Paper AR06

A Three-pronged Approach to Central Monitoring to Identify Potential Risks and Ensure Data Quality

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ABSTRACT

Centralized Data Review, leveraging real time data, is a key component of Analytical Risk-Based Monitoring. Continuous monitoring of the data increases trial oversight and enables the right action to be taken at the right time.

At Janssen R&D, we have adopted a three-pronged approach to centralized monitoring that better identifies potential risks and drives improved data quality. The following central monitoring oversight capabilities will be shared: 1) Use of a dashboard with (standard) Key Risk Indicators to indicate potential risks in countries/sites. 2) Use of Study-Specific Reports to indicate potential risks in countries/sites related to quality of critical study data. 3) Use of Central Statistical Surveillance to identify data anomalies.

INTRODUCTION

Sponsors of clinical trials have the responsibility to guarantee the safety of the subjects and to ensure the data collected is accurate. Therefore, it is essential that a robust monitoring plan is set up in order to detect, prevent and mitigate risks that are characteristic for the study. To improve effectiveness of study monitoring, the monitoring activities should be adequate to the specifics of the data collected. The potential impact of data issues on trial integrity and subject protection needs to be considered as well as the likelihood of occurring and detectability of issues. In addition, monitoring activities need to be flexible as potential quality issues can change over the course of a study. Because on-site monitoring largely determines the cost of a clinical trial, effective central monitoring can reduce clinical development costs by allowing resources to be used more efficiently while increasing effectiveness. Over the last 6 years, Janssen has invested much to improve oversight in data quality and to enhance the detectability of potential data quality issues. In this paper, we will go over three centralized monitoring strategies that have been developed and implemented in our company.

DASHBOARDS OF KEY RISK INDICATORS

To follow up on key risk indicators (KRIs) during trial conduct, dashboards are of paramount importance. They improve the monitoring of critical aspects and provide an overview of KRIs that are common across different studies, allowing a standard implementation. KRIs for a study are determined at the study start, when the Analytical Risk Based Monitoring plan is set up.

At Janssen, dashboards are available for several operational KRIs as well as KRIs linked to subject safety such as adverse events. The dashboard enables to look at the data across the whole trial, but also enables to focus on data by country or site, or to zoom in on specific visits or time period. The comparison between countries, sites and timeframes permits a swift identification of both data quality issues and trends. Thresholds are available to detect sites that are below or above the mean.

Working group meetings to discuss and document potential issues are set up regularly. During these meetings, further escalation actions are identified and planned. The outcome of the issue investigation is then brought back to the team, documented and closed.

STUDY SPECIFIC REPORTS

Besides these standard dashboards, there is a need to create visualizations to follow up on risks that are specific to a protocol and therefore require a more customized approach. The growing complexity of trials and the continuous implementation of new analysis techniques call for flexibility in monitoring strategies. Study specific reports (SSRs) were introduced to fill this gap. These reports use raw data, which allows the possibility to follow up on critical to quality (CtQ) factors in ‘real time’ and very early in the study, immediately at first patient in (FPI). At the later stage in the trial, SSRs can be developed to follow up on additional risks that were identified during the study that warrant close follow up.

Which SSRs are needed for a particular study will be determined during study set-up and discussed during the protocol de-risking process, when CtQ factors are identified, and mitigation plans and monitoring strategy are established. The details for the specific SSR requests are brought to a dedicated team where requirements are set up and the report is developed in SAS® Life Science Analytics Framework and TIBCO Spotfire®. A typical example of an SSR is the follow up of biomarker samples (see Figure 1). Biomarker samples generally need close monitoring as they are often a critical endpoint of the study. The SSR checks if the correct biomarker samples were taken at the correct visits. Moreover, it allows to follow up if the expected samples are also received by the different vendors doing the lab analysis. The visuals provide the possibility to look at the data by country and site and to zoom in on issues identified. By comparing data between sites and countries, data quality issues and trends can be detected.

