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How to Take the Risk out of Risk Based Monitoring

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ABSTRACT

Risk-based monitoring has been an increasing part of a programmer's role since FDA and EMA released their reflection paper and guidance on this in 2011. However, the role and requirement is very different in different organizations. This paper will look at what analyses are typically performed and what programmers can do to take the risk out of risk-based monitoring. Risk is typically calculated using data from many different sources, including fraud detection, screening failure rate, CRA feedback, EDC metadata and data quality. In addition, checks on the data that change during the different phases of trials need to be programmed, maintained and submitted by programmers. All these results not only impact how much data is monitored by CRAs at the site, but also what is monitored and how often. Hence the role of programmers in risk-based monitoring is key and growing, for which we must be prepared.

INTRODUCTION

The principle risk for a trial in taking a risk based approach to monitoring is the under monitoring of data, leading to harm in patients. Over monitoring can also be extremely expensive and waste valuable resource for large trials, and therefore is also a high risk for individual trials. Centralized risk based monitoring approach is based on defining a risk management plan, identifying the key risks within the trial and then performing continuous assessments on those risks by check programs on the trial data and meta data. The results are then reviewed by central monitors. This not only provides clear oversight of the trial for safety, it also assesses the quality of the data provided by each site and identifies their weakness so that they can be addressed before they become serious.

There are many risks defined within the Trancelerate position paper on risk-based monitoring methodology ⁽¹⁾ that organizations can perform continuous assessment on, however, not all are required for every trial. There are some key risks that must be assessed for all trials, and then of course some trial specific ones, but if too many are reviewed, then there will be many false positives requiring further investigation or site inspections, making the overall process inefficient. Therefore care must be taken to not only identify the appropriate risks to assess, but to also give the correct weight to each risk being assessed if the centralized risk-based monitoring is to be a success.

CENTRALIZED MONITORING

Centralized monitoring is based on the philosophy that "everything that can be done remotely should be done remotely". These tasks can then be performed regularly in a timely manner and issues can be identified sooner. As the data checks are programmed, they only need to be written once and can be run as often as required on the latest data. As these are logical checks they are far more likely to identify systemic or random data issues within patient, within site or across sites than CRAs reviewing data on-site. This not only leads to lower risk of safety issues being missed, it also leads to better quality data overall. In addition it is far cheaper, and given that the cost of monitoring can be almost a third of the cost of a trial, it leads to significant savings based on reduced on-site monitoring.

Central monitoring focuses on Risk Indicators, and although the primary aim is the review of centralized data rather than a centralized review of individual site data, being able to program site level checks mean that this can also be performed centrally with little extra effort.



TYPES OF DATA REGULARLY CHECKED CENTRALLY

Key items of data that are regularly assessed, especially with regards to the safety aspects of the trial are:

1. Protocol deviation rates
2. Data entry and query resolution metrics
3. Adverse event trends or outliers
4. Subject discontinuation trends
5. Unusual data trends or patterns
6. Error rates in Critical Data/Processes
7. Fraudulent data detection

Critical data and process includes primary and secondary endpoints, data and processes critical to patient safety and ethical treatment, and processes that underpin data quality. These data items are monitored very closely, both centrally and manually during on-site visits.

As the aim is to reduce on-site monitoring, increase off-site monitoring and the frequency with which the data is checked, the following checks are also programmed and regularly submitted on the latest trial database:

1. Confirm timeliness and quality of data entry, the quicker data is entered after a visit the better the quality
2. Review query resolution, how many queries raised per page and how quickly they are resolved
3. Assess site's recruitment and enrollment
4. Monitor investigational product
5. Monitor frequency of changes in key site staff

TYPES OF DATA REGULARLY CHECKED ON-SITE

Centrally assessed data helps to identify data issues that may occur either due to site issues or due to systemic problems in the process; however, they are there to support the on-site visit, this is still key in terms of resolving site specific issues. In addition to checking data centrally, RBM approach can also be used to define what is checked on-site. These must be pre-defined in a Risk Management Plan.

On-site visit takes time and is expensive, it is therefore important to ensure what is checked on-site essential for patient safety, data quality, trial conduct and GCP. However, RBM allows for a variable approach to RBM, where how much data is checked on-site is based on the quality of the site. As the risk of a site is determined centrally by the various quality checks, so the site's risk score can be used to determine how much data is checked using the various methods. These can also be programmed by the programmer and allocated to each site for the Clinical Research Associates (CRA) to carry out.

