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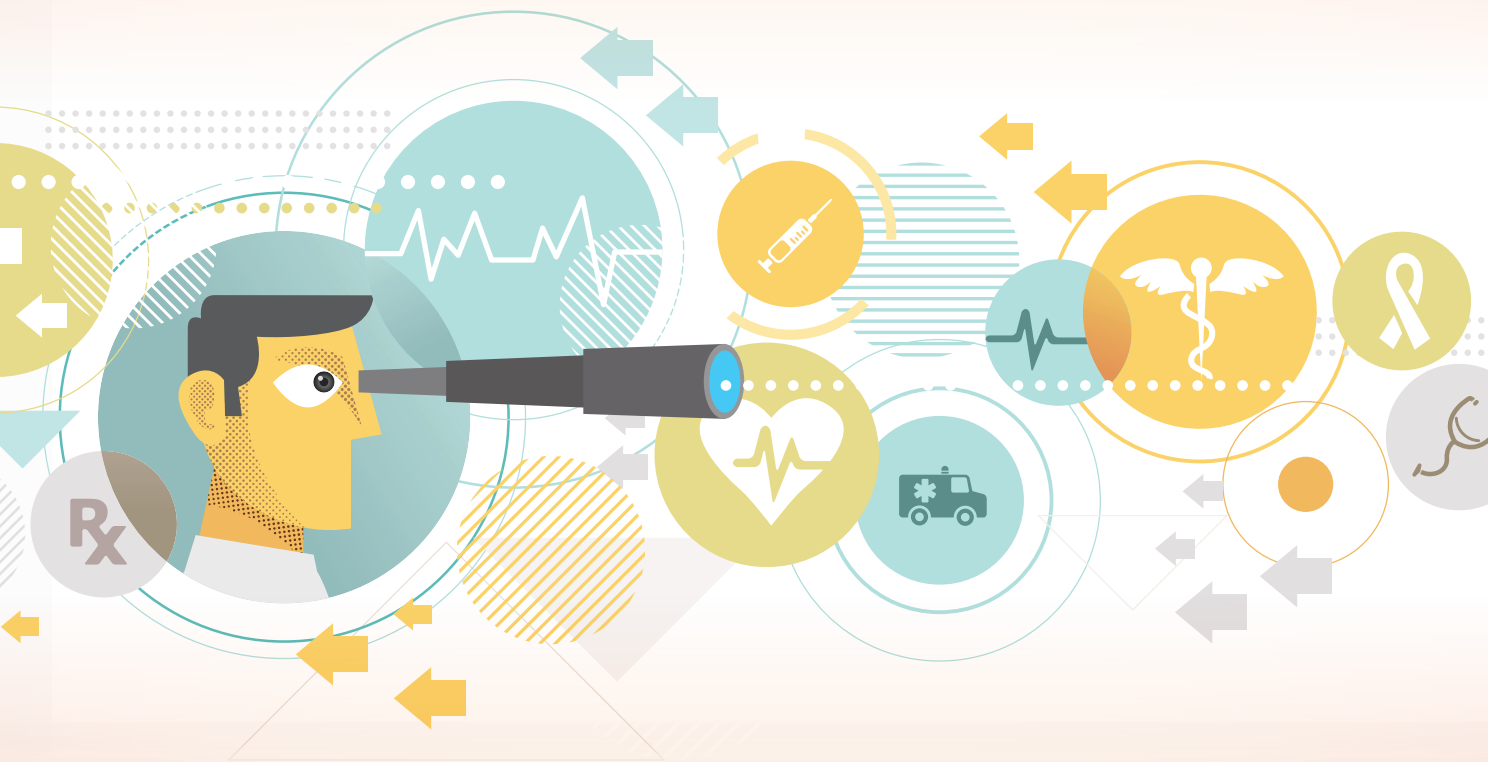

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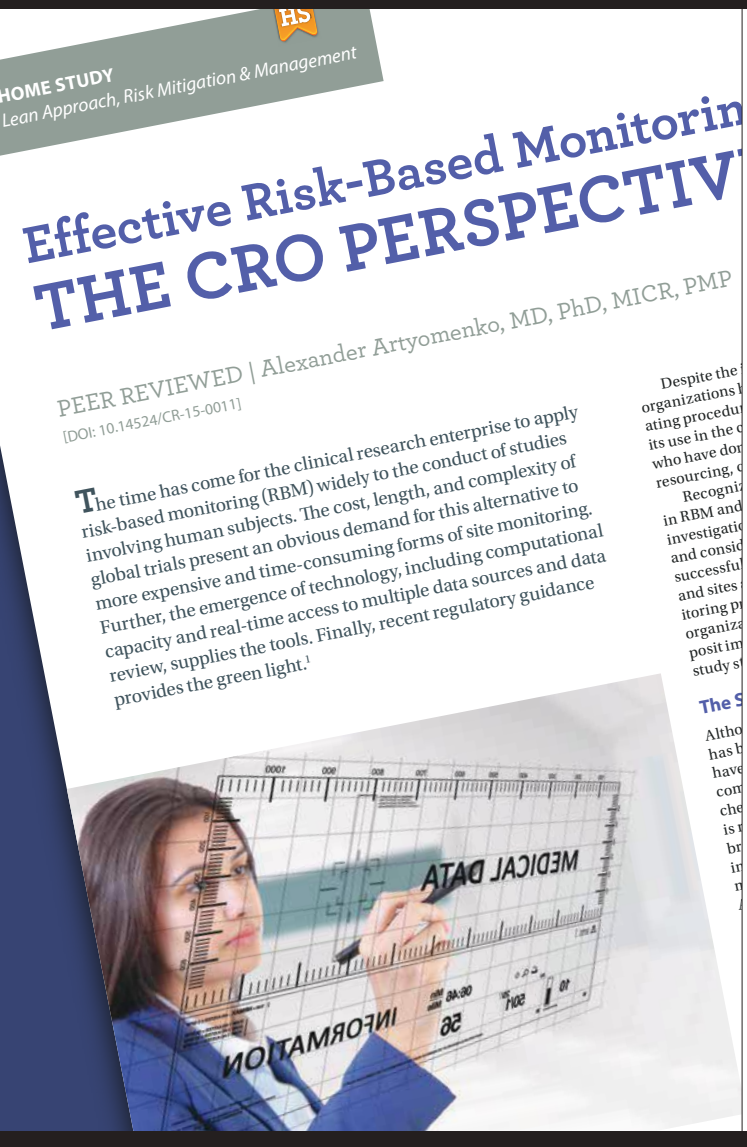
Effective Risk-Based Monitoring:
THE CRO PERSPECTIVE



Despite the industry buzz about RBM, most organizations have yet to develop standard operating procedures (SOPs) and processes governing its use in clinical research. Moreover, those who have done so face new challenges related to resourcing, quality, and change management.

