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RISK-BASED MONITORING CONSIDERATIONS IN RARE DISEASES TRIALS

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The industry phrase risk-based monitoring (RBM) initially may appear to be a poor fit with rare and uncommon diseases. However, applying an adaptive and intelligent approach to RBM can lead to a more focused review of critical data elements that are essential to end point assessments. Conventional wisdom in the rare diseases space dictates the use of 100 percent source document verification (SDV) and frequent on-site monitoring. This traditional approach provides a sense of quality and robustness to the monitoring process, but does not address the issue of errors in the data that may occur between reviews or procedures at sites that are not detected until the on-site monitoring event occurs. Adaptive and intelligent monitoring offers solutions to improve data flow, and has more frequent and ongoing assessment of data with trend analysis to detect and prevent issues. Moreover, small patient populations do not deter this approach as the combination of new monitoring methodologies allow for data to be assessed in a number of ways improving the opportunities for detection and correction.

ADAPTIVE AND INTELLIGENT SOLUTIONS APPLIED TO RISK-BASED MONITORING

Over the last decade, RBM has been an evolving platform in the biopharmaceutical industry. In its early stages, RBM was simply a reduction in review of the total number of patients or the case report form (CRF) fields. These early approaches included basic sampling guidelines. For example, monitoring every fourth patient at a site, which does not work well in rare disease studies, where very few patients are enrolled at each site. With the expansion of electronic data capture (EDC), simple SDV sampling assignments could be made in some EDC systems to support a field level sampling approach. However, these had to be determined at the start of the study and could not be easily modified based on site performance or the emergence of new execution risks as the study progressed. In addition, monitoring plans did not always clearly indicate how sampling assignments should be applied and how additional data reviews should be performed when site performance problems emerged. Until recently, this has been an active forum discussion in the industry with no clear or standard direction for how RBM should be applied. In order to encourage consistency and innovation in the RBM space, the U.S. Food and Drug Administration (FDA) issued draft guidance[1] in 2011, followed by final guidance[2] in 2013, providing an opportunity for the biopharmaceutical industry to comment as well as provide a framework for a voluntary review process for RBM monitoring plans. The industry now recognizes the importance of this topic, as evidenced by the TransCelerate BioPharma Inc.[3] release of its 2013 position paper outlining a methodology for risk-based site monitoring and several other papers on topics such as centralized monitoring and how to assess the success of an RBM approach.

PPD recognized that many past RBM approaches relied heavily on reduced source document verification and sampling of patients and data. Until recently, there was no consistency in how RBM plans were adapted based on the data quality and data trends. Previous plans relied upon the clinical monitor's intuition or complex algorithms and reports. PPD did not see robustness in the adaptive approaches of many plans presented to us for execution, and many teams had difficulty implementing complex plans that relied upon manual reporting and comparison. Our team demanded a consistent process that could be adapted to individual protocols, as well as a suite of technology solutions that allowed for ease in detecting trends and anomalies, data currency and robust statistical methodologies to identify sites that are outliers in performance.

Through customization of CTMS, the expansion of Preclarus®—our robust portfolio of technology solutions—and the development of a process driven by data analytics, PPD created our comprehensive RBM strategy. PPD's approach begins with a cross-functional risk assessment to drive customization of our functional management plans (monitoring plan, data validation manual, data analytics plan, etc.) and uses real-time data delivered through the dynamic analytic dashboards of Preclarus and new workflows and processes such as event triggered real time review (ETRTR), remote interim monitoring visits (IMVs) and site health assessments, which clinical research associates (CRAs) and clinical team managers (CTMs) use to detect and identify anomalies in data, analyze clinical key risk indicators at a site level and react to risks identified through data analytics. A root cause analysis is performed, when discrepancies are identified, to prompt remote and on-site visits with a focus on enacting process changes at the site, ultimately mitigating risks before they arise. We are utilizing techniques prescribed in the FDA guidance, following the progress within the TransCelerate publications and applying both to our industry-leading people, technology and processes to provide clients effective and efficient adaptive monitoring plans, while changing the way clinical teams do their jobs. By implementing conclusions drawn from remote monitoring, monitoring teams are able to shift their approach and mindset to identify core problems through analytical tools and to make better decisions from the available study data.

