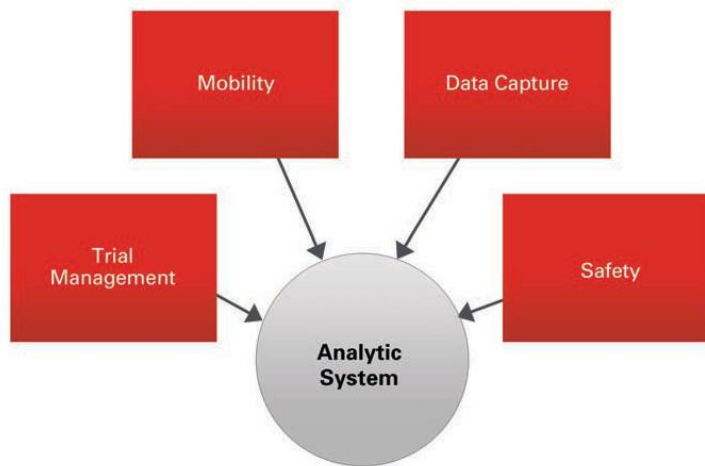
Figure 2. Critical to ensuring quality and managing risk is a comprehensive analytics system, integrated with key systems and with the ability to pull data from any standards-based EDC system.

Innovative mobile apps are emerging that provide CRAs with visibility into real-time trial and site operational data. For example, they can determine, based on critical data and process indicators such as screen failure rates if they can skip a planned visit or make an unplanned visit – all while on the road. CRAs can then leverage this increased mobility to help them manage the on-site visits they do make so they are more efficient and productive, and can adapt more quickly to changes – since "adaptive monitoring" is one of the common principles of risk-based monitoring.

How Oracle Health Sciences "Monitoring Cloud" Platform Supports Risk-Based Monitoring Best Practices

To be successful, risk-based management technologies must execute three functions well: developing an upfront risk assessment that takes into account the critical data and processes involved in the study; designing for quality and consistent application of risk assessment practices across the organization (e.g. people, partners, processes, and investigator sites), tracking trial workflow (the clinical systems, protocol design and trial design); and quickly and easily evaluating the critical data and processes involved in risk assessment.

Oracle Health Sciences leveraged input from our own domain experts, feedback from customers, as well as regulatory guidance from the FDA, the EMA's reflection paper, and best practices advocated by industry thought leaders to develop a holistic platform that supports risk based monitoring of clinical trials. This flexible, cloud-based platform integrates key enabling technologies and has the flexibility to evolve to meet the changing requirements of clinical trials.
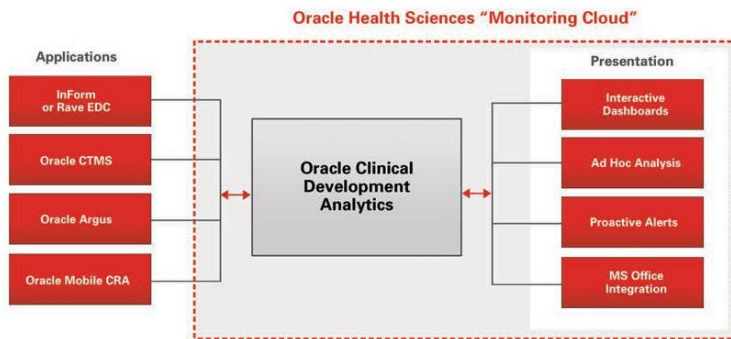
Figure 3. The Oracle Health Sciences Monitoring Cloud offers integrated performance analytics, trial management, safety and mobile monitoring, with the ability to pull data from any standards-based EDC system such as Oracle Health Sciences InForm or Medidata Rave.