Download this article to learn:

- **The current state of RBM and why it's necessary**
- **Challenges in implementing RBM in clinical studies**
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Changes in RBM: Insights and Observations

Moe Alsumidaie, Lisa Henderson

We gathered our latest interviews, reviews and conference material together for RBM trends.

The realm of RBM continues to evolve; the role of monitors are changing, and the way RBM is incorporated in study design and monitoring plans are reshaping the way clinical trials are executed. Moreover, non-profit organizations are now interacting with regulatory authorities to reform policies. Moe Alsumidaie, frequent contributor to *Applied Clinical Trials*, had the opportunity to speak to Jonathan Helfgott, former Investigator and Compliance Officer at the FDA, about changes in RBM.

Can you elaborate on trends that are occurring in biopharmaceutical quality management systems (QMS)?

I'm seeing trends from a vertical integration perspective, where a lot of models are trying to insource some of the key core activities of developing and managing the day-to-day operations of a functional quality system; it's always going to be driven on the kinds of products that are needed to execute quality systems. So, if you're bundled together on the same product types it's much easier to stay more narrowly focused; whereas if you are managing a more diverse portfolio, you're more likely to rely on outsourcing because the ability and practicality of developing that diverse expertise in-house is difficult.

From a senior management standpoint, the decision making points will drive the quality system. It's almost a given that you're relying on personnel at the front-lines that are doing the actual monitoring, who are developing the reports that are ultimately generated to reflect the overall state of compliance within a clinical trial, or a multitude of clinical trials managed in the quality system. The ability to have access to real-time information through leveraging technology combined with a strategic business perspective allows companies to implement a true quality management system.

How will sourcing models change as RBM gains adoption?

The "grunt work" is what's going to be commonly outsourced, such as source data verification and monitoring visits. But, the people that are getting that dashboard view in real-time, and seeing how many patients are enrolled (a role that merges ClinOps and data management, if you will); that's what's being insourced now. In an outsourced model, we used to think, "okay, I'm just going to let the CROs manage the whole study and gather data;" now it's, "we want to keep our fingers on the pulse of the study." We don't have the luxury anymore of letting it go all the way to the end to figure out who is first to fail. It's a civil engineering concept: you want to fail as early as possible, you want to find out as early as possible if you don't have a high probability of success.

Can you describe FDA's approach towards implementing quality management systems?

As a former FDA investigator and compliance officer, the agency has been trying to adopt its own quality management and systems approach across all levels towards clinical inspections, which applies at the highest level (Sponsors that are conducting clinical research), the applications level (submitted NDAs), and the site level (the individu-

als, the academic universities, and other sites that are conducting research).

FDA has also developed a risk-based site selection tool that stratifies/aggregates NDAs by clinical investigator sites, and the tool is accompanied by a draft guidance - Providing Submissions in Electronic Format–Summary Level Clinical Site Data for CDER's Inspection Planning. This tool allows the agency to use the stratified data, and subsequently, drives decision making when selecting sites for GCP pre-approval inspections. The FDA's ultimate purpose for investigating clinical sites is twofold: firstly, to verify appropriate Human Subject Protections & Data Quality at the site,, and secondly, the FDA tries to establish the overall state of quality for the entire study, as well as potential issues and risk indicators that could be indicative of non-compliance and potential public health issues.

What types of risks/pitfalls do you expect to see as more companies start executing RBM?

Making sure study teams differentiate between establishing, upfront, the critical endpoints during protocol design and monitoring plan setup, and the clinical data that's going to be reflective of the critical safety/efficacy endpoint. If you still treat all data equally, you're not going to be able to leverage the true value that RBM has to offer. In order to leverage RBM, companies need to use decision making based on critical data that's as simple as a reduction in blood pressure, size of wound, and how do patients feel, etc. I find that a lot of companies realize late in the study that it's always these particular data points that are most critical for evaluation. When study teams evaluate fifty other data points and don't differentiate and classify upfront, based on their monitoring plan—that's when they fall in the trap of myopia.

Another pitfall is monitors that are accessing the data in real-time without adequate data training; they don't necessarily pay careful attention to some of the other data trails and when changes are made. As a rule of thumb, you should have 100% QC of any modification made to any data point that's at all reflective or related to any primary safety/efficacy endpoint. The new monitoring role does not only involve looking at the information, but also training themselves on how to think in this new environment; they have to be able to adapt and keep track of any changes that study personnel and sites are making. When you implement a true RBM system, you have to take the best of the old world and merge it with a different mentality and approach. The people, processes, and technology in-place must always complement each other when implementing RBM in any clinical study.

TransCelerate recently announced the development of a QMS Framework and are collaborating with regulatory authorities. Are they on the right track?

Yes, I think TransCelerate, as an organization, is able to leverage the public-private partnership that's been established with the agency, and can serve as a valuable avenue for being able to support adoption and implementation of a quality management system at every level—at the industry level, at the academic research level, and at the agency level. There are other types of public-private partnerships as well, such as Clinical Trial Transformation Initiative (CTTI) that also embarked on similar types of discussions. I think all of these efforts are extremely important in making sure that there is an equal voice, as critical decisions are made that are shaping the future of clinical development policy making.

From the Conference Circuit

At CBI's "Risk-Based Trial Management, Is It Only About Monitoring?" conference in early November, it sought and answered it's own question. Basically no, it's not only about monitoring.

Discussion at the RBM conference has our editorial staff now wondering how we should be defining the acronym RBM. Is it Risk-Based Monitoring or Risk-Based Management? This year's conference proves the discussion has really moved from implementation and monitoring to next steps in RBM: what it means to the quality of the data, and the trial, as a whole.

Not to say that monitoring is not central. Many speakers discussed monitoring as a triad—on-site, remote and centralized—the misconceptions of those legs and how they are evolving, or in some cases, not evolving.

For example, remote monitoring to some sponsors has meant extra legwork for the sites. It means not sending an on-site monitor to perform Source Document Verification (SDV), but for the site to fax in every piece of documentation to a remote location for review. "That was never the goal or intention of RBM," said Jules Mitchel, President of Target Health. Other speakers shared how their entities—sites, CROs, and sponsors—have accepted the change in on-site monitoring as one that empowers the monitor and strengthens the data that sites produce.

