PEER REVIEWED

Study Oversight Models & Implementation in Clinical Trials

With clinical studies becoming more complex, there is increasing demand for study oversight to ensure high-quality clinical data and efficient site performance. Drug developers want to ensure their clinical trial is a success and reduce the potential reasons for failure of a regulatory submission – and data integrity or poor site performance are common reasons for failure.

Traditionally clinical research associates (CRAs) are sent to sites to validate data and check site performance. This generates a large cost for CROs and pharmaceutical companies who are responsible for the monitoring of the trial, and the industry has seen new and novel ways to perform study oversight remotely with new technologies, as well as acceptance from regulatory bodies to reduce trial costs with the ICH GCP E6 (R2) addendum. The addendum allows for a degree of source data verification (SDV) to no longer have to be done on site, as well as to reduce SDV from 100% where risk permits[1].

Emerging technologies allow for the industry to move away from this traditional monitoring technique and use a remote monitoring approach performed from a central location where source data verification is performed remotely, known as rSDV.

As well as the ability to remote monitor, instead of investigating every site in a trial, which can become inefficient when there are multiple sites in large studies, a triggered monitoring approach can be implemented and study oversight is conducted when a set KPI is missed. This is also known as risk-based monitoring (RBM) and key risk indicators (KRI) must be defined to trigger these KPIs, which are defined in the study design of the trial. One of the disadvantages of RBM is that if a KRI isn't defined, then a potential issue at site can go undetected or unnoticed.

Centralised Statistical Monitoring (CSM)

This is where centralised statistical monitoring comes into play and has emerged in light of the proliferation of monitoring techniques. CSM addresses the need to review the data received from trial sites for integrity issues resulting from potential errors, misconduct or fraud occurring at trial sites.

CSM is an approach for identifying and managing issues affecting data integrity as quickly and efficiently as possible. It combines centralised monitoring with statistical monitoring. Centralised monitoring is when site data is evaluated for risks from a single off-site location, rather than reviewing risks directly on site at each investigative site. Statistical monitoring is the detection of data anomalies and data outliers with the use of complex statistical algorithms recommended by TransCelerate (and other statistical tests at the discretion of the CRO or pharma) to analyse data of various forms. This would include patient data but could also cover investigation-site data, laboratory data, and metadata. The statistical analyses' findings inform various monitoring, escalation or communication actions in line with the communication plan and the trial master plan (TMP).

It has been suggested that CSM should be performed at limited times during a trial and before any major analysis, such as interim or final analysis[2]. It is best to agree the schedule with the study team and some examples include every six weeks in line with traditional on-site monitoring or at recruitment intervals (such as 25, 50, 75 and 100% of target patients population being recruited), in alignment with independent data monitoring committee data cuts[3]. This permits the study team to properly investigate and resolve or mitigate identified issues without being swamped with frequent alerts.

Improving Data Quality with Data Quality Oversight

Data quality oversight (DQO) is the performance of running the statistical analytics within CSM and generating reports to identify outliers and anomalies, and improve the quality and integrity of clinical trial data. Monitoring and clinical data management teams can then investigate and resolve potential issues.

Performing DQO during study conduct and improving data integrity (the maintenance of, and the assurance of the accuracy and consistency of, data over its entire life-cycle), leads to improved data quality in the final submission data used to demonstrate an investigational new drug's (IND's) efficacy and safety.

Large trials with multiple centres and manual on-site monitoring via investigators are more time-consuming from a cost and clinical research associate (CRA) perspective. Importantly, they are more inefficient in the detection of data issues. This is because traditional on-site monitoring does not permit the easy application of statistical methods to detect data anomalies in important variables.

Investigators cannot perform data oversight as well as they could and are not detecting issues to improve data integrity as quickly as they could, meaning that with a 100% SDV approach, issues can exist for longer and go unnoticed. RBM allows a much easier integration of key risk indicators (KRIs) into protocols and monitoring plans and can significantly expand the kind of KRIs a sponsor is able to consider. Detecting data quality issues early is important so that corrective action can be taken during the conduct of the trial and helps prevent future issues[4].

