Webinar Q&A

Understanding Risk-Based Monitoring Post-ICH E6 (R2)

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Questions submitted by audience participants.
Responses provided by Crissy MacDonald, Jeff Kingsley, and Steve Whittaker.

Q1) Have other companies shared monitoring plans with sites before?

A) Yes, because different methods of monitoring can have a substantial impact on site time as well as site budget.

Q2) Do you think 100% monitoring is a waste of time in Phase 2 trials? In critical care?

A) Yes. Most data points have nothing to do with the trial endpoints. Tufts' analysis shows that, on average, trials produce one million data points that never get used. That's a waste of time and resources with 100% SDV, whether early phase or not.

Q3) How have sites adapted to a risk-based monitoring mindset? In our experience, sites oftentimes confuse RBM with remote monitoring.

A) This is completely true, and it is not just the sites; the whole industry continues to confuse risk-based with remote. Sites are only beginning to adapt to risk-based monitoring. To really adapt, sites must develop their own internal QA/QC programs; identify the type of monitoring plan prior to contract and budget negotiation; identify what qualifies as 'high risk'; and improve accordingly.

For clarity, remote (or off-site) monitoring can be a component of risk-based monitoring as RBM encompasses a thoughtful balance of Centralized, Remote, and On-site monitoring in a risk-based fashion focusing on risks that matter to patient safety or data integrity/interpretation.

Q4) What are your thoughts on early development or Phase 1 studies on risk-based monitoring?

A) In this day and age, all trials deserve a risk-based approach, but the earlier the phase, the higher the risk. Earlier phase studies deserve RBM even more.

Q5) Do you have data that CRAs should continue to 100% SDV during on-site monitoring visits? Like safety assessments? AEs? Medical history? Concomitant medication? In addition to the primary endpoint?

A) I do not believe 100% SDV provides benefit compared to a risk-based approach. Most data points have nothing to do with the trial endpoints. Tufts' analysis shows that, on average, trials produce 1 million data points that never get used. That's a waste of time and resources with 100% SDV, whether early phase or not.

Q6) What approach is recommended for Investigators who are reluctant to move to RBM or do not seem to understand the benefit of implementing RBM as opposed to traditional on-site monitoring that uses 100%?

A) Interestingly, Investigators have always been responsible for the quality of their data. They have become accustomed to 100% SDV. Risk-based monitoring returns to the Investigator the responsibility for the quality of their data. Investigators need to implement their own QA/QC plans.

Q7) Are remote/off-site communications of potential anomalies/deviations happening for studies that are RBM? Does that inform the site of potential issues for follow-up and/ or errors?

A) That's precisely how it should happen. Anomalies should be communicated to the sites involved.

Q8) RBM might call for 100% eligibility and AE reporting SDV, which may appear to the site like full monitoring. What is the site's perception of an on-site monitoring visit under a risk-based monitoring plan?

A) A risk-based monitoring plan would not preclude on-site visits. However, an elevated risk would spur an increase in on-site visits.

Q9) Why does the site not implement a quality program within their site? I have seen this work well at several centers. Sites should not be solely dependent upon a CRO or Sponsor to inform them of their quality. Additionally, sites are informed by their CRAs of many quality metrics – number of data entry errors, days to enter data, days to answer queries, protocol deviations, etc.

A) I completely agree with you. Today, only the largest sites have their own quality programs. Real quality programs are expensive and difficult to implement and maintain. Sites aren't reimbursed in a way that encourages or incentivizes them to implement a quality program. Most sites are too small or too poor to do so, but that needs to change.

Q10) How do you see the FDA inspection process results affected by less than 100% SDV and risk-based monitoring? For example, an FDA 483 included 5 source/EDC discrepancies from PRO docs. The site screened 48 subjects.

A) If a site received a 483, the error is owned by the site. The FDA has stated its support of a risk-based approach.

Q11) Dr. Kingsley said that sites should be empowered to deliver high quality work. Does he not think this is happening now? Sponsors believe that this is already what they are paying for.

A) Producing high quality is costly. For a site to run a true QA/QC process is costly. Yet currently, the paradigm is that sites are paid to give data. Sites aren't paid any differently to provide high-quality data versus low-quality data.

Q12) In the case of on-site management monitoring, CRAs have to give reasons for not following the limited/risk monitoring system. Therefore, if some sites are not qualitatively sufficient, 100% SDV has to take place until the quality improves. Even if we involve the sites centrally (as CRAs are supposed to share the quality issues with the sites) into the dialogue for RBM with data, the result is expected to be the same. What does Jeff see that would motivate the Investigators differently than to read the follow-up letters of RBM CRAs?

A) I'm in favor of a pay-for-performance model where sites are paid higher if they produce high-quality work and paid lower the more errors they make.

