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Risk based monitoring in clinical trial-a review

Vishal Rastogi[1*], Umasri vijayagiri[1], Aparna manasa[1], V.C.Randeep raj[2]

[*1] Interns, Clinosol Research PVT Ltd, Hyderabad

[2] SAS Programmer, Visakhapatnam.

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Abstract

Risk based monitoring is the targeted approach in clinical trials for maintaining proper data integrity, protection of safety, rights of subjects and good of the trial subjects. The system of onsite monitoring by CRA was time uncontrollable and very effective. But now a day's technology advancements and pandemic are encouraged to remotely collecting and imaging large data including data tracking site performance. Also enabling identification of trends, risk before selling the drug. The US FDA, proposed these approach of risk based monitoring (RBM). The drive to RBM at assiduity position started in August 2013. These review composition grounded on approach to RBM substantially concentrate on safety of subjects, quality of data and also for quickly and effectively mitigati.ng pitfalls before they compromise trial quality. These paper also provides the information regarding impact of covid19 in clinical trial monitoring and displacements of trial conditioning during the pandemic period. The pandemic situations forced companies to calculate substantially on remote and centralized monitoring due to point closures. The RBM geography check showed remote site monitoring increased and on site monitoring dropped at the peak of the pandemic in April compared with the pre-pandemic. These check also showed that chance of remote point observing visits increased from 18 in February to a high of 93 in April. The check concluded that RBM relinquishment before the COVID- 19 pandemic wasn't as wide as anticipated.

***Corresponding Author**

Vishal Rastogi

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Introduction

Risk is an uncertain event or a condition which if it occurs may negatively impact outgrowth of an anticipated event. In terms of clinical trials, a threat may negatively impact achievement of its intended substances which could include punctuality, costs and quality of cessions [1]

Clinical trial operation is a complex endeavour taking careful planning, compliance with regulations, and collaboration between multiple stakeholders similar as guarantors, investigators, and contract exploration associations (CROs) [2].

Clinical trials are conventionally monitored by source data verification that's expensive, requires ample resources, and exhibits several boundaries. The International Council for Adjustment(ICH) has handed guarantors with the inflexibility to initiate a new approach called risk based monitoring(RBM) to enhance quality operation in a clinical trial [3].

Regulatory authorities similar as European Medicines Agency (EMA) define RBM as a process that involves identification, assessment, controlling, communicating, and reviewing the pitfalls in a clinical trial before its beginning. With this methodology, not only would the circumstance of the assessed threat be averted, but it would also minimalize onsite monitoring duties to some extent [3].

RBM has a stronger focus on the present and unborn, particularly when it includes real- time monitoring and prophetic modeling. These forward-looking conditioning impact not only covering functions but also overall trial operation. In other words, RBQM is a holistic, quality operation, systems- grounded approach to trial perpetration, and RBM as a monitoring strategy [2].

To exfoliate light on the state of RBM relinquishment and perpetration, the Association of Clinical Research Organizations (ACRO) a trade association of CROs and technology companies conducted a geography check of RBM use in clinical trials ongoing at the end of 2019. After COVID- 19 surfaced as a worldwide trouble in early 2020, ACRO also gathered fresh data from January to June 2020 to determine the impact of the pandemic on trial operation, with a specific focus on monitoring [3].

Benefits of Risk Based Monitoring

Lower costs

The cost of a clinical trial is tied up in monitoring conditioning. Thus, if we can optimize the RB monitoring, we can significantly lower the costs.

Faster, concentrated results

Due to data analysis and centralized monitoring, the results can be found quickly and more accurately [4].

Low error rate

When paralleled with traditional studies, RBM studies have reduced number of missing pages by 45% and brought down the critical data error rate by as much as four times.

Real- time data entry

RBM encourages real-time data entry. Relative studies show that sites that deploy RBM are 5 times more likely to enter study data within 7 days.