Oracle Health Sciences' approach to risk based monitoring leverages analytics to examine and continuously amend the monitoring plan based on issues and risks identified throughout the study. Oracle Health Sciences Clinical Development Analytics (CDA) provides a comprehensive, centralized view of clinical program and study activity across all levels of the organization. This "single version of the truth" has the capacity to integrate data from multiple sources. Oracle CDA combines a series of prebuilt role-based dashboards and reports based on best practices as well as business attributes. Prebuilt extract, transform, and load (ETL) programs source data from Oracle Health Sciences InForm, Oracle Clinical, Oracle Remote Data Capture, and Oracle's Siebel Clinical Trial Management System (CTMS).
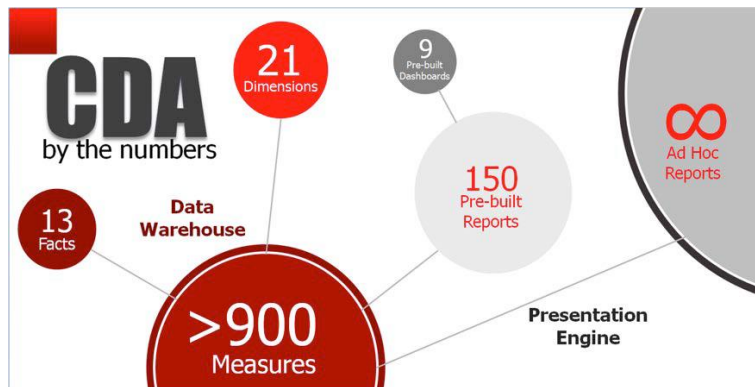
Figure 4. Oracle Health Sciences Clinical Development Analytics offers extensive algorithms and pre-built measures, as well as configurable filters, triggers, and business rules that can be applied to customizable data thresholds – providing you with a comprehensive yet highly flexible platform to support risk-based monitoring best practices.

Central and off-site monitoring, the foundations of RBM monitoring efforts, are dependent on the timely entry of data and query resolution. CDA offers an intuitive and user-friendly interface for the site user as well as real-time reporting for the sponsor and/or CRA to track metrics.

This centralized point of view saves time and clinical analytics labor and reduces manual data processing for operational reports. CDA can identify non-performing sites earlier as well as trends in query reporting, evaluate completeness and cleanliness of data and opportunities for process improvement. CDA can identify and categorize risk levels to drive alerts. For example, a sponsor could trigger a medium threshold to alert the central monitoring committee to review a site or schedule additional site training.

With Oracle Clinical Development Analytics, you can easily set up and monitor risk, for example:

Set Up Study Risk Profile

» Identify deviation from expected/plan so that you can fix issues or revise plan

» Identify patterns so that you can revise plan

Set Up Study-Site Risk Profile

» Identify outliers so you can address issues

» Identify patterns so that you can revise plan

Set Up Site Risk Profile

» Determine whether current performance is outside of the norm for that site (e.g. quartile rank within each study)

» Identify patterns to determine site suitability for new studies

Figure 5. Oracle's analytics platform, combined with out-of-the-box integrations with key clinical systems, provides a highly flexible system to conduct centralized and off-site monitoring in real-time.

Oracle Siebel CTMS leverages the deep functionality and flexibility of the Oracle Siebel life sciences CRM platform to manage trial contacts such as clinical investigators, institutions, sites, and internally assigned study resources – leveraging automated workflows, pre-built templates, and checklists to improve real-time decision-making into study and site performance. The software enables holistic and strategic monitoring while facilitating site payments, processing, and tracking – reducing trial risk and cost while improving quality, compliance, and site performance.

EDC and Targeted SDV

Successful execution of risk-based monitoring involves specifying a data quality plan at the study outset to highlight critical data points and specify SDV strategy. Implementing targeted SDV entails measuring site performance to determine how the current SDV strategy is working.

InForm Data Viewer, InForm Reporting and CDA provide data on demand to help identify site outliers and adjust SDV strategy as appropriate. These allow study planners to build quality into the system through iterating and adjusting study processes according to ongoing monitoring and measurements.

» InForm Platform – provides partial source verification settings by targeting SV at the Study, Site and Subject levels.
» InForm Data Viewer – gives a high-level view indicative of overall study status, providing a view of summarized status of operational data by Site.
» InForm Reporting – Operational Data provides query counts and Query Response Cycle times, including subject enrollment, highlighting outliers and tracking by reason. The clinical data tracks patient safety, adverse events, protocol deviations, missed visits, dropouts, and complex and unintuitive study designs, as well as error rates.

Together with CDA, InForm enables identifying deviations from the expected, patterns and outliers, comparing site performance, as well as determining site suitability patterns for new studies.

Oracle Argus is a comprehensive pharmacovigilance reporting and monitoring platform that provides data on Adverse Events (AEs) and Serious Adverse Events (SAEs) directly to the InForm EDC suite. This enables manufacturers to make better safety decisions, optimize global compliance, and easily integrate risk management into their RBM strategies.