Challenges of Risk-Based Monitoring in Rare and Uncommon Diseases

RBM traditionally has been avoided in rare and uncommon diseases because of patient populations, risk of poor data quality and resulting financial implications. Costs per patient are high in rare and uncommon disease trials, making RBM strategies seem attractive to clients at face value. Because of the small patient populations and low data volume, missing end point data or incorrectly performed procedures at the site could lead to unusable data that have implications on the statistical power and primary end point analyses. For this reason, the traditional prescribed monitoring approach has been 100 percent SDV and frequent monitoring visits, although this still does not completely protect against these possible implications. In traditional models, even the best CRAs lack an ability to flawlessly aggregate data trends across subject visits, subjects and sites when the monitoring often occurs across several IMVs, weeks apart, looking at one or two subject visits at a time. Certain RBM methods assist in providing multiple sets of eyes on the data (CRAs and remote monitors), aggregated looks at data (data analytics), more frequent review of data remotely (remote IMVs) and standardized assessment of site performance overtime (site health assessments) which can improve subject safety, patient retention, quality of data and protocol compliance.

Another area often debated in rare disease trials is the viability of standard statistical approaches given small site and patient sample sizes. While site to site comparisons may not work particularly well when there are so few patients at each site, or a small number of sites, there are other ways to screen the data. For example, we can further group sites into region, or we can go the other direction and look at patient level data for outliers. Adverse event (AE)under/over reporting from a larger study with lots of patients/site will give you a more robust signal, but even then, it's just a signal to be investigated, it doesn't tell you the site is doing something wrong.

A flexible approach to use of analytics to identify signals and data anomalies can overcome the statistical challenges normally faced with low numbers of patients and sites. When the goal is to interrogate the data to identify sources of risk on a trial, it's imperative to refocus the lens to fit the characteristics of the trial. Effective use of analytics and data interrogation in this context is measured by the ability to raise signals that something may be amiss, followed by robust investigation and confirmation where the goal is to ensure quality data is being gathered to deliver a successful trial.

It is a common misnomer that one RBM technique will fit all indications. This belief is flawed, particularly when applied in the rare and uncommon diseases space. Although many diseases are grouped under the rare and uncommon designation, they each have their own challenges and risks that need to be assessed. A traditional RBM approach fails to meet the individual needs of rare and uncommon diseases as it often takes a study data approach when, in fact, a per patient data assessment approach is better, as is a focus on real-time data. With an adaptive monitoring approach, individual elements of traditional RBM strategies must be reviewed to determine if they are an appropriate fit for specific rare or uncommon diseases study designs.

With this individualized approach, rare and uncommon diseases studies can benefit from the application of adaptive and intelligent approaches to RBM that adjust the monitor's focus based on real-time trends in data. This approach also encourages centralized in-house monitoring of data to provide consistency within the dataset on an ongoing basis and allows for peer review of monitoring.

Using three different rare diseases trials as examples, we will demonstrate how trials with unique challenges can benefit from using a risk-based approach to monitoring.

+ **Study A:** Phase II/III long-term treatment of a genetic disorder in pediatric patients with cognitive impairment to slow progression of cognitive and functional impairment
+ **Study B:** Phase IIb long-term treatment a genetic neurodegenerative disease in pediatric patients
+ **Study C:** Phase III treatment of an uncommon acute emergent condition

RBM provides the benefit of a risk assessment, in-house monitoring and various tools to access and review data. By having a consistent strategy applied to all data there is an improved opportunity to recognize data concerns early and intervene before they have been repeated at subsequent visits. This paper will explain the primary components of an RBM approach and then outline how they might be applied across these three different rare diseases trials.