Better focus on the primary objective

Personnel have more time to concentrate on their core places and liabilities, as their executive tasks reduce significantly [4].

Increased safety

With admin tasks reduced, resources can be allocated more efficiently, and concentrated towards ensuring safety of patients.

More compliance

Data driven insights and other digital tools facilitate early discovery of problems, improved site training, and identification of implicit fraudulent activities. These factors automatically results in better compliance.

Increased collaboration

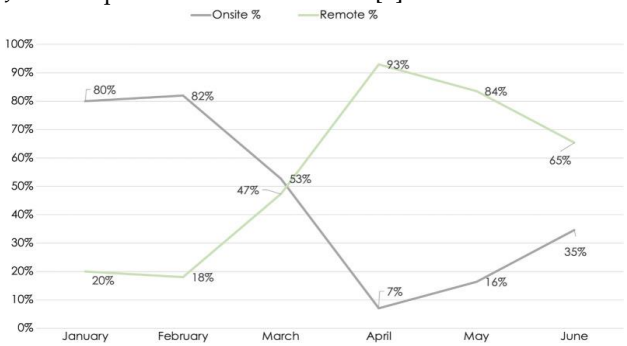
RBM encourages further collaboration and sharing among co-workers [4].

Impact of covid19 in clinical trial monitoring and disruption during pandemic

Impact of the covid-19 pandemic on clinical trial monitoring

On March 11, 2020, the World Health Organization (WHO) declared the COVID- 19 outbreaks spreading across the globe to be a pandemic. This unknown worldwide dislocation presented major challenges in clinical trial operation by forcing companies to depend on remote and centralized monitoring due to sit e closures and stay- at- home orders. At the same time, the pandemic created commodity of a natural trial, allowing ACRO to collect early data on the impact of this shift in trial monitoring to round the larger- scale RBM landscape dataset [2].

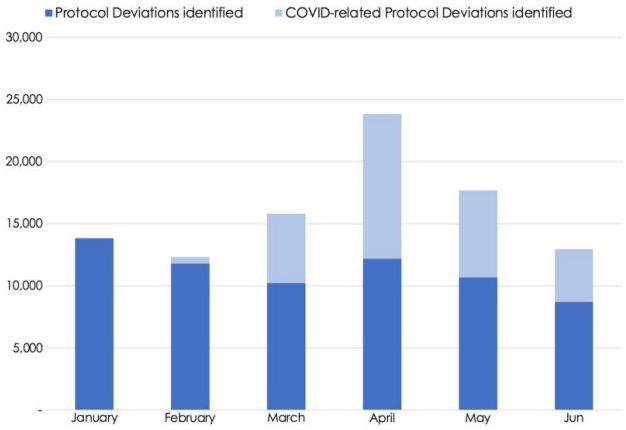
Data from 3 member companies covering trials from January to June 2020 showed remote- point monitoring increased and on- point monitoring dropped at the peak of the pandemic in April compared with the pre-pandemic birth in February. These trends began to reverse themselves post peak, but the chance of remote-point monitoring visits was still markedly advanced in June compared to the birth chance [2].



Graph shows Increased Remote Monitoring Visits and RBM in Response to the COVID-19 Pandemic [2].

Remote-point monitoring effectively captured protocol diversions as the pandemic evolved. A corresponding peak in COVID- related protocol disruptions was also seen in April month, declining over time through June, but remaining above the pre-pandemic situations. specially, the total non-COVID protocol diversions detected each month from March to May were

analogous to the February birth, indeed as the chance of remote- point monitoring visits increased from 18 in February to a high of 93 in April. This suggests that the rapid-fire shift in monitoring styles allowed for sufficient oversight and monitoring durability, advancing confidence in data quality and patient safety [2].



Graph shows Clinical Trial Protocol Deviations Detected by RBM during the COVID-19 Pandemic [2].