Oracle Mobile CRA is an innovative mobile app to provide real-time trial and site operational data to help CRAs respond to trial developments and make decisions while on the road. Mobile technology drives timely completion of monitoring trip reports which then enables more productive site visits and helps sponsors quickly update site records within CTMS systems. Sponsors can significantly shorten cycle times by obtaining and delivering higher-quality data more quickly.

## Sample Use Case: Supporting a Risk-Based Monitoring Workflow

A. Set up risk indicator triggers in Oracle Clinical Development Analytics according to your risk assessment criteria
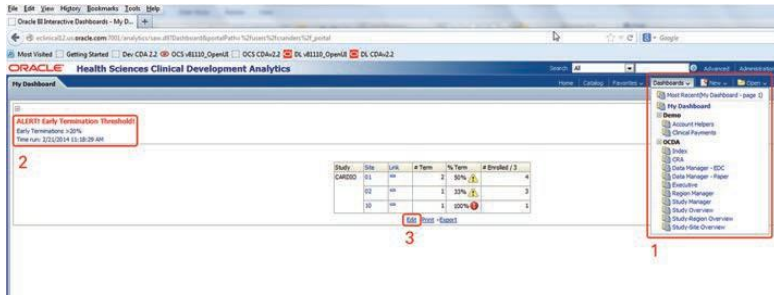

1. CDA provides multiple out-of-the-box CDA dashboards, which are primarily role-based to streamline workflows.

2. Any alert developed will occur in real time as Oracle CDA pulls live data from other clinical systems such as EDC or CTMS.

3. In this case, Study Manager Greta Bauer is going to assess an alert based on updated quality criteria.
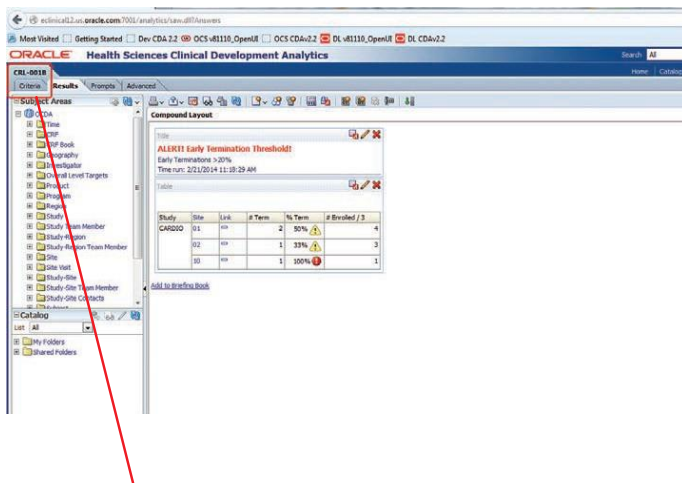
Greta views the underlying criteria for this alert.
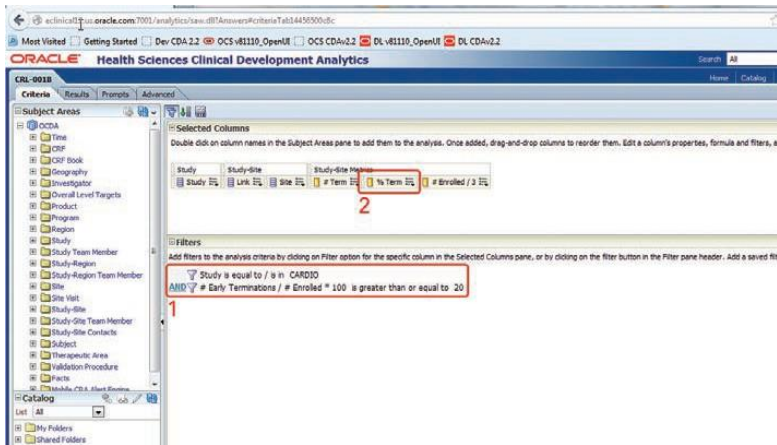
1. She observes that this alert is based on risk indicators and threshold triggers for the CARDIO study. Different alerts and triggers can be defined for other studies.