KRIs and the monitoring techniques that a trial will perform must be clearly defined within a monitoring plan and the FDA have actively encouraged the RBM approach. The FDA states: "*At the same time, increasing use of electronic systems and records and improvements in statistical assessments, present opportunities for alternative monitoring approaches (e.g., centralised monitoring)*

that can improve the quality and efficiency of sponsor oversight of clinical investigations. FDA encourages sponsors to develop monitoring plans that manage important risks to human subjects and data quality and address the challenges of oversight in part by taking advantage of the innovations in modern clinical trials. A risk-based approach to monitoring does not suggest any less vigilance in oversight of clinical investigations. Rather, it focuses sponsor oversight activities on preventing or mitigating important and likely risks to data quality and to processes critical to human subject protection and trial integrity."[5]

With this level of endorsement, it is no surprise that the use of RBM has risen over recent years – research has shown that between 2009 and 2013, the adoption of RBM has risen from 33% to over 50% among industry stakeholders[6], and a survey in 2018 shows continued growth with 64% sponsor adoption and 71% CRO adoption[7].

Outsourcing Models Influence on Study Oversight

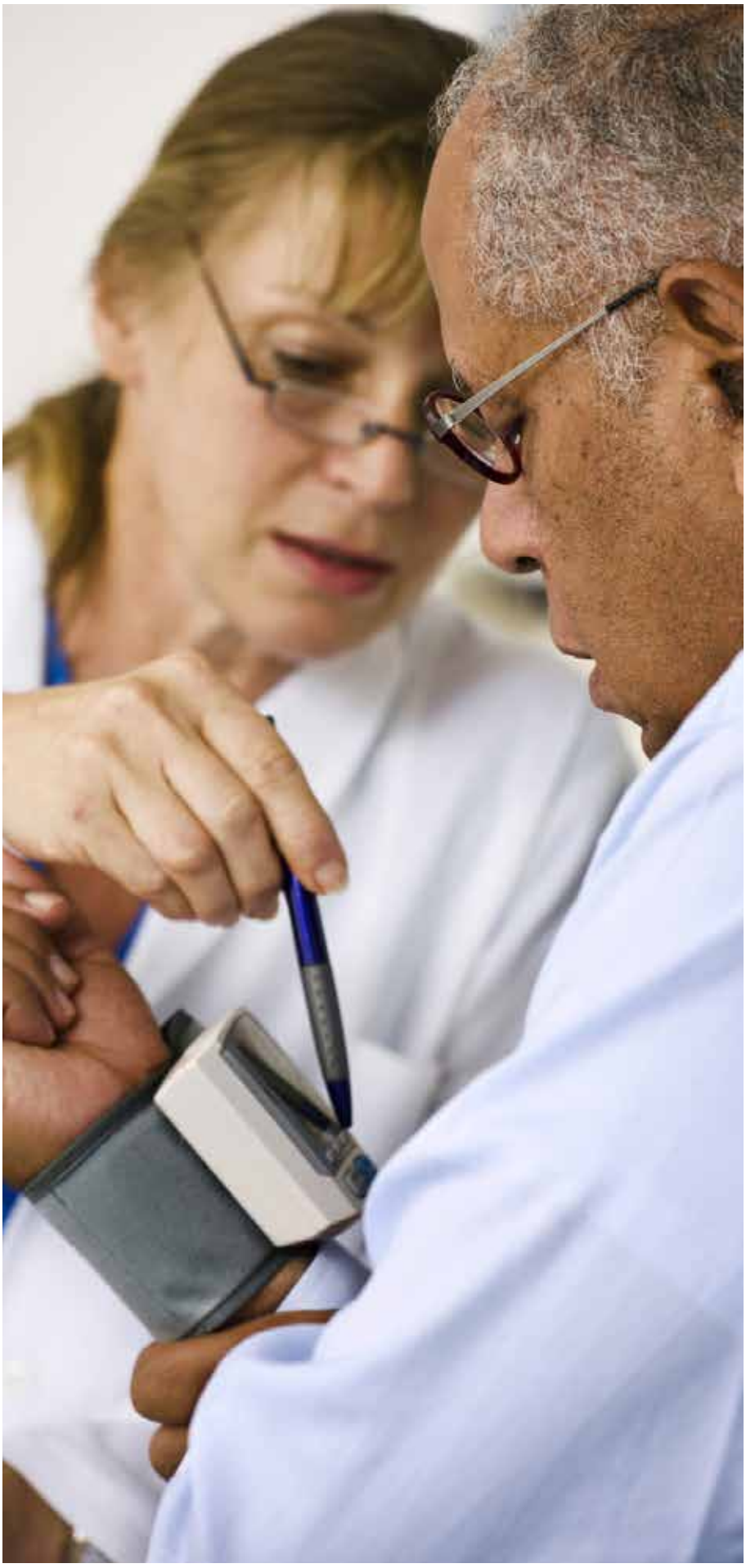
CROs have been a major force in the development of RBM and CSM solutions and, as such, are relied upon by many pharmaceutical companies. The demand for CRO-conducted clinical trials continues to rise – the market for CRO-conducted clinical development in 2015 was $25.7 billion and $34.5 billion in 2018, and is expected to reach $55.3 billion by the end of 2024[8].