Trial Disruptions during the COVID-19 Pandemic

1. Fresh data exfoliate further light on the scale of the trial disruptions as the pandemic approached its first peak, complementing the monitoring data. In less than a month (March 14 to April 6, 2020), 3 companies reports were collected and 1 company reported that the chance of institutions where point monitoring visits for the company trials were disintegrated jumped from 10 to 49%. An alternate company reported that 33% of planned trial visits were disintegrated in March, and by the end of March, roughly 70% of sites were inapproachable. New subject registration in trials managed by a third company was reduced by 65 in March 2020 compared with March 2019. The RBM landscape data generated from a survey planned before the COVID- 19 pandemic covering further than 6,000 clinical trials provides a pre-pandemic birth for RBM adoption and implementation. The data ollected for this analysis are representative of studies where CROs have contracted services.(2)
2. The key takeaway from the landscape data is that adoption of RBM is less expensive than anticipated, likely because companies are fully commit to changing their practices and protocols. For illustration, centralized monitoring, the most constantly used RBM element, was enforced in lower than 20 of the trials in the dataset. still, off- point/ remote- point monitoring was used in only 10 of the trials, suggesting lesser acceptance of remote data evaluation than relief of on- point visits with remote visits [2].
3. One reason frequently cited for the deficient relinquishment and partial perpetration of RBM is hesitance on the part of trial guarantors and CROs to reduce the quantum of SDR/ SDV in favor of a more targeted approach. In our experience, more sponsors who agree to reduced SDV also accept reduced SDR, and our landscape data are generally consistent with this assessment [2].
4. The RBM landscape check showed that RBM relinquishment before the COVID- 19 epidemic wasn't as wide as anticipated, despite the proven benefits and clear eventuality of this approach [2].
5. The current findings and a wealth of practical experience are supporting the uptake of RBM and the industries may continue to lean into more adoption of out- point/ remote- point monitoring and other RBM practices in the post-pandemic environment. ACRO gathering data on trial monitoring practices through the pandemic. And further encourage the in d u s try at large to continue to advance best practices and promote adoption of RBM [2].

Executions and current comprehensions of RBM:

The perpetration approaches may vary across the organizations and the change has been impacting several places in the operation chain. Then, below describes the comprehensions of CRA's, and spots about RBM and changing the part of data manger and medical observers in the new model. These functions are involved in day to day monitoring of clinical studies.[5]

CRA perception about RBM

In 2014, the German Fedaral Association of CRO's conducted one-mail grounded check among CRA's in Europe (Substantially Germany) to assess their understanding and experience related to work in RBM model. In 2016, the check was repeated which in an internet grounded online check to assess their practical experience with RBM and how it changed their perception over a period of time. Christina estal, compared the both checks where 180 CRA shared in 2014 and 231 CRA party in 2016. CRA's with experience in monitoring (3 yrs of further) of RBM model were asked to respond on a specific questions concentrated on four crucial areas working effectiveness, effective point content, data grouping and patient safety and the responses are listed in table 1.

Table: 1Clinical exploration associates gests in RBM.

Survey Focus area	Responses
Working Efficency	Case safety 57% repliers in 2014, 46% in 2016
Point Co-operation	Good working effectiveness and probative tool.CRA felt that it was more delicate to get set co-operation.
Data quality	In RBM 55% (2014) and 48% (2016) independently. Patient scepticism, advanced in 2016 (73% vs 81%).
Patient safety	Significant enterprises over missed SAES and protocol diversions (over 60% in both the checks.

1. **Changing part of data director with RBM executions**

   The part of data manger play an import ant part for espousing and perpetration of RBM. Data operation is anticipated to play a part right from the protocol development stage where RBM relies fully on real time data review and analysis to identify the trends, pitfalls in the study with reduced onsite oversights. The inputs of data operation are critical at protocol and monitoring plan as well as during the study, as they contain critical data points, implicit assemblages area. After the study completion, they validate the assignments learnt during data operation function. Other changes similar as electronic clinical outgrowth assessements, real world data collected through smart phone, wearble bias from social media ,electronic health medical records, CRF's has come more grueling for the data directors as they handle data from delicate sources during the medicine development [5].