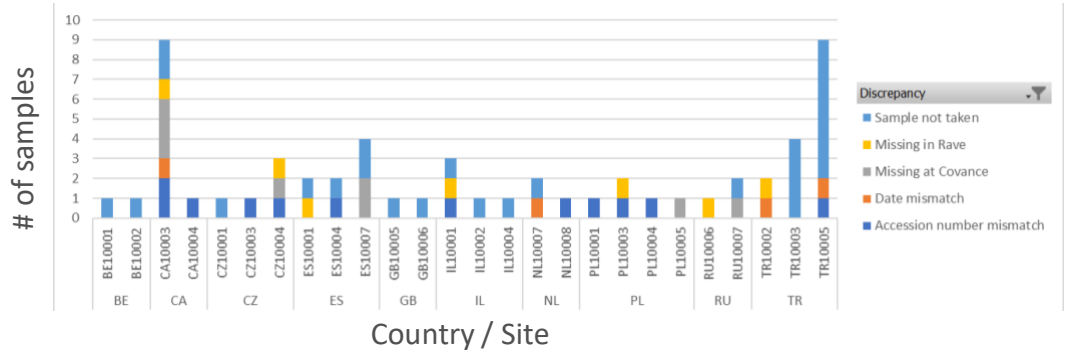

Figure 1: Overview of the number of samples per country and site. A higher number of samples not taken is seen in a specific country (TR).

Once created, the visualizations are made available to all members of the study team including the site monitor. Regular working group meetings provide a framework where issues are discussed and documented. Similar as with dashboards, data quality issues identified by SSRs follow an escalation path in order to address them efficiently and effectively.

CENTRAL STATISTICAL SURVEILLANCE

While dashboards and SSRs focus on the data quality of a study by comparing data errors and looking for trends at site or country level, central statistical surveillance (CSS) is used to detect issues in the data itself. It provides an additional layer of protection for subject safety and uncovers data quality issues that otherwise might have remained undetected as even the most careful onsite review will not always reveal unusual data patterns. Moreover, it provides the extra advantage that every variable in the case report form (CRF) can now be used as an indicator of clinical data quality and not only those variables that were previously identified as key risk indicators.

Statistical surveillance takes advantage of the structured nature of clinical data and of the naturally occurring relationships within a trial's data. These naturally occurring relationships can be identified:

- between clinical parameters: different measures taken from the same subject at the same time should be related to each other;
- in subject profiles over time: the same measurement from the same subject at different visits should be related;
- between subjects: the same measurement for different subjects should NOT be related.

These naturally occurring relationships on the study level can be determined and then used as a comparator to identify sites that behave differently.

At Janssen a set of central statistical surveillance tools were developed to detect potential data quality issues in sites during a clinical trial. After successful pilots in 2018, CSS was rolled out to all studies that meet certain minimum criteria. In order to use CSS, a study should have at least 20 sites with enough numerical data over at least 3 visits. The CSS tools are programmed in R and are available as a set of visuals in TIBCO Spotfire®.

During the pilot phase, the CSS tools were tested by running them on internal trials with known data issues. These are used as examples to illustrate how CSS is able to detect data errors.

The first example shows how relationships between numeric variables tested during the trial can help identify data quality issues. In one immunology study a strong relationship was found between 2 questionnaires taken during the study. One of the questionnaires was used to score the severity of disease and was filled in by the investigator at the site. The other questionnaire was a patient report outcome (PRO) measured by the subject. As expected, the questionnaires showed a strong relationship between each other. For 1 site however, this relationship between

questionnaires was found to be different (Figure 2). This difference might have been the result from a misunderstanding of the question or an error in the ePRO device.