Key Elements of a Risk-Based Monitoring Approach to Apply in Rare and Uncommon Diseases Trials

Protocol Risk Assessment. All RBM approaches should first include an assessment of risks inherent in the execution of the protocol. This risk assessment should include an evaluation of the complexity of the study design, eligibility criteria and treatment administration. Monitoring plans should be developed to ensure additional focus and attention are placed on the areas involved in the execution of the trial that are at highest risk for errors and could impact data integrity or subject protection. For example, in a study in which the design includes dose tapering or titrations that are triggered by meeting specific criteria, additional data surveillance to identify these triggers and confirm the sites have appropriately adjusted the dosage would be important to include in the monitoring plan. It is essential to assess eligibility criteria to determine which are critical to trial integrity and which are critical to subject protection. Focusing additional automated edits or planning for centralized remote monitoring of these criteria at the screening visit will prevent sites from randomizing those subjects that could be harmed by their participation and will ensure sites are only randomizing subjects that meet the eligibility criteria to maintain trial integrity. Additional components of a risk assessment include assessing the protocol specific

instructions around the timing and collection of safety and efficacy end points. By identifying the expected errors that sites could make, clinical monitoring plans can focus additional training and compliance checks around these end points. As a result of a risk assessment, an increased training and monitoring focus actually can improve the quality of the trial data and better ensure subject protection. The advantages of performing a risk assessment and developing the monitoring plan around that assessment include:

+ Proactive planning that leads to risk mitigation
+ Training for sites and CRAs that focuses on the areas of highest concern
+ Improved protocol compliance and ultimate data quality

Targeted Source Data Review and CRF Source Data Verification.

Source data review (SDR) is the process of evaluating the original clinic or hospital documentation of the assessment of the subject or the results of a protocol procedure, while CRF source data verification (SDV) is the process used to compare the corresponding data fields in the CRF or EDC system to the data in the source documents. Traditionally, CRAs have relied upon 100 percent of all source documents being reviewed and 100 percent of all CRF data being verified against the source documentation.

Historically this has been performed in one of two ways:

+ **Method A:** CRAs first review the source documentation completely to ensure logic and clinical process compliance (SDR), then compare that information and detailed results to the CRF (verification). In this method, SDR is a primary focus, while verification is secondary.
+ **Method B**: CRAs first look at the data entered in a specific field in the CRF and then review the source to find a "match" in the source documentation to support the CRF entry. In this example, SDR is not the primary focus, and is often not conducted as thoroughly as in the previous method.

Method A is the preferred approach because it focuses on site compliance with the conduct of protocol procedures, process and methods, as well as the accuracy of the data in the CRF. Method B tends to place more emphasis on accuracy of the CRF data and less focus on the overall conduct of the procedures and the way in which data/results are captured.

Despite the level of detail expected of the monitors using 100 percent SDR and 100 percent CRF verification, audits by CROs, clients and the FDA still reveal critical and major findings that were either not accurately addressed by the CRAs/clients in order to bring sites into compliance swiftly or were missed by the monitors all together. Further, TransCelerate published a paper in 2015 indicating additional analysis shows that <3.7 percent of data ever changes after it is entered into the EDC system, indicating the negligible impact of SDV[4].

Targeted monitoring is an alternative to 100 percent SDR and 100 percent SDV that could improve the ability of monitors and clients to reduce the number of these critical or major findings that are either not recognized or not handled appropriately. Targeted monitoring strategies emphasize areas of highest risk based on the protocol risk assessment conducted. Targeted monitoring assumes that reviewing a sampling of key source documentation and CRF data can provide an appropriate assessment of the site's compliance and accuracy to allow the CRA to identify areas where the site needs process improvements and/or additional training. Targeted monitoring relies on CRAs to detect trends indicative of poor performance and documentation practices early, assess the root cause of these issues or failures, and work with the site to put corrective and preventative actions in place.