Roger DeRaad, Director of Black Hills Cardiovascular Research, expressed his center's acceptance of the change in monitoring. "But we do want to know, just like sponsors do, what the metrics are. We struggle to collect metrics on the things that matter," he shared. Going back, he found a 46% decrease in on-site monitoring activity in a 2.25-year period, 2014 to current. DeRaad said the monitoring change is based on perception: "When a monitor is there it feels like they are there for us. But when it's on the phone, it feels like they are taking our time."

Interestingly, the move away from 100% SDV, while proven in many instances to not be the most efficient or effective use of a monitors' time or for translation into data quality, is not yet fully embraced. Examples included presentations of parallel implementations of RBM vs. SDV (or traditional monitoring approaches) to show improvements, as well as anecdotal information that sponsors and monitors alike still cling to the SDV and static on-site monitoring review plans. A*pplied Clinical*

Trials spoke to one small CRO executive who was attending to get more information and background on RBM. "We are getting ready that [our clients] will want to move to RBM, it's inevitable, but now they still want 100% SDV."

However, many presentations showed a clear path to RBM, and the use of technology to forge that path. Joanne Benedict, Senior Advisor at Roche, who presented a workshop on TransCelerate's view of RBM, said, "eSource will make the SDV and SDR discussion moot. Anything to make the process more automated will be accepted." She added that she was amazed to see what the technology companies have developed in just 18 to 24 months to facilitate that.

Some companies shared that they have implemented or tested RBM tools. Craig Serra, Senior Director and Business Process Owner, Data Management (Conduct and Closeout), Worldwide R&D for Pfizer, described its pilot use of CluePoints' centralized statistical monitoring product. "We wanted to take the CluePoints SMART™Engine for a test drive. The questions were: what use cases do we see for this software and are the statistically significant signals actionable in order to increase data quality?" Serra noted. With the successful pilot behind them, Serra said, "We are actively engaged in how we can include CSM as part of our development operations ecosystem moving forward, as the usage of CSM shows tremendous value in both RBM and data quality oversight frameworks."

Duncan Hall, CEO of Triumph and TRI, an RBM consultancy with RBM solution, noted that smaller firms are struggling with basic implementations and questions where they should start with KRIs. His company is offering companies a free list of the Top 10 KRIs to begin that process. It can be found on our website at www.appliedclinicaltrialsonline.com/rbm. "How many indicators? It's the Goldilocks' question. You could have not enough, which isn't helpful, or too many, which just creates noise." Hall notes that the KRI discussion should be a cross functional one, and one of ongoing refinement.

That sentiment rang true with the other presenters. While there are basic KRIs for every study, there will be indicators that are just predicated on a single protocol or therapeutic area. In addition, risk indicators will change as the trial progresses. What is a signal for a site early in a trial may not be a problem after the signal is detected and the site re-trained on the issue.

Which leads to the protocol. If you think narrowing down the number of Key Risk Indicators is a problem, reducing protocol complexity is an exercise in "the restraint of data exuberance," as explained by Sabrina Comic-Savic, Senior Director of GCP Compliance at The Medicines Company. She presented on the need to reduce complexity in design, setup up, analysis and implementation to achieve Quality by Design in a trial.

For protocol design, that means aligning the design with the practice ie., patient population, medication and timing of the procedures for a site, and reductions in trial-specific interventions. Comic-Savic said that each data variable counts as a data acquisition cost, which goes up exponentially with the number of patients and variables. She said that they aim for 200 to 250 data points to collect as their goal.

Mitchel too is a believer in eSource and of the simple protocol. He said that regulators want to know that informed consent is properly obtained, the protocol is followed and monitored, the primary endpoint is measured and documented properly, that all significant safety events are captured and reported and drug/device supply is properly managed. Mitchel also recommends that both FDA and EMA be involved early and often in an RBM-designed trial.

Excel-Based RACTs Go To The Cloud

TransCelerate has established the industry standard for risk-based assessment tools to assist study teams with defining, categorizing and quantifying clinical trial risk. Since its release, TransCelerate's Risk Assessment and Categorization Tool (RACT) has exhibited usefulness with study teams and has guided organizations, such as Cancer Research UK (CRUK) to adopt their own RBM questionnaires. However, Excel based tools present many limitations during execution.

To elaborate, Artem Andrianov of Cyntegrity, an RBM technology enterprise, recently wrote an article delineating deficiencies with Excel based tools. Most notably, the article argues that Excel-based RACTs introduce subjectivity, difficulty in visualizing study risk, creating challenges with collaboration efforts, lack audit trails, and are not validated.

In order to address these deficiencies, Andrianov, in collaboration with the RBM Consortium, developed a free technology-based RACT tool, @RACT. Moe Alsumidaie has used TransCelerate's RACT on numerous occasions, and has had the opportunity to also access and test out @RACT. This article evaluates his experiences in using @RACT, and delineate its impact on clinical operations compared to Excel based RACTs.

Free RACT: @RACT

Based on TransCelerate's RACT tool, @RACT is a free technology based tool to assist study teams with defining, categorizing and quantifying clinical trial risk. The system features a user-friendly layout (Figure 1) that contains the 13 risk categorization steps, and the ability for study teams to define study Impact, Probability and Detectability (IPD) and risk category completion status. Moreover, the system contains a sliding scale that enables teams to weigh the selected category against other categories.

What is particularly interesting about @RACT is that it enables study teams to standardize risk interpretation via a risk catalogue, which can reduce subjectivity. The tool features some definitions from PPH Plus' risk categorization catalogue, however, study teams can customize @RACT's risk catalogue

Risk Categorization

Source: Cyntegrity

Figure 1. The system contains a sliding scale that enables teams to weigh the selected category against other categories.

to their SOP infrastructures and cultures (if they choose to adopt the system internally). Study teams can also input risk mitigation plans, and elaborate on their rationale for completing individual risk categories.

Once some or all 13 risk categories are completed, the tool can display the study's overall risk assessment. This view contains overall and weighted visualizations based on risk, with high risk categories appearing as larger circles in red and vice versa for lower risk categories (in green). Study teams can also visualize IPD and risk scores for individual categories, and can generate a report delineating the entire RACT strategy. The system also contains an audit trail, assigned personnel tracking, and version control as the RACT is updated throughout the trial.