2. **Challenged faced by medical observers**

   Medical observers substantially concentrate on safety of trial subjects and relating the important safety signals. In an informal bean, 37% expressed that they were having topmost fear of missing the safety signal although it is not specific to RBM places but applicable to RBM model. The data collected on CRF is generally optimized for from the prisoner of source data from the point but design is not optimized for safety analysis. The data is present in different formats, after cleaning the data numerous times they may be an error. It is challenging for medical observers to snappily spot the meaningful trends and outlines without the help from technology platoon and statistician. RBM is the complicated by the fact that data operation is generally outsourced to the platoon may be in delicate main lands while the medical member where from USA or European Union where the real time co-ordinates in delicate. The review process is generally through excel grounded operation, e-mails and sticky notes where it is making complicated to track changes over a ages of time [5].

3. **Comprehensions about RBM monitoring and challenges faced by the spots**

   Clinical study is conducted and data is generated at spots, their understanding of RBM is pivotal for the success of model. In 2014 (July-September) a check was conducted in ten countries (6 emerging and 4 advanced) about their perception and understanding of RBM model in the mindset of staff.595 members were responded to the check from 3000 point platoon members. In 595, 289 askers aren't familiar with RBM they were barred from the analysis. From the remaining askers 100 from arising nations and 137 from developing countries who were familiar with RBM. From the 237 who had shared in RBM are more from developed countries and 19% from developing countries (Argentina, Brazil, China ,India, South Africa, Russia) 27% from developed countries (Unite States, United Kingdom, Australia, Germany) were having good abstract knowledge of RBM . The perception of all the actors was RBM reduces overall cost of the study conduct. when the actors were asked , whether RBM can be more effective in addressing the data quality, safety and findings frauds the experimenters from arising countries were more confident than the developed countries .

   Bois posy have written a commentary about perceived burden about spots with RBM perpetration is that there in increased work burden on the point, duty of unrealistic data entry timelines and reduced quality control by the CRA's. In system survey, the authors reviewed 91 implicit tools for RBM in which 24 were eligible for inclusion of assessment. RBM tools and their features are fairly new and vary extensively in clinical trials as they continues to evolve but it's

delicate to define stylish tool and where the point struggle for choosing the stylish tool of RBM .

All study spots faces a problem at study spots for hiring and maintaining good quality clinical exploration co-ordinators, (CRC) who is available all the time and acceptability of finances may not be assured continuously. Frequent CRC turn over can adversely impact for perpetration of RBM. The RBM point platoon should have high scientific and specialized chops CRC with acceptable training and so that CRA's don't visit the point constantly to support CRC [5].

Integrative approach in RBM

The primary thing in designing the RBM result was to allow the clinical staff who do not have formal training in data mining informatics, statistics is to make them readily identify data patterns and challenge their hypotheticals and to make further informed opinions.

Here, the methodology of threat grounded approach for covering clinical trials is grounded on quality by design, central monitoring and touched off adaptive data and remote monitoring [6].

1. **Quality by design**

   It includes protocol review, study threat assessment .study threat assessment includes subject participation and dataflow mapping, original point threat assessment, selection, criteria data and process, RBM plan development.

2. **Central covering**

   It includes the process of reviewing aggregate data from an ongoing trial and to identify inadequately performing investigational spots, to descry unusual patterns in cases and point position data ,to prognosticate implicit issues and to identify areas of threat and to correct problems in executing a clinical trial. It also includes the operation findings and issues throughout the process in a holistic manner.