2. Greta goes to view the Study-Site Metrics
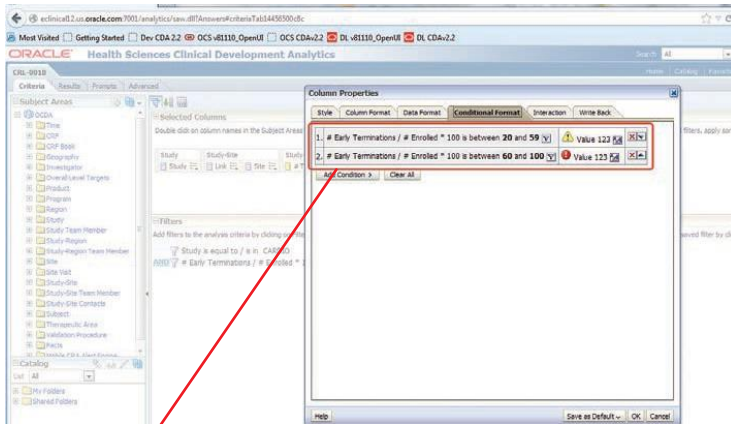
Greta sees that % of early terminations between 20% and 59% would trigger a yellow indicator; and between 60% and 100% a red indicator. She could easily edit this alert but determines it's within guidelines.

Setting up Oracle Clinical Development Analytics to match your risk assessment of critical data and critical processes is fast and easy, and as we've seen can be updated at any time as the trial progresses to reduce risk

B. Monitor performance and risk indicators and trends centrally using CDA embedded within Oracle Siebel CTMS
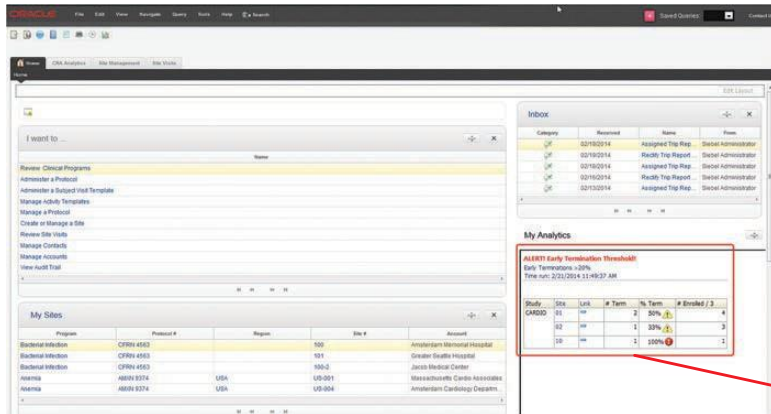
Here we can see the alert working within the home page.

Oracle Siebel CTMS enhances monitoring efficiency and productivity through focused views relevant to each role, specific sites CRAs are responsible for, workflow-driven tasks in one place, and more
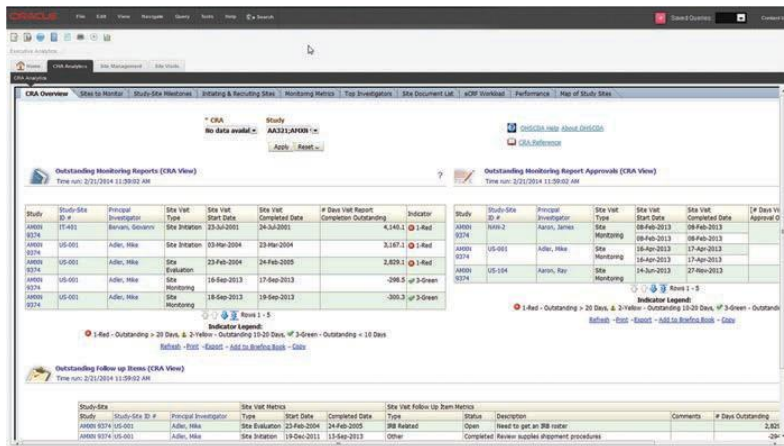
Oracle Clinical Development Analytics dashboards can also be exposed within CTMS based on role to increase monitoring efficiency.