What @RACT Means for Study Teams

- Reducing Subjectivity. A big challenge with Excel-based RACTs is that they does not provide specific examples of risk categorization. Implementing risk catalogs/definitions through technology can help study teams standardize their approaches towards interpreting risk on an organizational level.
- Better Version Control and Collaboration. Tracking data and versions through Excel is antiquated, not validated, and poses issues with version control. Many cloud-based solutions are emerging to address the need for management to more accurately interpret and access aggregated insights. @RACT's integrated collaborative tools and audit trails for clinical trial risk categorization allows for better version control and collaboration.
- Enhanced Risk Amendments. Oftentimes (if not always) risk profiles change as a study takes course. Understanding how these risks change over time enables study teams to optimize their approaches by prioritizing risks that matter, and downgrading risks that were initially perceived as a priority. @RACT's overall study risk categorization visualizations allow teams to compare how risks have changed over time, and gain an enhanced perspective on the bigger picture across all functions.
- Easy Integration into RBM Systems and Aggregate Reporting. The beauty about technologically based systems is that they can seamlessly integrate into other systems for enhanced risk assessments, tracking, execution, and reporting.

Why is @RACT free? Andrianov said, "We're offering this system for free to improve the overall risk management awareness in the industry. We have similar goals as TransCelerate to propagate proper clinical trial risk planning, but, we also want to enhance operability, quality and ease of use through our technology."

Moe Alsumidaie, MBA, MSF, is Chief Data Scientist, Annex Clinical. Lisa Henderson is Editorial Director of *Applied Clinical Trials*.

RBM Experiences Among European CRAs

Sarah Litterscheid, Christine Künzl, Yvonne Rollinger, Ute Engel, Michael Sigmund, DVM, Brian S. Raftery, Burkhard Breuer, Ludger Beckmann

Survey shows skepticism of risk-based monitoring with distrust of current practices.

The risk-adopted monitoring approach is gaining more attention in the pharmaceutical industry and clinical development. According to a survey,[1] about 87% of the respondents working in Western European pharmaceutical companies or contract research organizations (CROs) currently use or plan to use RBM. However, a widespread ambiguity and insecurity how to perform RBM seems to exist among clinical research associates (CRAs), and also among people designing and implementing RBM. This could result in RBM systems not fully fit for purpose. The German Bundesverband Medizinischer Auftragsinstitute (BVMA), is a federal association of more than 40 German CROs, conducted a survey among European CRAs, monitoring in 22 European countries to determine the status of their experiences and highlight the requirements for an optimized RBM environment.

The questionnaire was distributed in August 2014 by the BVMA via European Clinical Research Organization Federation (EUCROF) to its member companies. CRAs of these companies were asked to complete the survey voluntarily and anonymously. The survey contained 21 questions,19 questions could be answered via tick boxes, often with the option to enter additional comments, whereas two questions were open-ended asking for free text answers. In total, 180 completed questionnaires were received and analyzed in January 2015.

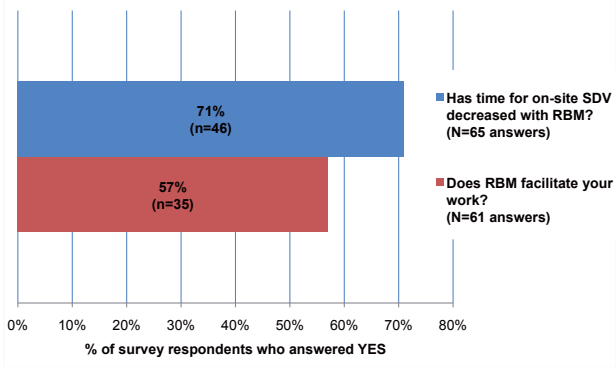
Table 1: Experience and Working Environment of CRA Respondents

	Number of respondents, who.....				
...have experience as CRA	18 (10%) <1 Year	34 (19%) 1-3 Years	35 (19%) 3-5 Years	93 (52%) >5 Years	
... conduct monitoring visits in country*	70 (39%) Germany	32 (18%) Czech Republic	25 (14%) Austria	22 (12%) Netherlands	In a total of 22 European countries
...are employed with	70 (39%) Large CRO	47 (26%) Mid-sized CRO	47 (26%) small CRO	12 (7%) Freelancer	3 (2%) Other
...conduct RBM for*	51 (28%) Large Pharma-Companies	8 (4%) Mid-sized Pharma-Companies	2 (1%) Biotechnology Companies	8 (4%) Academic Institutes	3 (2%) Other
...use RBM in study phase*	9 (5%) Phase I	13 (7%) Phase II	51 (28%) Phase III	13 (7%) Phase IV/ Post marketing	1 (<1%) Other

(N=180), *multiple answers possible

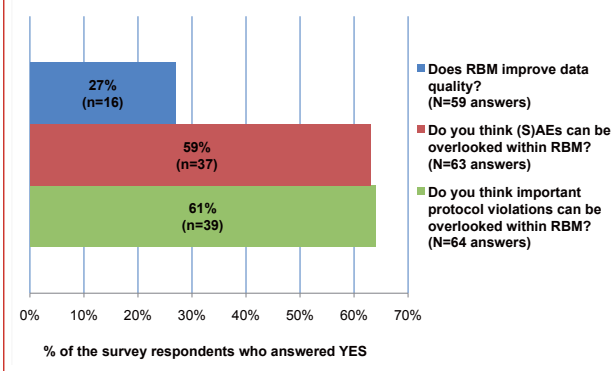
Source: BVMA Survey of European CRA's, January 2015

Figure 1. Working Efficiency with RBM



Source: BVMA Survey of European CRA's, January 2015

Figure 2. Data Quality/Patient Safety with RBM



Source: BVMA Survey of European CRA's, January 2015

Results Analysis

Table 1 summarizes five introductory questions of the survey and gives an overview about the experience and working environment of participating CRAs.

74% (n=134) of responding CRAs (N=180) were familiar with the term RBM and 36% (n=65) already monitored studies using RBM (hereafter labeled as "RBM-experienced" CRAs). 68% (n=44) of those RBM-experienced CRAs (N=65) feel sufficiently trained on risk-based monitoring strategies of the respective trial.

The following sections present the results of the survey structured in three main topics: working efficiency, data quality/patient safety and site contact. Only the RBM-experienced CRAs (n=65, 36%) among all participants (N=180) were asked to answer the RBM-specific questions of these topics. However, not each RBM-experienced CRA answered each of the scheduled survey questions resulting in varying numbers of respondents ("N").

More than half (57%, n=35) of RBM-experienced CRAs (N=61) think that RBM facilitates their work, whereas 43% (n=26) deny this work simplification giving the following reasons among others:

- "More emails and phone calls that are in total more time consuming than dealing with the same work face-to-face."
- "The need to go through complete source documents to check for possible unreported SAEs remains."
- "Only SDV is reduced, other work remains the same."