On-site monitoring activities that can be allocated using an algorithm based program include the following:

1. Source Data Verification (SDV)
2. Source Data Review (SDR)
3. Unreported Events Review (UER) where appropriate
4. Informed Consent Review
5. Investigational Product Accountability
6. Essential Documents Review (if appropriate)
7. Face-to-face training and discussions with site staff

ROLE OF PROGRAMMERS IN CENTRALIZED MONITORING

Internal surveys of different pharmaceutical organizations have shown that more than 90% of all findings detected during on-site visits could have been achieved through centralized monitoring. This has led to a shift in mindset as it is possible to program the checks ahead of time and then submit them regularly to check the trial database without having to send someone on-site. For large trials or trials with few patients spread across many sites, this is now the norm, hence programmers are being involved in tasks they never performed in the past.

In addition to the data quality checks, performing checks to assess data for fraud is now also a regulatory requirement. As this integrates well with the Risk Based Approach to monitoring, where assessing the quality of the



sites based not only on data quality from the site but also on the possible risk of site containing fraudulent data, the role of programmers in centralized monitoring is firmly established.

PREPARATION AND STANDARDIZATION

CDISC standard data is now commonly used in many pharmaceutical organizations, however, the raw data that is collected is still not in a standard structure. Companies therefore have to determine whether the programs for performing fraudulent data checks and other data quality checks should be based on SDTM or on the raw data. This goes further in that if the checks and subsequent risk calculations lead to monitoring tasks being assigned, then those must be based on the raw data as that is the data the CRA will be confronted with on-site.

Typical fraud detection analyses include:

1. Checking inliers and outliers using correlation
2. Incorrect dates, national holidays and weekends
3. Last digit preference and rounding using plots
4. Serious adverse events rate
5. Cluster analysis of efficacy results
6. Distance between planned and actual visits

The tasks faced by the programmer can be split into different parts when it comes to centralized monitoring; fraudulent data detection, data quality, patient safety monitoring, and finally monitoring task assignment. If SDTM structured data can be generated from the start of the trial data collection, then all programming except monitoring task assignment can be performed on the SDTM data. This not only helps to develop standard programs that can be used in most if not all trials, providing programmers with more time to further investigate trial specific data issues, it also raises the quality of the programs, reducing their risk factors.

Modular designed macros for performing individual checks based on SDTM structure allows individual studies to determine which checks are required, including those considered to be standard and should be used in all studies, such as serious adverse events monitoring. Each type of fraudulent data check can also be performed in a separate macro, again, allowing the possibility for each study to determine which are required based on their particular data collection. This then allows the programmer to select the macros to be called without having to write or validate them for each study, not only saving time and resource, but reducing the risk of checks being missed, or more commonly incorrectly implemented.

The task of assigning which raw data should be monitored based on the risk can be either done in the form of listings for the CRAs to use while on site, by triggering flags within the Electronic Data Capture (EDC) system or by creating task assignments in an external monitoring system. If only one of these approaches is used within an organization then this too can be structured in a modular macro system, helping not only to reduce time for programmers, but to also provide all CRAs a consistent approach to monitoring across studies, thereby reducing the risk of data quality or patient safety issues being missed.

CONCLUSION

Given the cost of monitoring can be up to a third of the cost of a trial, the cost savings resulting from the implementation of a risk based approach to monitoring cannot be ignored, and implementing it at least on the larger studies is no longer open for discussion. It is therefore firmly established in most organizations, as is the role of programmers to provide support in implementing it. The risk based approach however is not just for monitoring, it also applies to program development, maintenance and usage as well as associated validation. The more standard a program is, the more it is validated for usage across studies, and the more it is used without any issues being identified, the lower the risk factor it has.

From a programmer's point of view, the use of a standard data structure such as SDTM is key to reducing the risk when it comes to implementing an RBM approach. This allows for the development and implementation of small standard macros that perform individual checks and analysis that may be required. Using these across all studies not only reduces the risk of missing fraudulent data, data quality or patient safety issues, it also reduces to the risk of incorrectly implementing risk based monitoring. This will also highlight the effectiveness of a risk based approach to both monitoring, programming and program validation.



REFERENCES

1. Position Paper: Risk-Based Monitoring Methodology, TransCelerate BioPharma Inc., 30th May 2013.
2. Guidance for industry: Oversight of Clinical Investigations - A Risk-Based Approach to Monitoring, U.S. Department of Health and Human Services Food and Drug Administration, August 2013.

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