In this example, the CRA Analytics dashboard from CDA is exposed for each CRA, which furthers their ability to manage areas of responsibility on an exception basis to make sure everything is running smoothly and that risk issues can be acted upon in a timely manner.
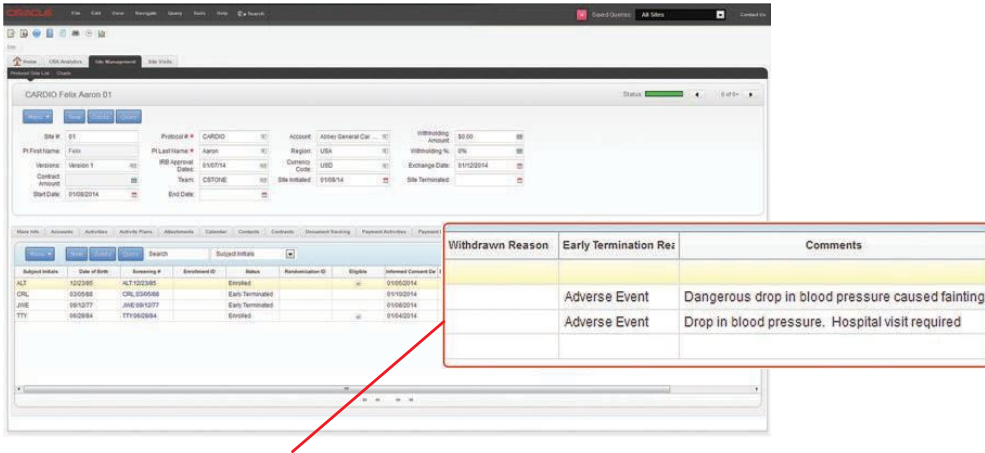
CRA Cindy Stone drills into the alert and in the list of subjects finds that two that withdrew were based on an Adverse Event. The Comments show more details to indicate that there is a clear safety issue.

Based on the action plan defined for this study a site visit would need to be carried out in order to discover the root cause with the PI.
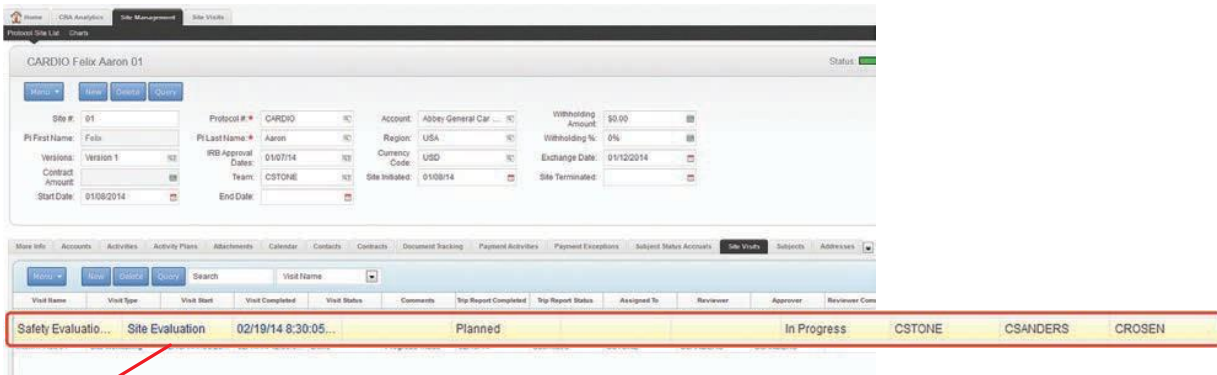
Based on the defined alert and action plan, she'll use the workflows in Oracle Siebel CTMS to automatically set up a site visit.

The next step will be to travel to the site to complete this trip report using Mobile CRA.