According to the respondents, detailed instructions for particular situations and standard methods are often missing in the monitoring plans of RBM trials. Another aspect considered as critical for RBM was the fact of lower visit frequency leading to more work during the few on-site visits. In addition, it appears more difficult to meet the decreased Source Data Verification (SDV) criteria instead of doing the routine. As one CRA stated: "The time needed to check what has to be SDV'd is the same as to perform 100% SDV."

Conventional 100% SDV requires between 70% to 90% of the CRAs on-site time and 71% (n=46) of RBM-experienced CRAs (N=65) agreed that this time is reduced within RBM approaches. But independent of the reduced number of critical variables, which have to be verified against source data on site, many CRAs still see the need to go through the complete source documents of a patient to check for possible unreported SAEs, although such a process is often not requested by the RBM monitoring plan. (See Figure 1).

Figure 2 shows the majority (73%, n=43) of RBM-experienced CRAs (N=59) do not believe that RBM improves data quality. Further on about 60% fear that important protocol violations or even SAEs can easily be overlooked when applying RBM.

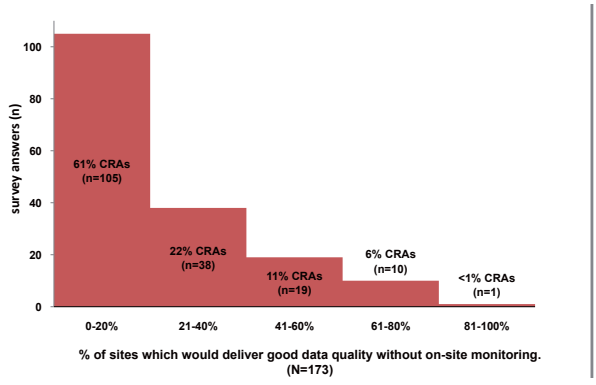
Figure 3 shows a slight majority, 55% (n=34) of RBM-experienced CRAs (N=62) consider that cooperation with sites has become more difficult with the implementation of RBM. The CRAs state that the approach is easier to handle with experienced in clinical trials and sites with dedicated study coordinators/study nurses. However, for sites that do studies besides routine clinical care, the CRAs believe it is difficult to find the resources and time to adequately perform a risk-based study approach. For those sites, the more frequent on-site CRA support seems to be the better solution.

The following citations of single survey responses are exemplary for the CRA opinion:

- "If people are not effectively trained in RBM and informed about the benefits of the new concept then quality might drop by poor implementation and limited escalation of issues."
- "Not all sites are ready for implementation / change of concept."
- "Site staff are not happy with this approach, they want face-to-face contact and they appreciate on-site monitoring because they feel the study data and their study management are being reviewed appropriately that way."

And 61% (n=105) of all participating CRAs (N=173) assume that only 0% to 20% of the sites would deliver good study

Figure 3. Site Performance



Source: BVMA Survey of European CRA's, January 2015

data quality without any on-site monitoring. Additionally, 67% (n=42) of the RBM-experienced CRAs (N=63) feel restricted in their decision to adjust the on-site monitoring frequency for each individual site to an appropriate level in a distinct study.

Discussion and Outlook

The concept of RBM is not entirely new; however it has been formalized and encouraged by regulatory bodies for the first time in 2013.[2,3] The pharmaceutical industry has reacted and steps have been taken to change traditional study management to a risk-based approach and taskforce groups[4,5,6] concentrate on establishing corresponding modern processes. In support of this strategy, some have shown that "only 2.4% of the queries in critical data were driven by SDV, suggesting that SDV has a negligible effect on overall data."[7] Another review article analyzed how many findings identified through on-site monitoring, could also be found with a centralized monitoring method--concluding that centralized off-site monitoring activities could have identified more than 90% of these findings.[8] With evolving technology, real-time data review and analysis becomes easier and risk analyses, as well as trend analyses, can be run across study data or even across studies. A benefit of these analyses is that data anomalies can be seen, which would not be detected by on-site monitoring.

The quality of a RBM study depends, among others, on a well-designed study protocol, which clearly defines study objectives, critical variables and corresponding risk indicators. Risk-based thinking has to start early in the process. The FDA recommends in its guidance that sponsors who consider risk-based approaches for monitoring should "prospectively identify critical data and processes that if inaccurate, not performed, or performed incorrectly, would threaten the protection of human subjects or the integrity of the study results."[3]

One other important prerequisite for a successful implementation of RBM in clinical trials is that modern electronic data capture (EDC) programs distinguish between SDV on site and central verification and offer the opportunity to check large amounts of data centrally and in real-time, so that off-site compliance checks and review for recurrent system errors can be performed. The EMA Reflection Paper illustrates schematically a risk-based quality management system and thereby provides a tool that can be used to develop a strategy for a risk-based study conduct. One important point listed there is that an on-going reassessment of the risks by review of new information emerging during the conduct of the trial (e.g. new investigators or site personnel, new pre-clinical data, new safety data, updated Investigator Brochure, Protocol Amendment) and the outputs of trial management activities (e.g. monitoring output, data management, Data Monitoring Committee Meeting output, audit reports) contribute indispensably to effective risk-based management. Such ongoing, repeated re-assessment of risks and analysis of data is a very important aspect, and maybe has not yet been fully implemented in the initial RBM studies. That might have contributed to a more skeptical perception on the CRA side.

A common pitfall to deal with when introducing RBM in clinical trial management is to think that workload and costs will automatically decrease. However, RBM does not mean to do less, it actually means to do smart monitoring.[9] Data quality in RBM studies depends strongly on how a CRO or a sponsor has understood RBM and has implemented this in appropriate monitoring strategies, tools and training. The idea of "data quality fit for purpose" must be embraced.

The data of the present survey reflect that the currently used RBM approaches achieve their main objective with 71% of CRAs confirming a reduction of SDV on-site time when working in RBM studies. Thus, CRAs can use that found time to get a better oversight on what is happening on-site with regards to patient recruitment, training needs or investigator file handling, and become aware of potential (systematic) issues at the site. It is important that CRAs internalize that on-site time SDV should be reduced, otherwise the other components of RBM will fail.

The current survey data with responses of RBM-experienced CRAs revealed one important prerequisite for a successful RBM study conduct: CRAs and site personnel, both, have to be well-trained to execute a RBM study—not only regarding source data and its verification, but also concerning patient's informed consent process or study document filing on site. Currently, 61% of the respondent CRAs think that only up to 20% of the sites are capable of delivering good study data quality without any on-site attendance of a CRA. Our survey results reveal that it is advisable to only start the RBM process and reduce SDV in a clinical study, when the whole team is well trained on the RBM process, the risk profiles of each site are clearly described and a clear communication plan is established if violations of pre-defined thresholds occur.