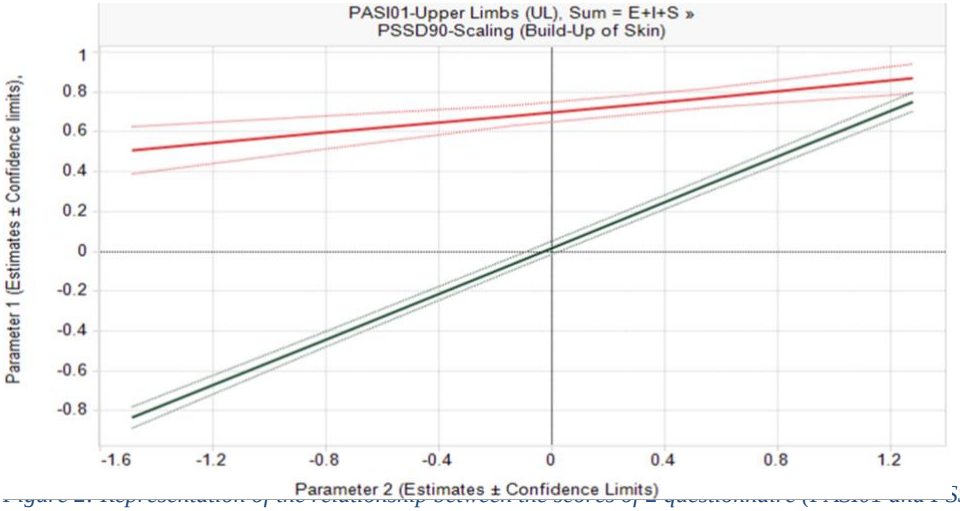

Figure 2: Representation of the relationship between the scores of 2 questionnaires (PASI01 and PSSD90). The red line represents the result of the site under investigation, while the green line represents the study average (study average includes all data except for the site under review).

The second example demonstrates a difference in site profile over time of one site versus the other sites. When looking at the pulse rates of subjects from one site it was seen that these were consistently higher than study average (Figure 3). Potential root causes of this type of issue might be the use of faulty equipment, the data being entered in the CRF wrongly or pulse rates taken by someone who isn't qualified to do the assessment. Also, demographic differences can provide an explanation for these differences as the subjects at this site may fall into a demographic category that typically has higher pulse rates. In any case, further investigation at the site or a more detailed review of the data is needed to determine the appropriate corrective and preventive actions.

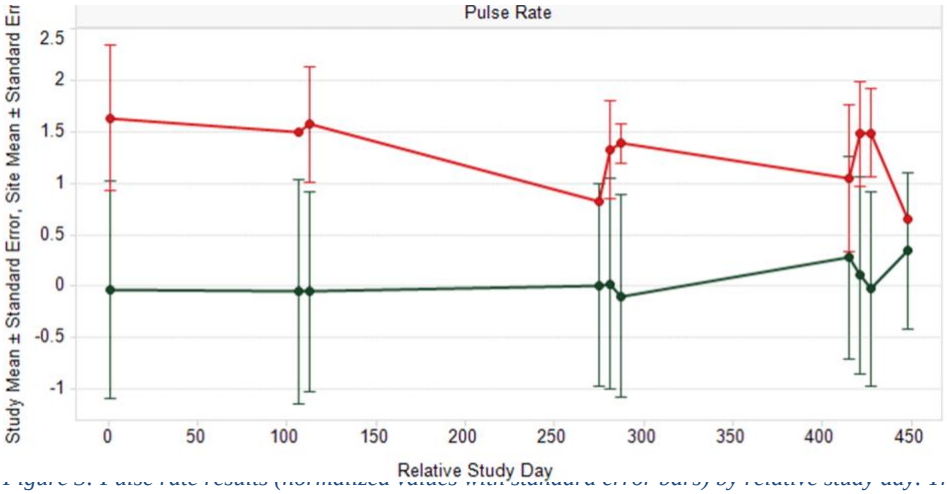

Figure 3: Pulse rate results (normalized values with standard error bars) by relative study day. The red line represents the site results, while the green line represents study results (study average includes all data except for the site under review).

The third example shows a site where the difference of certain measurements between subjects was lower than seen in the other sites. When looking at the alkaline phosphatase values, this site had lower differences between subjects at multiple collection times as compared to other sites (Figure 4). Further investigation of the laboratory results or review of the source notes is then required to identify the potential root cause.