There are a number of ways that clinical trial data can be targeted for SDR and CRF verification:

1. **Data point sampling** – Identifying which data points are critical and focusing SDR and CRF verification on those that are critical. For example, critical data only might be primary safety and efficacy end points. Critical data will be monitored at a higher percentage—even as high as 100 percent—and less critical data will be sampled at a lower percentage, or not sampled at all, and rely only on electronic EDC edits and listings. This is most easily performed using monitoring method B described above and is therefore a less desirable option.

2. **Subject visit sampling** – Identifying which subject visits are critical and focusing SDR and CRF verification on those that are critical. For example, critical subject visits may be the screening, baseline, end of treatment (where the primary safety or efficacy end point is measured), early termination and unscheduled visits. Critical subject visits will be monitored at a higher percentage, as high as 100 percent, and less critical subject visits will be sampled at a lower percentage, reviewed remotely or not reviewed at all and rely only on electronic EDC edits and listings. This sampling strategy is best aligned with monitoring method A described above and works very well on studies of any size, provided the number of visits per subject is of an appropriate size (>10 visits/subject).

3. **Subject sampling** – Identifying a certain percentage of subjects for SDR and verification. For example, 25 percent of all subjects enrolled will have source and CRF verified at 100 percent, while the remaining 75 percent of subjects enrolled will rely only on electronic EDC edits and listings. This sampling strategy is best aligned with monitoring method A described above. However, it only works well on studies where each site is enrolling a minimum of 20 or more subjects.

4. **Subject or subject visit sampling for SDR combined with data point sampling for CRF verification.** This would include a 100 percent review of the source selected for that subject or subject visit, followed by CRF verification of only a portion of that data. This strategy is more complex to track and manage and requires close collaboration between the clinical teams and EDC vendor.

Different sampling approaches can be created for a single protocol based on the difference in expected site performance. For example, a sampling plan for high-, moderate- and low-risk sites can be developed, and CRAs can adapt the sampling plan used for that IMV based on the site's recent performance.

In addition, this sampling approach can be used during on-site or remote interim monitoring visits (rIMV) to oversee a site's compliance and performance.

The advantages of using targeted monitoring approaches are:

+ The CRA's focus can be limited to data and processes that are critical to human subject protection and trial data integrity
+ Limiting focus to items that are critical allows for more time for training and oversight in these areas
+ Adapted throughout the study based on site performance

Remote Monitoring

There are a number of different ways in which remote monitoring can be implemented on a trial. PPD employs a combination of different approaches: centralized remote review, real-time remote review and routine remote review. Each approach offers some unique advantages for ensuring the quality of data in a clinical trial and protection of subjects.

Centralized remote monitoring is the review of general study data or subject specific data at a specified frequency or in real time. Centralized remote review is conducted by dedicated staff from a centralized location for all sites globally. For example, a weekly review of all lab data to ensure pharmacokinetic (PK) samples have been received at the lab for all subjects who completed a specific visit

within the last seven days can be completed for all sites globally by a dedicated CRA. A second example of centralized remote review is having a dedicated CRA review all data entered into EDC for the first two screened subjects at each site globally to verify medical history, physical exam findings, concomitant medication and lab values meet entry criteria. Finally, centralized remote monitoring also can include a review of site metrics (such as the percent of screen failures or the percent of early terminations), key risk indicators (such as sites that are outliers in AE. Centralized monitoring can be conducted by a number of functional experts (medics, CRAs, data analysts, etc.) each looking at data with a different focus. Given the rare disease challenges of small sample sizes within sites and a small numbers of sites, statistical approaches for use can take a patient-centric focus over site-centric focus.