The current responses of CRAs suggest that the risk of underreporting SAEs or overlooking protocol violations in-

creases with decreasing on-site monitoring as some subject data and issues will only become obvious during on-site visits. Especially when AEs shouldn't be SDV´d 100% according to the monitoring plan SAEs can easily be overlooked. Therefore, as the survey responses indicate, many CRAs tend to check the entire patient files for (S)AE information. This might reduce the possibilities of time saving for on-site SDV within a RBM approach. When designing RBM strategies, new methods and methodologies must be implemented to ensure proper capturing of protocol violations, or to avoid SAE underreporting. In addition, it is indispensable to have a clear plan which describes what has to be done, if a key risk indicator (KRI) threshold is hit.

In addition, the experience of site personnel becomes more important with less face-to-face training time and collaborative corrective actions and therefore, the experience of site personnel might become an important aspect for site engagement activities. However, it is not common practice in clinical research to involve the sites early on in the process of establishing a risk-based monitoring strategy for a trial, although transparency would probably lead to self-improvement and self-reflection. The clinical sites as important stakeholder in this process should not be ignored.

Using the present survey responses and literature discussions, a site-based adaptation of on-site and centrally monitored data within one study seems to be justified. A flexible frequency of on-site visits and remote monitoring would enable a precisely fitting site- and CRA-specific adaptation of monitoring activities based on study progress and previous performance on site.

In conclusion, a RBM-driven trial demands well-trained CRAs who are able to integrate with a wide variety of information and make informed decisions about what is going on at a site using the risk profile information.

The goal of implementing RBM in the management of clinical trials cannot be a cost reduction by itself but an improvement of the cost-benefit ratio. As clinical trials themselves deal with a large range of different indications and study objectives and cover developmental stages from Phase I to post marketing authorization, no single tool or approach can address all issues. RBM is a very promising approach, which will certainly, once further developed, lead to a more goal-oriented allocation of monitoring resources. Nevertheless, RBM is not a „one fits all"-strategy and maintenance or improvement of data quality and highest patient safety must always be of top priority when new monitoring methods are adopted.

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It Takes a Village to Achieve Risk-Based Monitoring

Penelope Manasco, MD

Appropriate training, plans and clear communication are necessary to help sites and staff succeed.

Monitoring a trial involves many team members with different responsibilities, different skill sets, and often, different line functions. Risk-Based Monitoring (RBM) activities and responsibilities require all team members work together to identify risk factors, review the data, and make decisions about study conduct. Different team members will evaluate different risk factors and sometimes, different team members will evaluate the same item in a different context.

Risk analysis is the first step in developing a Quality Management Approach to instituting RBM. This starts in protocol development, and any opportunity to eliminate risk through the protocol design should be incorporated. Once that has been accomplished, the team must develop risk mitigation plans for all other risk areas which must be detailed, as the team develops its Quality Management, Data Review, Monitoring and Safety Management plans. The Quality Management Plan identifies who will review what data, the timeframe for the review, and the process for presenting findings to the larger project team. The team must identify critical data elements (e.g., primary and secondary efficacy elements), critical processes (e.g., rater reviews), patient safety indicators (investigational product management, dosing, administration, safety assessments), protocol compliance, and GCP compliance indicators. Once the issues have been identified, the team must define the impact, likelihood of occurrence, and how the data will be reviewed and by whom.

TransCelerate released a Risk Assessment and Categorization Toolkit (RACT)[1]. This tool facilitates a cross-functional identification and management approach to risk assessment and categorization, which can be used to assess risk, ideally prior to protocol finalization. Risk can be classified as program, trial, or site level.

Setting risk indicators tolerance levels for trials with greater than 10 sites can be done by using Z scores. This will allow identification of outliers (both high and low) at 2 or 3 standard deviations above and below the mean.

Another method for prioritizing review is to set risk limits for sites. Not all systems have this capability. In setting "risk levels" for sites, using a medium site risk is a reasonable choice for all but sites with new investigators, investigators that are also sponsors, investigators that are extremely busy, or investigators that have had a 483 or other regulatory action. Sites with these characteristics should be considered high-risk sites with more extensive oversight and a multiplier added to the tolerance levels to assure more extensive oversight.

When teams proactively establish what is needed to identify and review high-risk areas, systems (e.g. EDC, reports and data visualizations) can be designed to assure the data are available as needed for review, the person conducting the review is identified, and the frequency of the review is determined. Spending the time to how define how issues will be identified, and to identify actions required based on potential findings, assures team members work efficiently and appropriate

training, if needed, is instituted. Those who provide oversight must understand why a specific issue occurred (root cause analysis) and have the ability to devise plans to correct the root cause and determine that the issue has been resolved (remediation and confirmation of correction). While the remote monitor will primarily identify issues, the onsite monitor must identify root causes at the site level. The onsite monitor will need to research and confirm root causes, design a mitigation plan, and an approach to assess its effectiveness.

The change in timing of the review can significantly affect workflow and team assignments. Traditionally, data managers do not review data until after the monitors have completed their onsite monitoring trips. In RBM, data management review begins immediately. It is not focused only on the edits incorporated into the EDC, but is a more comprehensive review of data across all data systems and a rapid identification of deviations, missing data and assessments, and any other systematic data issue.

Both onsite and remote monitors' activities are also divided differently. The onsite monitor should begin the Source Data Review (SDR) immediately and start reviewing the informed consents. Since the site monitor will perform more management remotely, beginning these processes early should not pose a problem from a scheduling standpoint.

The central monitor evaluates the results of the data manager and site monitor review through trending on deviations and queries in addition to other areas.

Training and Expectations

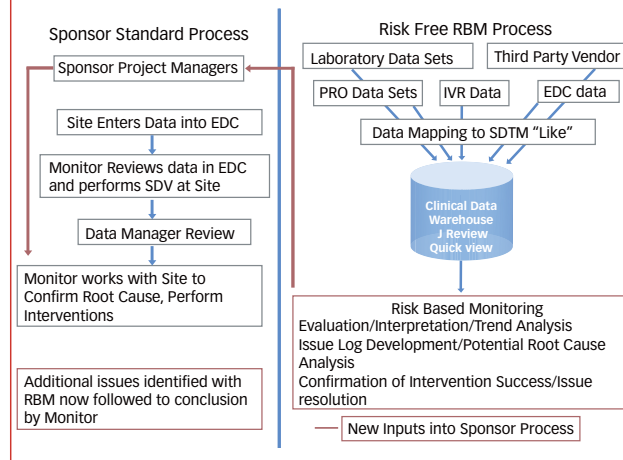
One challenge to adopting RBM involves the way onsite monitors have been trained over the past 10-15 years. As EDC became more prevalent, Source Data Verification (SDV) became the larger focus with less concentration on comprehensively reviewing site performance. New monitor training is needed to support building new, more comprehensive RBM skill sets.