3. **Adaptive ,touched off onsite and remote monitoring**

   Adapative touched off monitoring process is used during the subject enrollment and study maintenance phases of trial which situations of SDV, SDR of onsite monitoring and increased situations of remote monitoring, drivint the monitoring conditioning [6].

- This central monitoring methodology uses a entire approach to identify and manage pitfalls at the data point, visit, subject, site, study levels. To enable a comprehensive evaluation they've linked and addressed four broad classes of central monitoring threat review, medical review, statistical review, data review. This allows central observers, point observers and design directors to holistically manage all the issues in prosecution of a clinical trial. Staff who are trained in the threat operation reviews the system generated recommendations with crucial design platoon members. Point action report requires recommended interventions to be proved from this demand of remote or onsite monitoring is determined. Interventions were loaded in the threat and issue operation system and the action is taken by the point monitoring staff [6].
- Central monitoring is a repetitious process that involve periodic assessments (generally yearly) to identify and addressing the issues between the assessments (parallel/diurnal process) which generates touched off cautions and the automated announcements directly to the point monitoring staff. Individual members in central monitoring brigades are assigned with assessing the pitfalls in their sphere and their conditioning are coordinated by RBM lead.

4. **Technology**

   A holistic review is enabled by a technology result known as Xcellerate monitoring and it comprises the following crucial factors:

- Threat assessment and categorization tool: It's grounded on the template designed by TransCelerate which facilitates a companion threat program and design threat by cross functional brigades.. o Insure and identify document mitigations and integrate the threat and issue operation system that follow-ups to a resolution.
- Threat review tool: It allows central observers to perform regular review and to make changes and acclimate monitoring intervention grounded on individual threat pointers and overall point pitfalls.
- Medical review tool: It allows medically trained staff to review all the case data and to assess safety, protocol diversions and other clinical issues which may degrade the trial integrity.
- Statistical review tool: It allows the statistician to look for the arbitrary anomalies in the distribution of clinical data and this may be suggestion for dieting the process or outfit, bias or any other quality issues.

- Data review tool: It allows data directors to find out the missing and inconsistent data and to manage queries.
- The risk and issue management system offers advanced workflow for abroad range of issues and issue types with full support of audit trail, history, and metrics reporting and to mobile access for central and field monitors and to enhance the user adoption and productivity.
- Enabling this applications in a clinical data repository which supports the real time acquisition, mapping and integration of clinical trial data from any germane source including electronic data capture system, clinical trial management systems, electronic patient outcome record systems, interactive responsive technologies, electronic transferred by third parties such as central laboratory, biomarkers and imaging vendors [6].

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Challenges of transitioning to RBM

RBM technology has become an automated solution which helps the sponsors and CRO'S to implement comprehensive monitoring strategies from a single platforms to build in work flow and advanced analytics capabilities to here overcoming 5key challenges to ensure a smooth change over transitions of RBM.[7]

- Resistance to change
- Lack of proactive planning
- Selecting the right RBM technology
- Uncertainty about implementation
- Lack of appropriate resources.

Resistance to change: RBM concept makes a shift from traditional monitoring and drug developers may feel resistant to this change and it may be due to uncertainty how the FDA responds to the use of RBM techniques. If RBM modifications were not made CRO and sponsor should also consider about how the regulatory agencies will respond.

For companies who were uncomfortable in making a shift to RBM, there should be an useful exercise to evaluate the factors .and figure out how to address them. For companies that are ready to shift to RBM there can be a lot of changes and proactive change management is required. Shifting towards the RBM requires change management related to people, process and technology.

To ensure RBM in both companies and clinical trials there should be commitment at the leadership level along with the staff training and there should be clear understanding of roles and responsibilities of each team member.

Lack of proactive planning

Implementation of RBM requires proactive planning .if an organization is ready to transition to RBM and key stakeholders were identified, the following steps show be taken-

Identifying critical data and processes: what data has to be processed to ensure the patient safety and study integrity should be identified.

