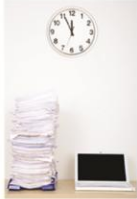


Centralised Risk-Based Source Data Verification

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1. Introduction

The cost of on-site monitoring is soaring, and with questionable results of 100% source data verification (SDV), regulators are encouraging risk-based SDV (rSDV). We discuss the possible risks of rSDV and show how centralised rSDV approach is more effective in improving study quality.



2. Current issues with SDV

Quality risk management in clinical trials is often interpreted as risk elimination when it comes to SDV. Pharmaceutical companies attempt to eliminate risk by performing 100% SDV. However, the cost of on-site monitoring is now around a third of the cost of a trial, so performing 100% SDV is a very expensive method of eliminating risk. Also, on-site monitoring involves many more tasks than just SDV, tasks that are important for the overall quality and compliance, and so must be performed. So how does the monitor perform 100% SDV and all the other tasks without spending a considerable number of hours at the investigator site?

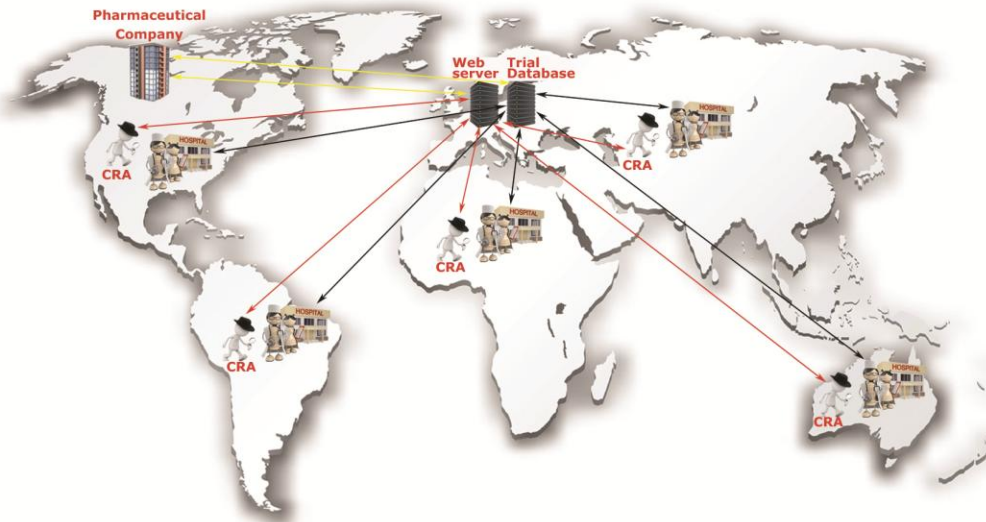
3. Risk of not performing 100% SDV

Studies have shown that less than 1% of data is changed due to 100% SDV, and the effect of this change on the primary analysis is negligible. Therefore quality risk is not directly affected by 100% SDV.

It was also often thought that regulators preferred 100% SDV, and therefore not to do this may raise quality risk concerns. However, recent papers from FDA (Guidance for Industry - Oversight of Clinical Investigations - A Risk-Based Approach to Monitoring, August 2011) and EMA (Reflection Paper on Risk-Based Quality Management in Clinical Trials, August 2011) are positively encouraging pharmaceutical companies to abandon the 100% SDV approach in preference to a more risk-based source data verification.

4. Tasks performed during on-site monitoring

- Check compliance with GCP
- Check compliance with Protocol and identify reasons for protocol violations
- Identify reasons for high or low drop outs
- Check correct equipment and methods are used
- Check training and quality of staff, staff turnover
- Identify systematic deficiencies and provide solutions to resolve them
- Identify fraud
- Check quality of data



Pharmaceutical companies receive data from investigator sites and feedback from CRAs. They have programmed centralised checks in place to check the data for fraud, consistency and accuracy. Risk is assigned to each site based on the data checks, CRA feedback and knowledge from previous collaboration. What data of which patient the CRAs should check is identified based on the risk.

Investigator sites receive queries raised by the pharmaceutical company. These issues are identified by automated checks which are run frequently on the latest data. They respond to the queries and enter data using Remote Data Capture.

CRAs receive details about which patients to check and to which level for each site they are responsible for. CRAs only check the data they are instructed to check. This leaves them more time to check:

- Quality of staff
- Changes in site staff
- Is site following the protocol specified process
- Additional data based on their instinct

5. What is centralised monitoring risk-based SDV approach?

Centralised monitoring can be thought of as moving a little bit away from the manual and subject process to an automated and logical process. As things are programmed, it is also possible to then identify key data issues for the monitor to check, and therefore in effect ask the monitor to target their SDV and just check the data which they are asked to check.

This process has a risk associated with it, as the monitor is not performing all the checks manually, and they are not looking at 100% of the data. However, the advantages of automating these processes far outweigh the previous manual process.



6. Advantages of a centralised risk-based SDV approach

- Systematic errors are easy to spot by looking at data trends and protocol violators
- Data errors, outliers, missing and inconsistent data are identified with programs and logic rather than the luck of the eye
- More complex fraud checks and statistical analysis can be programmed
- Site characteristics and performance metrics can be monitored over time by looking at high screening failure rates, eligibility violations and delays in reporting the data
- The automated checks can be submitted routinely on the database without the need to visit the site
- CRAs have less data to review when they are at the site, and so can verify the data and still have time to check the data
- CRAs have more time to do more GCP and Process checks at the site, provide more training and so on
- CRAs visit sites with issues more often and spend longer time there, and visits sites without issues less frequently

7. Risk involved with a centralised risk-based SDV approach

- One problem is that it is risk-based, so there is a risk that some mismatches between source data and the database may be missed
- The formula for assigning RISK will have to be adjusted over time
- The risk assignment should be continuously updated based on the latest data, meta data and CRA feedback. This will mean that the risk factor will increase over time for risky sites.



8. Conclusion

Although on-site monitoring can cost around a third of the total trial cost, the quality of the trial data must be unquestionable. Quality risk management is therefore essential. Applying a centralised risk-based SDV approach will reduce the amount of data the CRAs have to verify at every site, allowing them more time to target problem areas, whether that means visiting specific sites more often or specific issues within a site.

This approach will not only increase the chances of identifying data issues, both random and systematic, it will also help to check for fraud and increase the quality of the trial. As more time will be spent on automatic checks, and less on on-site monitoring, the overall cost of on-site monitoring will be reduced, and the savings will increase as the size of the trial increases from small to medium to mega trials.

9. References

Draft Reflection Paper on Risk-Based Quality Management in Clinical Trials (EMA/INS/GCP/394194/2011), EMA, 4 August 2011

Draft Guidance for Industry Oversight of Clinical Investigations - A Risk-Based Approach on Monitoring, FDA, 24 August 2011