Real-time remote review is the evaluation of data in "near" real time. It occurs within a specified period of time from the entry of that data into the EDC system or other electronically accessed system such as a lab portal or imaging portal. Real-time remote review is conducted on study data that is critical to be reviewed in a timely manner to prevent sites from making mistakes like enrolling ineligible subjects, or to prevent sites from repeating critical mistakes or omissions such as failing to decrease the dosage of medication at visits where their assessments show the subject is not tolerating the current dosage. Real-time remote review typically is performed on the first several subjects that have an event meeting real-time review criteria, such as screening, randomization, early termination, severe adverse event (SAE) or unscheduled visits. These are all common triggers that might require real-time review to monitor a site's compliance with protocol or Good Clinical Practices at critical stages in the trial. Depending on the likelihood of errors that significantly impact the trial integrity or subject protection, real-time review can be performed for all subjects when certain events occur. Real-time remote review can be performed by a centrally designated person on the clinical team for all sites globally or by the CRA assigned to conduct the on-site monitoring. How this review is coordinated depends on the pace of enrollment, the volume of enrollment and the pace of on-site monitoring requirements. Queries are issued by the CRA and, if applicable, the on-site CRA is notified when additional site training is needed. Deviations identified are captured in the clinical trial management system (CTMS) and if significant compliance concerns are identified, an on-site IMV may be scheduled.

Routine remote review is the review of EDC data or other electronically available data such as lab portals or imaging portals at a specified frequency. This also could include CRAs accessing a site's electronic health records, if available. This type of review is conducted as a component of a routine rIMV. For example, every six to eight weeks a CRA might conduct an rIMV. During that rIMV, the CRA will assess enrollment, regulatory communication and status, investigational product supply, temperature control and accountability records, delegation of responsibilities and training of site personnel. In addition, the CRA will assess EDC account access, confirm or assist sites in closure of queries or site issues, and additionally review data in EDC for a select sampling of subjects for protocol compliance, clinical logic, AE reporting and follow-up, and to ensure that all required visits and procedures have been recorded appropriately in the CRF and document any observed deviations. This may involve accessing a lab portal, electronic diaries, imaging portal or electronic health records for verification of key data. Queries are issued by the CRA and identified deviations are captured in CTMS. Findings found during the routine remote review are documented within the rIMV report and discussed with the investigator and other site personnel during the site/CRO phone call, a required element of an rIMV. The routine remote review and rIMV phone call with the site can be performed by a centrally designated person on the clinical team or by the CRA assigned to conduct the on-site monitoring, or the routine remote review can be done centrally and the rIMV phone call can be conducted by the on-site CRA. How this review is coordinated depends on the specific details of

the trial and what might be the most effective and efficient process, one detail that may impact this review are the local language requirements for the study.

Each approach has inherent advantages, including:

+ Centralized remote review
  - Ensures consistency of review and expectations of the data across all countries and sites globally
  - Detects weaknesses or inconsistencies in individual monitoring processes
  - Can compare each site to all study sites, other sites in a region or group subjects to identify outliers for further investigation
    - Leverages centralized statistical monitoring algorithms and data visualization capabilities to identify trends not visible by the CRA
+ Real-time remote review
  - Promptly identifies errors/omissions
  - Prevents repeated errors/omissions
  - Enables rapid identification of site weaknesses and of corrective actions
+ Routine remote review
  - Ensures oversight of subject data and site process between on-site IMVs
  - Allows for replacing some on-site IMVs with remote IMVs

Application of Risk-Based Monitoring Techniques in Rare Diseases Examples

A combination of the various monitoring approaches provides additional safeguards to data integrity and subject protection that are not possible or cost effective using only traditional on-site monitoring. Beginning with the risk assessment for study A, a 15-month study of pediatric subjects with subject visits every four weeks for 52 weeks, we find that this is a good candidate for using a RBM approach for the following reasons:

+ Large volume of visits/subjects (16 on-site and one phone visit).
+ Relatively safe profile for the investigational product and comparator (a data monitoring committee will be used as well).
+ Clear and distinct primary and key secondary efficacy end points (comparing baseline to week 52). Other important efficacy end points are measured at weeks 16, 28 and 40 in addition to week 52.
+ Additional safety measures—including training—have been planned for implanting neurosurgeons.