Perform a risk assessment: identifying , analysing and prioritising the risk and to determine whether the risks are to be modified by implementation control.

Develop a monitoring plan: monitoring plan should focus an prevent or likely risks to critical data and processes.

Selection the right RBM technology

There are number of RBM technology available, but the drug developers should select the software which delivers full benefits of RBM. Some RBM technologies only look at risk in isolation without contest or analysis may be limited to retrospective data, missing the critical capability to draw insight from emerging issues .when there is an incomplete approach for identifying, managing and analyzing risk introduces the complexity and cost without adding the value. If a system fails to fully assess risks, it could also introduce a new risk (a

false sense of security) sponsors and CRO's may believe that they are utilizing RBM with full of benefits.

A comprehensive RBM technology should approaches the risk from all the angles, operational, safety and quality. To evaluate an RBM software some of the factors to be considered as follows:

- Risk identification and assessment
- Risk control and mitigation
- Risk communication and action
- Risk review and updating

Uncertainity about implementation

As clinical trials become more complex, RBM technologies also became more complexity. A thought implementation is required for unlocking the full value of RBM technology. There is "no size fits all" approach to RBM and the implementation should be customized to the sponsor and the study.

The process of implementation involves requirement gathering, planning and testing and it should also covers the five key areas such as project scope, SOP/plan impact, communication, user acceptance of testing plan, oversight plan [7].

Lack of inappropriate source

The key stake holders driving transition to RBM will come from multiple departments within an organization (from clinical operations, data management, safety, training statistics) and regulatory.

Implementation team will have the stakeholders such as owner/drivers, decision makers, subject matter experts and users. User stake holder will be utilizing the RBM technology during the course of a clinical trial.

A multidisciplinary team is required for a successful RBM implementation, some of the sponsors and the CROs may have resource gap within their organization. Companies integrating RBM in their organizations, there are variety of external sources (ranging from online training to risk/quality, management consultant and RBM software vendors) which helps them in making decisions required for successsful implementation of RBM technology [7].

Monitoring of Investigation

1. Clinical investigations concerning drugs for human use, life products and devices, and combinations t are prerequisite to provide oversight to confirm adequate protection of the rights, welfare, and safety of human subjects and the quality of the data to be submitted **[8].**
2. Sponsors should be detect and perform & documenting the risk assessment on the critical data and processes that are important for human subject fortification and integrity of the investigation. The risk assessment serves to detect and realize the nature, sources, of detection and potential causes of risks that could affecting the collection of critical data or performance of critical processes. The risk assessment intimate the progress of a monitoring plan And, so supporting efforts to manage risks across a clinical investigation or across a product's progressing program.
3. The monitoring plan should consist of intimation in respect to identified risks and how the monitoring approaches will address those risk possibilities
4. There are few factors that affect monitoring of investigation
   - Complexity of the study design
   - Types of study endpoints
   - Clinical complexity of the study population
   - Geographic location of clinical investigator sites
   - standards of medical practice or less established clinical trial infrastructure
   - Electronic data capture to be utilized
   - Relative safety of the investigational product [9, 10].
5. **Planning of Risk based Monitoring**

   The monitoring plan should be consist of brief description of the study, its objectives, and the critical data & study procedures, clinical routine and site initimation, specific risk, policies and procedures, appropriate action regarding potential issues,
6. Sponsors of device studies wishing to solicit feedback on their monitoring procedures prior to the submission of the application may either submit a Pre-Submission, And contact CDRH's Division of Bioresearch Monitoring [11,12].
7. Components of Monitoring plan are
   - Description of Monitoring Approaches
   - Communication of Monitoring Results
   - Management of Noncompliance
   - Ensuring Quality Monitoring
   - Monitoring Plan Amendment [13,14]

Conclusion

Today's clinical trials demands an ideal RBM solution. One that is robust enough to meet the requirements of today's complex clinical trials. An effective RBM solution is built upon a modern system architecture that accommodates multiple sources of data capture and different operational solutions.