Q13) Dr. Kingsley, how many studies are currently open and accruing for your company?

A) The number of accruing trials per headcount varies depending on trial type (e.g., oncology vs. acute vs. chronic vs. rare disease).

Q14) Dr. Kingsley, is your risk-based approach documented and presented to your Sponsors?

A) Risk-based strategies are run primarily by the Sponsors and CROs. My internal method is a full QA/QC approach.

Q15) Why don't we change the industry standard of delegation of eCRF data review to Sub-investigators? And review data in eCRF at different time points in the study rather than at the end of the study?

A) I'm not sure I understand the question. eCRF data is reviewed continuously and not merely at the end.

Q16) Would it be beneficial if QTLs were outlined in the protocol for transparency to the sites?

A) Absolutely! We need full transparency on the data that matters, the algorithms that are used, and the data points that appear to be outliers.

Q17) Without sharing the exact plan, what is helpful for sites to know? The number of on-site/remotes? The critical quality focus?

A) I would suggest that it's imperative that a site knows the number of on-site visits anticipated as well as the critical quality focus.

Q18) If we share the monitoring plan, sites will work to the plan rather than 100% accuracy.

A) If you don't trust the site to produce high quality, don't accept the site on your trial.

Q19) If the monitoring plan were to be shared with the site, of what benefit do you think it will have in the quality/performance of the site?

A) The monitoring plan has a budgetary impact on the site, but if you want the site to be a member of your team, the site has to know the rules of the game.

Q20) In order to be more transparent to sites (KRIs, QTLs, etc.), would you prefer having an electronic dashboard or, e.g., monthly newsletters sent?

A) Great question! I would always prefer an electronic dashboard over a monthly newsletter.

Q21) Is there a risk of sharing risk-based monitoring plans with the site? I understand the need for transparency, but won't the site be diligent only for those subjects/visits that are identified to be monitored?

A) Risk-based monitoring doesn't mean you're only going to look at certain subjects or certain visits. It means you're going to look at all of the data coming in, and for outliers that suggest heightened risk, and data points that suggest anticipated behavior. Ultimately, all data is analyzed in the algorithm. Sites would not have the option/ability of doing less high-quality work.

Q22) In my experience, we do not share the data points to be monitored with the sites, so sites are expected to enter all data accurately and completely, not just focus on the data points to be reviewed by the monitor. How would you recommend this be relayed to the sites?

A) Refer to answer to Q21 above.

Q23) Sites are paid to give data; the expectation is the data given is accurate and complete and of good quality. Sites are responsible for the quality of data now as they have always been, so why does a site need extra compensation for quality review when they should be providing quality data from the beginning?

A) You're completely right! Let me quote you "Sites are paid to give data; the expectation is the data given is accurate and complete and of good quality." You're completely right. Sites are paid to give good quality. However, we're doing clinical research. Good quality should not be the bar. Phenomenal quality should be the bar. Six Sigma quality should be the bar. Immensely high quality is immensely difficult and very expensive.

Q24) What is/are the best way(s) to keep up with changing regulations in order to remain compliant?

A) Participating in industry conferences, establishing a regular cadence of reviewing regulatory webpages, and/or joining consortia like ACRP, Avoca Quality Consortium, etc.

Q25) In your experience, how many protocols are being designed to facilitate risk-based approaches to clinical trials rather than applying the principles to traditional protocols?

A) In our experience, risk-based approaches are being applied to traditional protocols. Oftentimes the risk-based approach begins after the protocol has been developed and not before. The scientific and operational teams do not typically work in conjunction in determining what data is "must have" or "nice to have" which often plays into how well risk-based approaches can be applied.

Q26) What does quality tolerance limit (QTL) mean? Do you have examples?

A) A quality tolerance limit is a threshold on a parameter that necessitates an action. An example of a parameter that would have a corresponding quality tolerance limit is patients lost to follow-up. In a clinical study, it is often known how many patients need to complete the follow-up portion of the study to have a high enough statistical power to determine scientifically the effectiveness and safety of the drug. If too many patients are lost to follow-up, the study becomes unevaluable. Therefore, a QTL associated with this parameter would be a value that is lower than the known number of subjects that can be lost to follow-up without losing power for the study. If that QTL were to be met, there would be actions required such as retraining Investigators and sites on the importance of not losing patients or enrolling patients who may not complete the follow-up period or can be determined if prior patients who were lost to follow-up can be confirmed deceased, etc.

Q27) QTLs are metrics that are across all study sites. Is it useful to share QTLs with the sites? It would seem KRIs would be more appropriate to share with the sites.