Despite the complexity of three different cohorts, study B is also a good candidate for a RBM approach for the following reasons:

+ Cohorts one and two have a large volume of visits/subjects. Cohort one (29 visits with most every two weeks) and cohort 2 (17 visits with most every four weeks).
+ Cohort three subjects require 15 subject visits of which 10 are conducted by phone.
+ Relatively safe profile for investigational product (a data monitoring committee will be used as well).
+ Clear and distinct primary and key secondary efficacy end points (comparing baseline to week 48). Subjects are considered evaluable if they have completed 24 weeks on the trial.

Based on the risk assessment, study A is a good candidate for a targeted approach to SDR and CRF verification. In this example, we would suggest monitoring 100 percent of all source and corresponding CRFs for each subject's screening, baseline and week 52 visits. All subjects could be monitored at weeks 16, 28 and 40 also at 100 percent, or this could be tapered depending on site performance

such as 100 percent for high-risk sites, 75 percent for moderate-risk sites and 50 percent for low-risk sites. For all other visits (weeks 4, 8, 12, 20, 24, 32, 36, 40, 44 and 48) a tapered approach could be suggested, but these could be an even lower percentage of sampling such as 50 percent for high-risk sites, 30 percent for moderate-risk sites and 20 percent for low-risk sites.

Study B is also a good candidate for a targeted approach to SDR and CRF verification. In this example, we would suggest monitoring 100 percent of all source and corresponding CRFs for each subject's screening, implantation, post-op check, baseline, and week 24 and 48 visits. For subjects in cohort one, monitoring would be tapered to weeks 4, 8, 12, 16 and 20 depending on site performance such as 100 percent for high-risk sites, 75 percent for moderate-risk sites and 50 percent for low-risk sites. For cohorts one and two, all other visits could follow a tapered monitoring approach, but these would be an even lower percentage of sampling such as 50 percent for high-risk sites, 30 percent for moderate-risk sites and 20 percent for low-risk sites. All other subject visits for cohort three would not be monitored on-site and could be monitored remotely.

For studies A and B, it is recommend that a 100 percent review be done on-site of all informed consents for all subjects, all investigational product accountability for all subjects, all unscheduled visits, all SAEs and all early termination visits because of the likelihood of errors that would impact subject safety or trial integrity in these areas.

To supplement the reduction in on-site monitoring for both studies A and B, it is also recommended to apply remote monitoring. Because of the low volume of subjects in these trials and how important each visit is in the data collection needed to power the trials, it is recommended that one of two approaches to remote monitoring be selected. In the first option any visit not selected for on-site monitoring will be monitored remotely. Alternatively, in the second option, a tapered sampling of any visits not selected for on-site monitoring will be selected for sampling based on site performance, for example, 50 percent for high-risk sites, 30 percent for moderate-risk sites and 20 percent for low-risk sites. The timing of the remote review also can be tailored for the study. For all three example studies, since they are rare diseases indications and any mistake made by the sites that are not identified and corrected before they are repeated can be significant, it is recommended that all remote monitoring be done in near real time, which means every four weeks in study A and every two to four weeks in study B. The remote review either could be conducted by the CRA responsible for the on-site IMVs, or, in this case, a centralized reviewer with a medical degree would be recommended for review of the subject visit data selected for sampling, and a centralized CRA could review the administrative compliance of each site, for example sample management, and the CTM would centrally assess key risk indicators (KRI) and performance metrics at the site.