There are still numerous challenges for RBM. First, individuals will need to get comfortable with risk-based approaches. Training in unfamiliar systems and methodologies is a good first step, but practical experience will help refine procedures and analyses over time.

RBM mainly focus on safety of subjects, quality of data and also for quickly and effectively mitigating risks before they compromise trial quality, also provides the information regarding impact of covid19 in clinical trial monitoring and disruptions of trial activities during the pandemic period.

Every organization faces unique challenges when it comes to implementing RBM. There is no one approach that will ensure success, as each organization has specific influencing factors such as therapeutic areas, existing processes, and technologies. There is tremendous ROI opportunity with effective RBM, including higher data quality and improved patient safety, greater resource efficiency, reduced on-site monitoring, and reduced study timelines.

References

1. Vyas, N. R. (2020). Future of risk-based monitoring in clinical trials. International Journal of Clinical Trials, 7(3), 221. https://doi.org/10.18203/2349-3259.ijct20203109.
2. Barnes, B., Stansbury, N., Brown, D., Garson, L., Gerard, G., Piccoli, N., Jendrasek, D., May, N., Castillo, V., Adelfio, A., Ramirez, N., McSweeney, A., Berlien, R., & Butler, P. J. (2021). Risk-Based Monitoring in Clinical Trials: Past, Present, and Future. Therapeutic Innovation & Regulatory Science. https://doi.org/10.1007/s43441-021-00295-8
3. Fneish, F., Schaarschmidt, F., & Fortwengel, G. (2021). Improving Risk Assessment in Clinical Trials: Toward a Systematic Risk-Based Monitoring Approach. Current Therapeutic Research, 95, 100643. https://doi.org/10.1016/j.curtheres.2021.100643.
4. Kumawat, J. (2022). Risk Based Monitoring: What is it and How Can You Benefit - Saama. Saama.com. Retrieved 30 July 2022, from https://www.saama.com/risk-based-monitoring-what-is-it-and-how-can-you-benefit/.
5. Jaguste, V., 2022. Risk-based monitoring: Review of the current perceptions and toward effective implementation. [online] Available at: <https://www.researchgate.net/publication/332193018_Risk-based_monitoring_Review_of_the_current_perceptions_and_toward_effective_implementation> [Accessed 30 July 2022].
6. Agrafiotis, D., Lobanov, V., Farnum, M., Yang, E., Ciervo, J., Walega, M., Baumgart, A. and Mackey, A., 2022. Risk-based Monitoring of Clinical Trials: An Integrative Approach. [online] Available at: <https://www.sciencedirect.com/science/article/pii/S0149291818302339> [Accessed 30 July 2022].
7. Coogan, A. and Stone, C., 2022. Tackling the Challenges of Transitioning to Risk-Based Monitoring. [online] Applied Clinical Trials Online. Available at: <https://www.appliedclinicaltrialsonline.com/view/tackling-challenges-transitioning-risk-based-monitoring> [Accessed 30 July 2022].
8. 21 CFR part 312, subpart D generally (Responsibilities of Sponsors and Investigators) and 21 CFR part 812, subpart C generally (Responsibilities of Sponsors).
9. Guidance for industry Electronic Source Data in Clinical Investigations (September 2013).
10. FDA/CDER/"Purdie, Florine P, A Risk-Based Approach to Monitoring of Clinical Investigations, https://www.fda.gov/media/121479/download
11. FDA's draft guidance Medical Devices: The Pre-Submission Program and Meetings with FDA Staff. When final, this guidance will represent the FDA's current thinking on this topic. 35
12. IDE regulations (21 CFR 812.25(e)) require that written monitoring procedures be submitted as part of the IDE application
13. ICH E6, section 5.19, 6, 11 and ISO 14155:2011
14. CDER User, Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring, https://www.fda.gov/media/116754/download