With increasing outsourcing and the growth of the CRO space, sponsors need to perform a degree of CRO oversight to make sure that their partners are performing and delivering the results they are looking for in line with ICH GCP guidelines. This is why the governance of any relationship is important, and setting KPIs between the sponsor and vendor with regular reviews is encouraged. Governance is an important part of an FSP relationship and supports the improved study oversight between sponsor and CRO.

Full Service

Many pharmaceutical and biotechnology companies have looked to large, full-service CROs to support much of their required R&D services. In some cases, this has progressed to the point where a product is handed to the CRO and the pharmaceutical company has a completely hands-off approach to its development.

The challenge to adopting such an approach is primarily the reliance on a very small number of CROs (sometimes only one) and that the expertise and capabilities in specific functional areas may not be as consistently



strong across the CRO. Since over 90% of the time and budget relates to the clinical operations aspect, the primary selection of a full-service CRO is based around capabilities in clinical operations and a functional or centralised approach may therefore be preferred to provide greater flexibility and to minimise risk.

The advantage of this model is that with a single service provider, study oversight is conducted by one party so efficiencies can be achieved when working with a single vendor, as they centralise data and follow their own processes.

However, there are some disadvantages because a single service provider (primarily focused on monitoring) may not have as much focus in a specific functional area that a niche provider can offer. Also, they may be less accountable as they are not working with other vendors, so study oversight does not have that extra layer of review. A sponsor that is using a full service approach should be advised to conduct regular data fitness checks with DQO.

Functional Service Provision

Many companies, particularly larger pharmaceutical, biotechnology and medical device companies, decide to split the outsourcing of functions further or have a single provider across multiple functions. It is usual though for two to five vendors to be selected per function. The idea is that using niche vendors allows pharmaceutical companies to focus more on developing each relationship and in turn, CROs will prioritise partnerships where there is a higher volume of work.

Whilst a small number of companies have formed exclusive partnerships, having more than one vendor enables some degree of competitiveness and prevents reliance on a single CRO. Functional partnerships are often preferable because it allows the use of vendor companies that have focused expertise in specific functions.

There can also be competitive benefits to having multiple CROs involved in a single study or programme, rather than a single CRO across all functions. Having

functional partners can still result in efficiencies across studies, that can then help to reduce the overall cost of the work, if programmes are outsourced intelligently. From an oversight perspective, study oversight reduces as performed by vendors, but the CRO oversight increases as there are multiple vendors to monitor and check against vendor performance KPIs.

Conclusion

Study oversight is a broad topic. We have reviewed how site performance and clinical data controls can be implemented across various monitoring techniques, as well as technologies which implement statistical algorithms to detect any data anomalies. These go beyond reviewing just clinical data as they also review various data sources and identify issues at site that may not have otherwise be known. Also, study oversight is a vital component in different outsourcing models and sponsor/vendor relationships. Not only is governance key in a functional outsourcing model with CRO oversight, but also the study oversight is influenced by the outsourcing model and the number of vendors working on a study for sponsor companies.

REFERENCES

1. https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm269919.pdf
2. http://www.phusewiki.org/docs/2016_Deerfield_SDE/Centralized%20Statistical%20Monitoring%20to%20Detect%20Data%20Integrity%20Issues%20-%20Alun%20Bedding.pdf
3. Quanticate White Paper – The Importance of statistical monitoring in the new ICH E6 (R2) Guidelines https://www.quanticate.com/the-importance-of-statistical-monitoring-in-the-new-ich-e6r2-guidelines
4. http://journals.sagepub.com/doi/
5. https://www.fda.gov/downloads/drugs/
6. http://www.appliedclinicaltrialsonline.com/current-status-risk-based-monitoring
7. http://www.appliedclinicaltrialsonline.com/rbm-barriers-adoption
8. https://www.marketwatch.com/press-release/contract-research-organization-cro-market-2019-industry-research-share-trend-global-industry-size-price-future-analysis-regional-outlook-to-2024-research-report-2019-05-14

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