C. Make site visit taking advantage of mobile monitoring
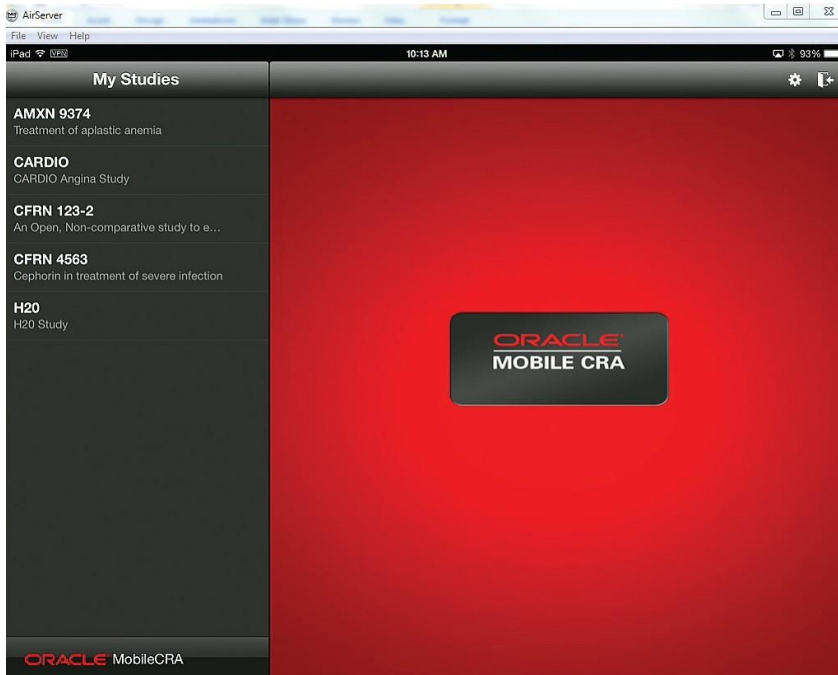
Cindy is now in the field and ready to meet with the PI at Site 01 to follow up on the early terminations. She logs into Oracle Mobile CRA on her iPad to view the list of studies she is responsible for and selects the CARDIO study.
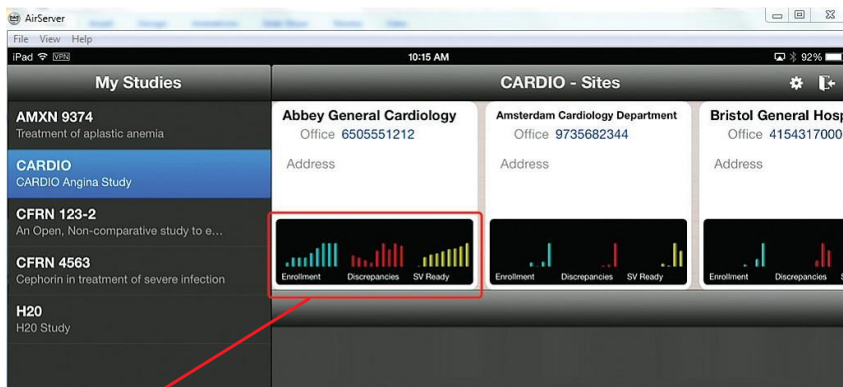
The USA Cardio sites appear in squares indicating the Account (location).

Small trending charts provide a quick visual on several KPI trends, in this case, Enrollment, Discrepancies and SV Ready. KPI's exposed here can be configured as desired.

Drilling into Site 01, Cindy exposes more KPI's and contact details for this site.

