

Centralized Risk-based Source Data Verification

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ABSTRACT

SDV is a very expensive process due to the time required to go through all the data at the various investigator sites. However, if we can target the patients and specify items the CRAs should look at when they visit a site, then the CRAs can spend more time looking at the important data but still spend less time overall. Although this may not be too useful for small studies, for large and mega trials this can and has already saved millions. This approach is also being encouraged by FDA and EMA as a possible method for improving the quality of trials and trial data. The key aspect here is defining the risk associated with a site, and how to change this over time. The paper will show why this is a very good approach to both reduce cost and improve the data quality at the same time.

INTRODUCTION

This paper will show why the current system of 100% Source Data Verification (SDV) is both costly and inadequate to deliver the high level of quality demanded by the regulators for clinical trials, and how a modified and simpler version can deliver better quality of trial data.

The cost of on-site monitoring clinical trials is soaring, and with questionable results of 100% SDV, regulators are actively encouraging companies to take a more risk-based approach to SDV (rSDV). We discuss the possible risks of rSDV and show how centralized rSDV approach is more effective in improving study quality than the current approach of 100% SDV. More importantly, it can achieve this improved quality and reduce cost at the same time.

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, including GCP measures must also be performed.

The challenge for the monitor is then to perform 100% SDV and all the other tasks without spending a considerable number of hours at the investigator site. This leads to rushing the site visit, and thereby either missing issues, especially if they are related to cross checks between different questions on multiple pages, or not having enough time to clarify and explain how to avoid certain issues.

RISK OF NOT PERFORMING 100% SDV

Studies have shown that only a very small percentage of data is changed due to 100% SDV, and the effect of this change on the primary analysis is negligible. Many of the data issues are identified and queried by Data Management during screening rules checks and consistency checks. Therefore quality risk is not directly affected by 100% SDV.

It was 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 approach. So the risk of problems from regulators for following such an approach is now also no longer an issue.

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TASKS PERFORMED DURING ON-SITE MONITORING

It is important to be aware of all the tasks that are performed during an on-site monitoring visit to fully appreciate why these visits are important and time consuming. Here is a list of the main tasks:

- 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

WHAT IS A CENTRALIZED MONITORING RISK-BASED SDV APPROACH

Centralized monitoring can be thought of as moving a little bit away from the manual and subjective process to an automated and logical process. It is moving away from looking at the data by eye to a process where all the data is checked by programs. As checks are then programmed centrally and run on all patient data, it then becomes possible to identify key data issues for the monitor to check, and therefore in effect ask the monitor to target their SDV and mostly check the data with issues.

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

- **Assign risk**
 - Receive data from investigator sites
 - Receive feedback from CRAs.
 - Use programmed centralized checks 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 and ongoing collaboration.
 - What data of which patient the CRAs should check is identified based on the risk.
- **Data queries**
 - Investigator sites receive queries raised by automated checks
 - Submit centralized check programs regularly to monitor data quality of the latest data as an ongoing process
- **Monitoring visits**
 - If a site has some types of data issues coming up consistently, then inform the CRA to provide more training to reduce those issues
 - Inform CRAs 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.
 - CRAs then have more time to check:
 - Quality of staff
 - Changes in site staff
 - Is site following the protocol specified process
 - Additional data based on their instinct

ADVANTAGES OF A CENTRALISED RISK-BASED SDV APPROACH

The advantage of a centralized risk based SDV approach is that systematic errors are easy to identify by looking at data trends and protocol violators. This means that if a site has misunderstood something this will become obvious. It also means that all sites are being checked regularly by the automated checks on the latest data, and there is not a wait until a monitoring visit has to be performed.

Automated programs also has the advantage that data errors, outliers, missing and inconsistent data are identified with logic rather than the luck of the eye, and more complex fraud checks and statistical analysis can be programmed very easily. Site characteristics and performance metrics can also be monitored over time by looking at high screening failure rates, eligibility violations and delays in reporting the data.

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All this means that the CRAs have less data to review when they are at the site, which leaves them with time to both verify the source data and check the data to ensure it makes sense. They also have extra time to do more GCP and Process checks at the site, provide more training if required and so on. CRAs will then be able to visit sites with issues more often and spend longer time there, and visits sites without issues less frequently. This all helps to improve the quality of the trial and the data.

RISK INVOLVED WITH A CENTRALISED RISK-BASED SDV APPROACH

One problem with the risk based SDV approach is that by definition, it is risk-based. So there is a risk that some mismatches between source data and the database may be missed. However, the quality checks and consistency checks should identify any data which is very different from the expected values. The key factor in this approach is the calculation and assignment of risk. The formula for assigning RISK will have to be adjusted over time as more data is collected for each site. 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.

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 centralized 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 addressing 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. This saving will increase as the size of the trial increases from small to medium to mega trials.

Finally a method promoted by the FDA and EMA, which improves the quality of the data in the trial and reduces cost.

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