Organizations that have not replaced SDV with the more comprehensive remote review envisioned in the Regulatory Guidance documents present another challenge. Monitors are asked to decrease their SDV of data within the trial, but there is no communication (or no corresponding comprehensive remote review) about how study oversight will be conducted. Simply eliminating SDV and not replacing it with remote study oversight does not comply with the FDA and EMA's guidance document.

Site Interactions

With fewer onsite visits, developing strong site interactions starts during site evaluation. Setting up processes for remote monitoring visits with the study coordinator and principal investigator must be discussed at the time of site selection and incorporated into contracts and other control documents. The sites should receive a full explanation of study conduct from a technology and study oversight standpoint. Satisfying RBM expectations requires rapid data entry, quick query responses, direct data entry, and electronic Investigator Site Files (eISF).

Figure 1. Implementing RBM with Centralized Remote Monitors



Source: MANA Consulting, 2015.

Intensive training at the site initiation visit, with the onsite monitor, can establish a strong working relationship with the site. Since the onsite monitors will not be traveling as much, the monitors can be more available and responsive, alleviating concern that the sites will not have adequate support. When onsite visits are scheduled, time is available to work with the sites on issues previously identified. Our findings confirm that time spent with the principal investigator is more productive when you provide metrics on site performance, rather than just generalities.

More site personnel may have to interact with new technology and perform different functions than required in their traditional roles. For instance, if eISFs are used, site staff must take responsibility for learning how to use technology to upload documents and to generate certified copies. All site personnel will need to access important study documents electronically. Access to the internet within examination rooms may be needed for some direct data entry systems. With fewer onsite visits, teleconferences with the sites assume a greater importance. Assuring study coordinators and principal investigators are available for these calls is critical. Checking connectivity and access to chosen electronic systems is a valuable activity during pre-study visits.

These issues are best approached at the time of study feasibility to assure everyone knows what is expected and study budgets can include these requirements. Recognizing the additional time in study budgets and setting expectations for training, data entry, query response, and regular calls are keys to successful RBM adoption. When sponsors actively engage in implementing RBM, it yields a very positive effect on the site adopting RBM.

Technology

Technology has enabled the remote review of more data and documents. Some technology solutions can be modified to enhance remote review and RBM.

Direct data entry can be accomplished though web-based EDC solutions and tablets. It is imperative that sites have adequate internet access to use tablets for direct data entry, although some systems have offline capability. Sites benefit from eliminating transcription of documents. Monitors and data managers also benefit from having immediate access to the data. Questions that document GCP compliance can be incorporated into the EDC or eSource. These fields (e.g., detailing timing for vital signs, informed consent processes) enable monitors to conduct SDR remotely. Many data managers may not be familiar with the additional questions the monitor will want to have documented, so cross-functional input into the EDC is needed during design. Tablet set up and testing ensures tablets work as needed by the site. The initiation visit should include site training on how to use the tablets to collect all data, including source data.

While no system has "site level" organizational structure,, EDC systems can be set up to collect key site data from the sites. Investigational product receipt and site delegation logs can be designed within EDC systems to support the reporting and oversight of these key components of trial oversight.

When electronic systems are used for data collection (EDC or eSource), no separate manual process is needed for faxing information to the company for manual entry into a separate database; which is the usual practice. A more efficient and effective use of resources is to have the SAE data entered into the EDC/eSource system by the site, then transferred to the safety database, if present. All questions about the episode should be generated as queries in the EDC system so the EDC system contains the most current and complete SAE data.

When data are integrated throughout the trial with the EDC containing the most current version of SAEs, there is less time needed for SAE reconciliation resulting in a shorter time to database lock. In addition, there will be a common understanding of the SAE by all team members. Similar approaches can be used for integrating IVR data into the EDC. When a web services interface from an IVR system to the EDC or inclusion of randomization within the EDC is used, it saves time for the site, allows more workflow control, and eliminates transcription of data from one system to another.

eConsent/Informed Consent Form (ICF) errors routinely rank as one of the top five findings during site audits. The complexity of the informed consent process (e.g., multiple consents required for the study and sub-studies, such as genetic testing), the frequency of amendments, the number of different languages required, and the number of organizations managing the trial all increase the likelihood of informed consent errors.

eConsent systems are an excellent option for large trials that require the use of multiple languages because the translations can be incorporated directly into the eConsent system. This simplifies the process of informed consent review, particularly when there are amendments to the protocol. The systems that provide eConsent can also provide educational materials to help the research subject better understand the process. An audit trail confirms who signed the document and when. Ideally, on the same date the subject signs the informed consent, it is transferred to the EDC system. This data transfer step eliminates the risk for transcription errors. Costs increase when the ICF requires multiple amendments. The benefit is that there is a greater likelihood that the correct version of the ICF has been provided for the site to use because they are loaded and delivered from a central system, which has been through a validation process.

Implementation and Change

There are many different approaches available to implement RBM and there is no one size fits all approach. Figure 1 illustrates one alternative for adopting RBM when working with a standard CRO model with onsite monitors that may not have the training and skills needed for the central analytic role. This approach enables the onsite monitor to focus on site interactions, evaluate root causes for problems, provide interventions, and evaluate its effectiveness. The training requirements are less and the role continues to be focused on site interactions. This still requires a mind shift and emphasis on eliminating SDV and demonstrating how quality will be assessed.

Standard Operating Procedures (SOPs) can also affect implementing RBM successfully or not. Assuring SOPs are aligned with this new approach is crucial and requires a careful review of all SOPs. For instance, review of the processes for database lock must not require that all data is SDV'd. Monitors and sponsors can agree to perform limited SDV and adopt a plan for oversight but if the data management SOPs do not allow for "SDV complete" checkboxes to be empty, the entire process can be derailed.

Change management is a critical step in successfully implementing RBM. If staff does not see how they will fit into the new operational model, they will find ways to sabotage its adoption. Helping staff understand how they benefit from new opportunities or new, expanded roles, creates a favorable environment to adopt RBM.