Cindy selects Trip Reports from the icons at the bottom

She now has access to all previous trip reports for reference. The trip report that was just planned is positioned at the top.
Cindy clicks on the Safety Evaluation Visit to download it from Oracle Siebel CTMS
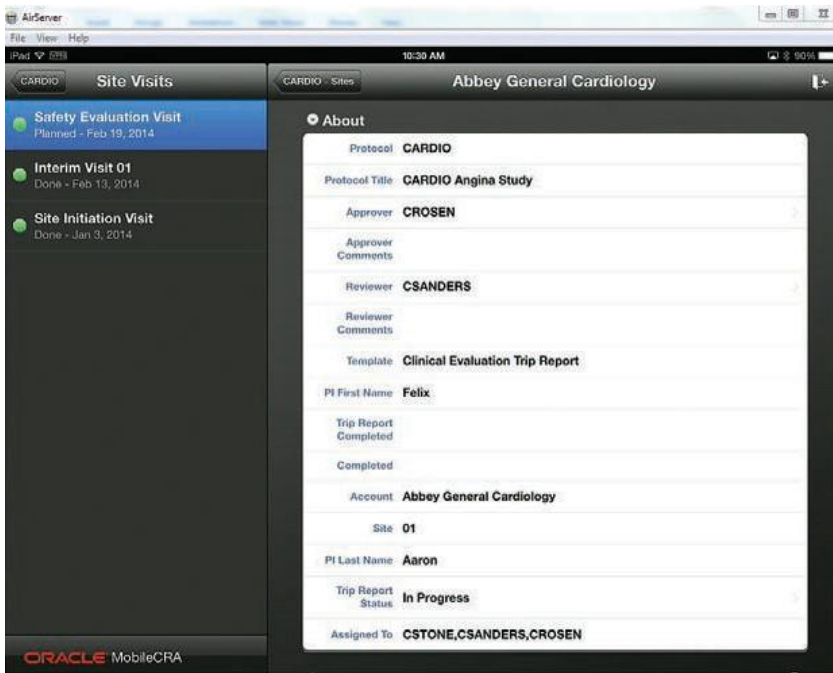
The header information from the trip report appears. Cindy scrolls down to complete the checklist.
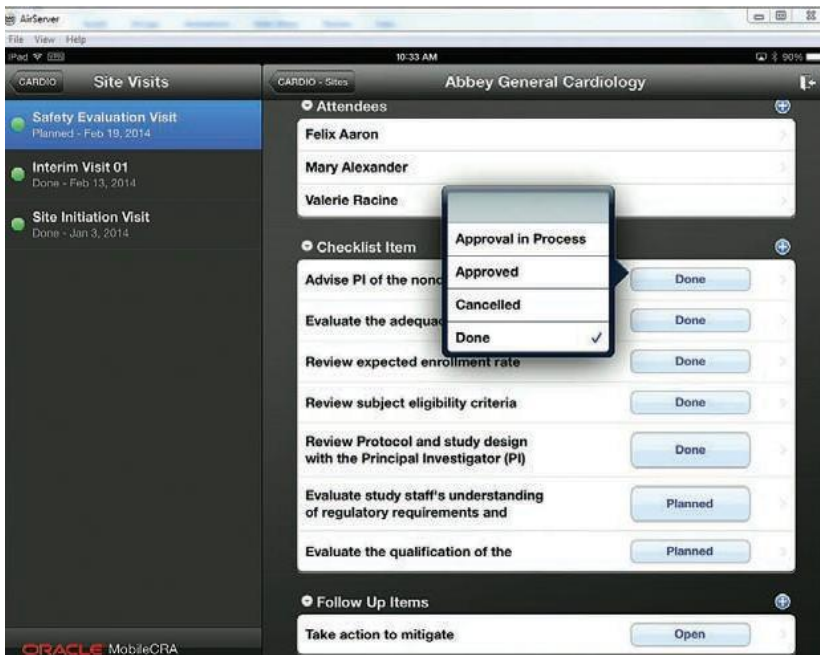
If needed, additional attendees can be assigned based on the Site Contacts list from CTMS. She simply clicks on the "+" icon on the right to select.

As each checklist item is completed the Status can be updated to "Done" by selecting from a list of values. Cindy clicks on the Status button to update it.
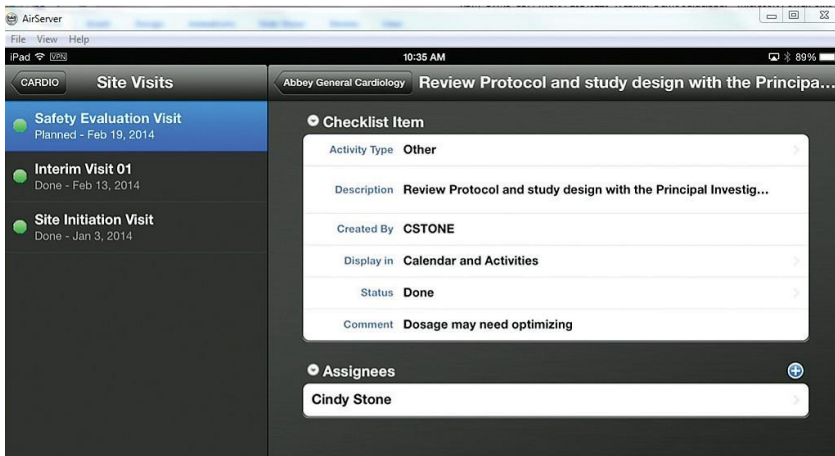
Cindy adds comments that will be helpful in researching further whether a change in the dosage may be needed, or a change in the inclusion/exclusion criteria.
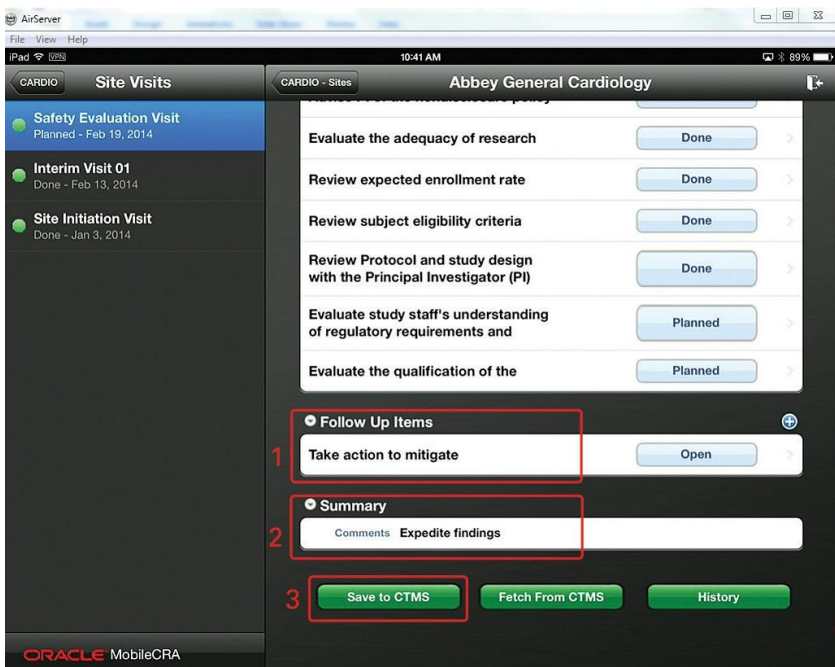
1. Scrolling down further, Cindy can add a Follow Up Item. This will create a trackable activity to ensure that the appropriate action is taken place to close this risk issue. Clicking on the "+" icon allows the appropriate information to be entered.