Despite study C involving a single dose of a marketed product, it is not a perfect candidate for targeted SDR and CRF verification for the following reasons:

+ The primary efficacy end point is the Time to Meeting Discharge Criteria (TMDC) based on an investigator assessment of angioedema associated upper airway symptoms. The TMDC end point will be calculated from the time of study drug administration to the earliest time point at which the symptoms of difficulty breathing and difficulty swallowing are absent (score=0) and the symptoms of voice change and tongue swelling are mild or absent (scores of 0 or 1). This end point could occur at any subject visit.

Conversely, study C could benefit from applying near real-time remote review of the data as it is entered into the EDC system as described above. The benefits of customizing the monitoring plan based on the protocol specifics and site performance allow the CRAs to focus

a targeted SDR and CRF verification on the data that is critical and allows more time for reviewing the site's processes and compliance to the protocol and regulatory requirements. This diligence that is applied to strategically timed remote monitoring can increase subject protection and improve overall data quality.

Centralized monitoring could be applied across all three trials, despite a small population of sites or subjects/site. In a rare diseases trial, small adjustments to the central monitoring data cuts can be customized to ensure nothing is being obscured. In studies where the patient to site ratio is low, adjustments can be made to group patients other than by 'site' when helpful to tease out signals or trends. Numerical and statistical challenges related to small sample sizes and sites can be circumvented through patient specific focus, and other exploratory mechanisms using appropriate visualization tools. Some exploratory methods may be subjective in nature but nevertheless highly effective in patient level or site level risk assessment given that the review and interpretation is performed by skilled analysts.

In these types of studies where concurrent enrollment is low within a site, additional effort should be focused to leverage the openness of these rare disease communities to fluidly share compliance, procedural and other site-level feedback across all sites or regional clusters of sites to drive greater protocol familiarity than would be natural in a low enrolling study. So as issues are discovered in any method of monitoring, special effort should be made to ensure all sites are benefiting from the lessons learned of others.

Additional financial benefits are derived from applying these adaptive and intelligent monitoring approaches. Because of the decreased volume of data required for review at each on-site IMV, targeted source and CRF verification can reduce the number of on-site IMVs required for ensuring adequate oversight of the trial. Supplementing on-site IMVs with remote monitoring visits that are estimated to be a third of the cost of an on-site IMV ensure more frequent oversight of site performance.

Assessing sites for risks and adapting the monitoring plans based on site performance ensures that high-risk sites will get more time and attention. This also allows for refining the number of on-site and remote IMVs to the specific number required for managing all high-, moderate and low-risk sites with little excess.

Current Application of Risk-Based Monitoring Techniques

In late 2013, PPD first began utilizing our adaptive and intelligent approach to RBM, utilizing Preclarus for real-time data capabilities and dynamic analysis. This approach allows us to manage trials with a reduced frequency of on-site visits and reduced SDV while still maintaining high quality and close oversight of clinical trial sites. PPD has recently layered-in a Data Analytics function, using a centralized Cross-functional Data Liaison (CDL). The CDL plays an important role in RBM trials, analyzing a variety of data sources to surface anomalies and trends in the data that indicate risk to the project and to ensure project teams are focusing on the issues that matter.

Each monitoring plan is customized based on a detailed evaluation of the protocol. Site level visit schedules are then adapted through the life of the trial, using quantitative reports and qualitative clinical assessments. This helps us target the appropriate level of monitoring effort to specific sites based on the risk level.

Additionally, Preclarus allows our CRAs and CTMs to view site health assessments and risk indicators—in addition to other site performance data—in order to trigger site investigations or modify the monitoring schedule for the site. These combined process and technology innovations allow us to identify sites with potential problems faster, drive better site performance and data quality, optimize CRA time on-site, and reduce the overall costs of clinical research. PPD has more than 15 studies utilizing adaptive monitoring techniques in queue for implementation within the next three to five months.

CONCLUSION

A comprehensive RBM approach in the rare and uncommon diseases space allows for a flexible solution in which the benefits of real-time data can be applied while maintaining a focus on quality and timely data.

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