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Novartis' Adaptive Monitoring RBM Model

Moe Alsumidaie

Novartis relies on a multi-faceted, technology-enabled model with plenty of qualitative input.

The world of RBM is continually changing as biopharmaceutical enterprises are dabbling into different approaches and methods. There are several outsourced models that exist, when approaching RBM, such as integrating cloud-based solutions to provide centralized monitoring teams with analytics, or fully outsourcing RBM functions and technologies to CROs. However, some companies, such as Novartis, appear to be in-sourcing their RBM technologies and functions.

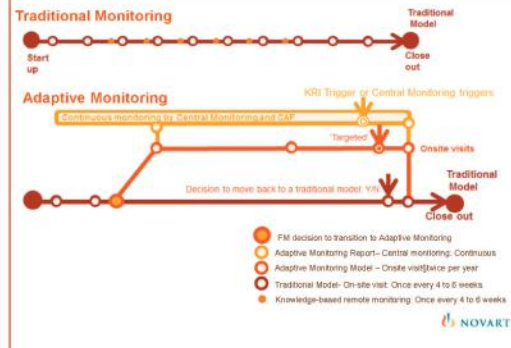
Roland Rich, Quality & Compliance Excellence Operations Expert, DevQA at Novartis, recently elaborated on Novartis' approach towards the centralized and risk-based monitoring function at CHI's Clinical Trial Oversight Summit. Novartis' RBM System is activated by a well-designed RBM process, and an in-house technology system, namely Trends and Pattern Alert System (TAPAS™).

Novartis' Approach on Adaptive Monitoring

Any well designed technology enabled system requires solid and efficient business processes, and Novartis has invested in a simple and adaptable methodology on executing RBM. Novartis' RBM process is multifaceted; they initially focus their on-site monitoring activities during the site initiation phase, and evaluate study site quality specifications (i.e., does the site need training, are they prone to making protocol deviations, misconduct and noncompliance, etc.) (Figure 1).

Once the field monitor familiarizes themselves with the study site's quality, they make a recommendation to the central monitoring team as to whether the site can proceed to continuous centralized monitoring or not. If the site does not meet quality expectations, the field monitor will continue monitoring the site traditionally.

Figure 1: Novartis' Adaptive Monitoring Process



Source: Novartis.

Figure 1. The initial focus is on-site monitoring activities during the site initiation phase and evaluate study site quality.

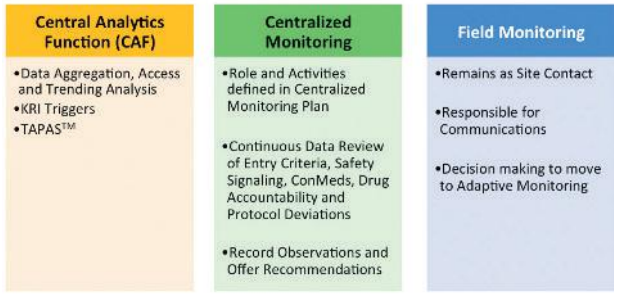
If a site is rolled over to the Adaptive Monitoring category, Novartis monitors the site via its centralized analytics function team (CAF) using mostly TAPAS©, and its centralized monitoring team. This team monitors the data in nearly real time to uncover inconsistencies, deviations, and data errors. Moreover, the team conducts performance assess-

ments to unveil poor performance, potential noncompliance, and misconduct. If key risk indicator (KRIs) thresholds are met, the centralized monitoring team triggers a field monitor to conduct a targeted monitoring visit.

Novartis' RBM Functions

In order to efficiently execute RBM, Novartis has organized its monitoring activities into three functions, as illustrated in Figure 2. and delineates that the centralized monitoring function utilizes the CAF team to access and analyze data quality and site performance data in aggregate, and coordinates with the field monitoring team to qualitatively evaluate site performance and address data discrepancies. This continuous model with separate roles and functions enables Novartis to efficiently oversee clinical trial data quality and monitor site performance.

Figure 2: Novartis' RBM Functions



'Source: Novartis.

Figure 2. Novartis organizes its monitoring activities into both centralized functions and field monitoring functions.

Centralized vs. Field Monitoring

An RBM system is inoperable without specific roles and responsibilities. Novartis has designated specific roles for data analysis and monitoring activities for each function. Naturally the CAF team, mostly supported by TAPAS©, explores through operational data coming from clinical trials looking for risk signals that enables data aggregation for centralized monitoring. Centralized monitors' roles are defined in a centralized monitoring plan. They are continuously monitoring clinical trial data to ensure it is completed and correct as well as they leverage the CAF team to evaluate data consistency and quality, including inclusion/exclusion criteria, AE/SAE signaling, vital sign abnormalities, Concomitant Medication management, drug accountability and protocol deviations. field monitors are responsible for conducting qualitative data assessments including evaluating source document accuracy and completeness, protocol compliance, investigator oversight and drug accountability; ultimately, field monitors spend more time building relationships with sites.

TAPAS©: Food for Thought on the Outsourcing Model?

As mentioned earlier, Novartis' CAF team (powered by TAPAS©) enables the centralized monitoring team to access clinical trial analytics, and analyze site data in aggregate. What is particularly interesting about this model is that TAPAS© is a fully in-sourced system that appears to be compatible with in-sourced clinical trial models, where centralized monitoring and FM functions are employed directly by the sponsor.

So, how can enterprises utilize in-sourced systems, such as TAPAS©, in an outsourcing model? In this case, it's a matter of which functions the sponsor chooses to outsource. FDA's RBM guidance indicates that sponsors should ensure that trials are adequately monitored, and that the sponsor should determine the nature and extent of monitoring with a basis on study objectives, complexity, purpose, blinding, design, endpoints and size. Correspondingly, outsourcing the FM function to a CRO while maintaining centralized monitoring in-house would mitigate oversight risks. Alternatively, sponsors may enable in-house centralized monitoring team functions and models, while allowing CROs to simultaneously activate their RBM technologies, centralized monitoring and onsite monitoring infrastructures. However, this model can pose conflicts in terms of RBM process consistency, and whether outsourcing centralized monitoring is financially feasible.

What Can Smaller Biopharma Enterprises Learn?

Developing a system like TAPAS™ is a massive financial and strategic undertaking, and would not make sense for smaller biopharmaceutical enterprises that run fewer clinical trials (and would not benefit from scalability) to approach RBM like Novartis did. Nevertheless, smaller biopharmaceutical enterprises can benefit from mimicking Novartis' RBM functions (Figure 2), while outsourcing their technology systems to a cloud-based RBM solutions provider.

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