2. She enters a final summary note to summarize findings and next steps. This will add relevant information for the Reviewer and Approver to close out this site visit.

3. Once done, Cindy simply clicks on the "Save to CTMS" button to return the updates to Oracle Siebel CTMS for finalization, and then submission for review and approval
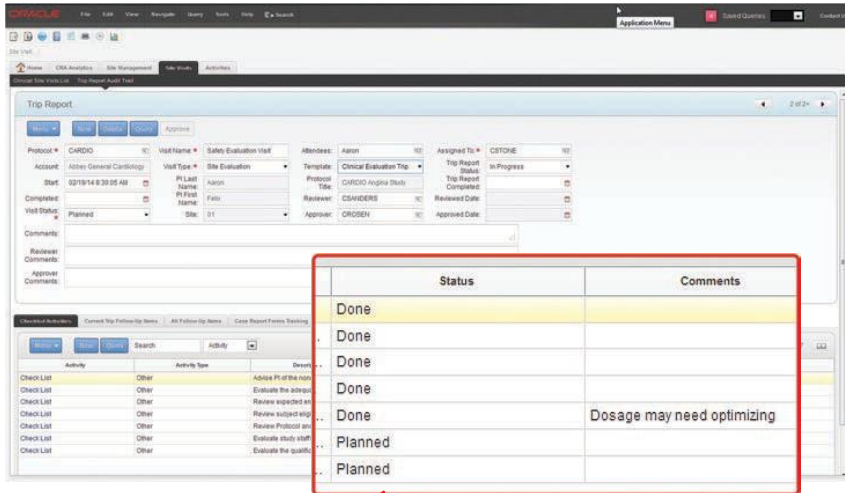
Coming back to Oracle Siebel CTMS, we can verify that the data that we saved from Mobile CRA made it safely. The Status on the checklist items are updated and comments that were entered are in the system.

Information collected and insights gathered from this site visit will help the study team determine corrective action if needed.

Closing the loop, central and targeted monitoring using CDA will continue to ensure that corrective actions were effective.

Summary

As clinical trials become more numerous and complex in terms of structure and data handling, it is imperative to build quality and safety into the trial process from planning to post-market follow-up. Global regulators as well as industry experts recommend the concept of risk-based monitoring to prioritize and quantify risks to data integrity and trial participant safety, while innovative new technologies are now making risk-based monitoring practical and effective.

Oracle Health Sciences is uniquely positioned to empower sponsors and CROs to implement risk-based monitoring to drive clinical trial efficiencies with an emphasis on data integrity and patient safety. Our approach, built on comprehensive, real-time analytics, offers a strategic yet highly pragmatic approach to implement effective risk-based monitoring.

About Oracle Health Sciences

Backed by the resources of a Global 500 company, Oracle Health Sciences offers the industry's most comprehensive end-to-end clinical R&D platform supporting early to late-phase development, safety, and healthcare to help you reduce cost, risk, and time-to-market, while enhancing patient safety. With thousands of professionals in offices throughout North America, EMEA, and Asia, Oracle Health Sciences offers unmatched resources to enable your organization's goals today and in the future

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