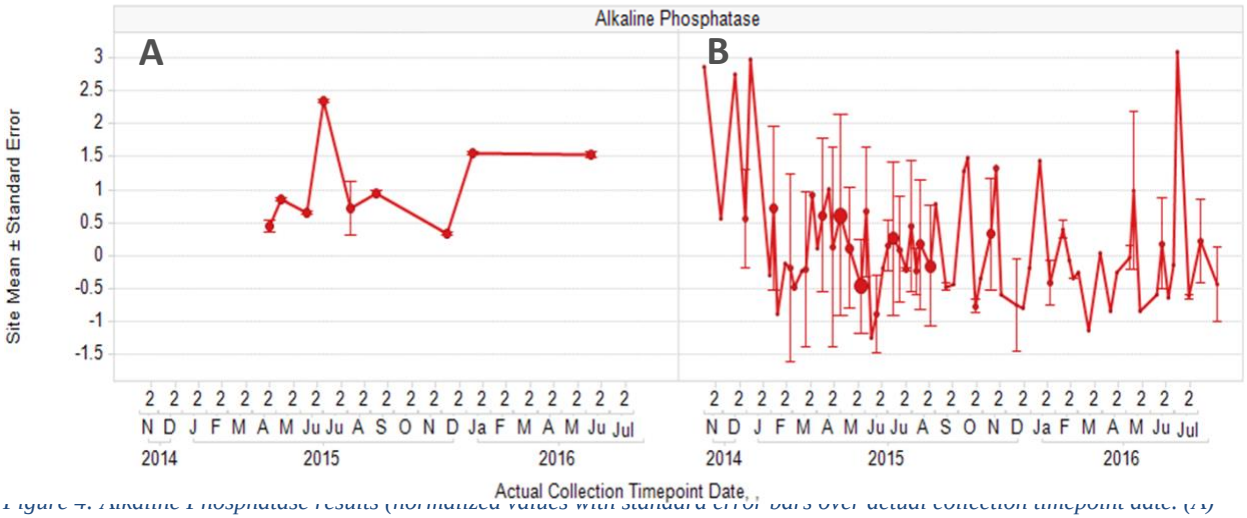

Figure 4: Alkaline Phosphatase results (normalized values with standard error bars over actual collection timepoint date). (A) represent the results of the site under review which shows a lower difference between subjects as compared with (B) the study results.

After the CSS tool is run, the results are assessed by a dedicated team that analyzes the output and presents it to the central monitor of the study. Because of their knowledge of the specifics of the study, the central monitor manager (CMM) will then discuss the outcome during the monitoring meeting, where for each finding potential root causes and follow-up actions are suggested to the study team. The necessary escalation steps are taken and documented.

POINTS TO CONSIDER

As with any change, there are points to consider when implementing new centralized monitoring strategies. Here we sum up some of our lessons learned during the roll out of SSRs and CSS.

For SSRs, raw data needs to be available early in the study. This requires a good collaboration between Janssen personal and the different vendors. Also, it can pose issues for smaller vendors that have technical limitations which may not be resolved easily.

In addition, due to the non-standard nature of the SSR report, standardization can be challenging.

The implementation of CSS requires specific skills to correctly interpret some of the more complex analyses. This was overcome by providing a thorough training to only these central monitoring managers that have a more technical background and by setting up a subject matter expert group.

Secondly, CSS analyses can only be applied to studies that contain sufficient amount of data. Therefore, there may not be enough data to perform the CSS tests early in the study.

Lastly, statistical monitoring relies on data captured electronically. However, some data (e.g. signatures) are still collected on paper. Consequently, all data errors cannot be completely prevented by statistical monitoring. In such cases, on-site visits or audits are still necessary.

CONCLUSION

Centralized monitoring provides an opportunity to improve data quality while using resources more efficiently. The successful implementation of KRI dashboards, SSRs and CSS improved the follow up and detectability of issues during the clinical study. It reduced the risk and enhanced the overall data quality by identifying data errors early in the study, effective issue resolution and reducing the need for on-site monitoring.

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