A) All metrics that are being tracked that sites are being measured on are great measures to share with them so that they can improve their processes or even benchmark themselves on how they are performing against others. That being said, a majority of parameters being tracked with QTLs associated with them are directly related to activities the sites are performing. Therefore, letting them know whether or not the study is in danger of not being evaluable can help to ensure that they are laser focused on the key areas of the study and making sure that they are not enrolling patients who aren't eligible, ensuring they are getting their patients to complete follow-up visits, etc.

Q28) Does technology (beyond EDC) help to facilitate the communication and management of risk based-trials, RBM, QTLs? Which platform is best at this?

A) Technologies are helpful, with the understanding that clinical sites often are participating in 100s of clinical trials at a time, so if there is not consistency in how to use or access these systems, then the benefits are decreased because of the sheer volume of log-ins, trainings, etc. that the sites need to do in order to find the information that they need.

Q29) If I have 150 sites, it would be a gargantuan effort to tailor the Site Monitoring Plan based on site experience. Do you agree?

A) Yes, a better plan would be to stratify the sites based on their level of risk and have a Monitoring Plan that designates how high/medium/low risk sites will be monitored.

Q30) If we agree that 100% SDV is largely a waste of time, should we also be re-evaluating the data that we are collecting? In some cases, it seems like the volume is a catch-all that doesn't always provide value.

A) Absolutely! The complexity of many studies is often less to do with the primary endpoints but the secondary and exploratory endpoints. By increasing the complexity to gain data that may or may not be used in the future, we are putting at risk the evaluability of the current trial.

Q31) How do we change the mindset away from 100% SDV?

A) Experience. Until the industry has an example of what good looks like in terms of risk-based monitoring and everyone is aligned on why it is beneficial, it will be difficult to get everyone on board. Similarly, because it is new and there have not been many inspections on risk-based monitoring types of studies, there is still too much unknown. Our industry is risk averse, so until there are more experiences shared on risk-based monitoring inspections, findings or lack of findings, it will be difficult to convince those that are accustomed to the status quo.

Q32) If we do not perform 100% SDV, what do you recommend? If not performing SDV on all data, then is the data really needed? Please provide examples.

A) It is not that the data is not needed, but is it related to a study endpoint? What is the likelihood that a transcription error occurred on that data that wasn't caught by standard edit checks? SDV'ing every lab value on a study may not be relevant for all studies, perhaps only AEs, etc.

Q33) If we decide <100% SDV, how do we decide what percentage should be SDV? Is it across all patients?

A) It can be a combination of any of this. I've seen studies where the first patient at each site is 100% SDV'd but then the SDV percentage decreases after to only key datapoints. The SDV percentage can also be based on the risk level of the site and not necessarily at the patient level.

Q34) Wouldn't the type of study affect the type of monitoring?

A) Yes, absolutely.

Q35) What do you think about doing a percentage of 100% SDV, like 10% of subjects 100% SDV? Is it a good option of way to do risk-based?

A) While this can be done, it is an artificial threshold placed up front and is not truly based on centralized analyses of actual data to determine the risks and what should deserve attention. So, this is not truly risk-based monitoring but is actually "reduced monitoring".

Q36) Given Investigator responsibility for quality, shouldn't there be a Site Quality Management Plan and or/quality metrics built into the Site Clinical Trial Agreement?

A) This is a brilliant idea and actually an area of focus for the Avoca Quality Consortium in 2019.

Q37) How do we add risk-based monitoring to our company policy? Where do we start?

A) Developing and piloting a process that is deemed successful is the best way to start with developing a risk-based monitoring policy in order to show that the processes were created in a thoughtful and meaningful way and fits into the organization's structure and QMS.

Q38) How do you suggest dealing with the transition of shifting some of the responsibilities to the site? There is a risk here that the site staff is not experienced with this type of work.

A) Most of these responsibilities are already at the site and the Sponsors are responsible for oversight. It is true that site staff could potentially not be experienced, and that is where oversight and risk analysis of the site plays into what level of oversight and monitoring will happen at each of the sites.

Q39) Should CROs/Sponsors start thinking about establishing QAGs (Quality Agreements) with sites?

A) Absolutely, and this is an area of focus for the Avoca Quality Consortium in 2019.

Q40) It sounds like you are talking about sites that are busy with many studies. What about academic centers that run studies? How do Sponsors/CROs influence them to ensure quality is included (regardless that it has always been their responsibility)?

A) As Dr. Kingsley mentioned in the webinar, academic centers are equally as responsible for quality as other sites, and the only way to ensure that quality is happening is by penalizing those sites who are not providing high quality, and that penalty is to not utilize them in the future. If you still choose to utilize those sites, know that perhaps a more stringent Monitoring Plan would be required for them as they would be a higher-risk site.