

PRACTICAL IMPLEMENTATION OF CENTRAL STATISTICAL SURVEILLANCE IN CLINICAL TRIALS

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ABSTRACT

Being able to detect potential data quality issues is key to the success of multicenter clinical trials. Equally as important is the ability to accurately interpret the data, clearly communicate the potential issues, conduct a root cause analysis, and take the appropriate corrective and preventive actions. At Janssen R&D, Central Statistical Surveillance (CSS) Analysis is used to detect unusual data patterns and potential data quality issues within clinical data. To ensure the CSS Analysis review is scalable, we have trained a team of Central Monitoring Managers, selected based on their analytical aptitude and clinical operations experience, to analyze, interpret, and translate complex statistical concepts into reports and presentations easily understandable and actionable by clinical operations staff. While this approach enables trial teams to complete a root cause analysis of the most critical findings and implement corrective and preventive actions, it requires a well thought development and roll out roadmap.

INTRODUCTION

Good Clinical Practice guidelines⁽¹⁾ state that a robust oversight plan for ensuring data quality is essential in all clinical trials. It is of paramount importance that potential data quality findings, identified because of pre-defined data oversight plans, are interpreted and communicated to clinical operations team members so that timely investigation and mitigation are completed. At Janssen, CSS is used to identify sites within a clinical trial where data patterns differ from the patterns observed in the study norm⁽²⁾, giving insight into potential data quality issues. Although development of CSS was completed in 2017, it has taken approximately 1 year to determine the best way to operationalize this new data surveillance due to its complexities. In 2018, we successfully piloted a process for interpreting, documenting, communicating and actioning the CSS findings. The process will enable us to provide CSS support for all Analytical Risk Based Monitoring (ARBM) trials by 2020.

STAFF TRAINING

The first step to meeting this objective was to identify and train existing Central Monitoring Managers (CMMs) as Central Statistical Surveillance Analysts [CSSA]. CMM is a role within the Risk Management Central Monitoring Department that is responsible for the oversight and conduct of the protocol risk management plan. An assessment of CMMs in each Therapeutic Area (TA) was completed, and those determined to have the background best suited for understanding the statistics and analytics were chosen for the pilot team of CSSAs. In choosing these CMMs we also considered their TA experience, so that we could better understand the nuances of each TA and adjust the CSS analysis was set to fit each TA.

CSSAs are responsible for the interpretation of the CSS output and translation of the results into terms that clinical operations team members can easily understand. The initial three-day training was conducted by the CSS Subject Matter Expert (SME) and CSS Statistician and included:

- The statistics behind the CSS Analysis Model
- How the outputs are converted into an interactive dashboard and how to interpret the dashboard
- How to Translate the observations noted in the dashboard from statistical terms to easily actionable clinical terms
- Didactic and hand-on exercises

Once trained, CSSAs were assigned trials within their existing TA to aid in their interpretation of the analysis by leveraging their experience and understanding of TA specific protocol nuances. TA alignment also allowed for an eventual assignment of a CSS Subject Matter Expert (SME) within each TA, who will assist in the support of future CSSAs.

Additional support was provided to the CSSAs via ongoing one-on-one sessions with the CSS SME. In these sessions the CSSAs discussed their ongoing reviews and observations not seen during training with the CSS SME and thus continued to build their expertise. In bi-weekly meetings the CSSAs present these new cases to the entire

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team to spark discussion and share the knowledge. Through the combination of both, we continually add to the CSSAs' knowledge base and promote consistency in analysis interpretation across TAs.

DOCUMENTATION PROCESS

The next step was to develop a process for documenting the CSS review process, the CSS findings and follow-up actions for potential data quality issues. Janssen maintains a dedicated Analytical Risk Based Monitoring structure and process that is well embedded in the overall clinical operations process. CSS Analysis has been mapped to this existing process.



Figure 1. High Level Central Statistical Surveillance Analysis Process Map.

Integrating the process for running the CSS analysis into an already established process negates the need for SOP updates and/or process changes and training.

Core documents, systems and procedures within RMCM include:

- Integrated Analytical Risk Based Monitoring (iARBM) Plan. This document outlines all identified trial risks and mitigation strategies. CSS conduct and are now documented in this plan.
- Centralized Findings identified during the central reviews are documented in mCTMS and assigned to the appropriate role for follow up and closure. CSS findings are now documented as Centralized Findings.
- Central Monitoring Working Group (CMWG) is a structured cross functional team meeting led by the CMM to review central findings identified from various systems. CSS results will be reported out at the CMWG where potential findings can be discussed, and recommended follow-up items agreed.

COMMUNICATION OF OBSERVATIONS

The final step in the implementation of CSS is the translation of the complex statistical outputs of the analysis to easily understandable and actionable items for clinical trial teams.

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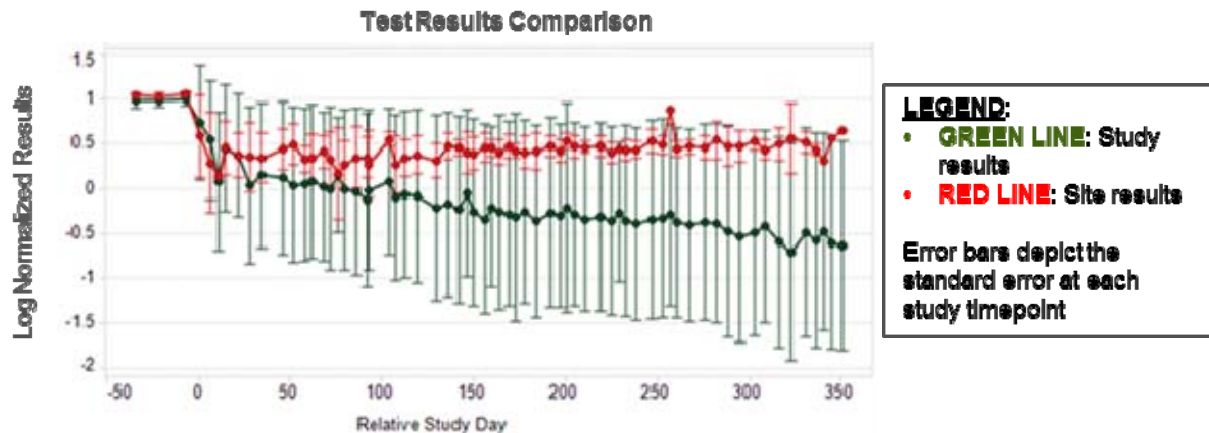


Figure 2. CSS Result of a clinical parameter (e.g. Depression Scale) compared to the study average. Subject Scale scores overall and at each study visit are more alike at each study time point and across time than the average for the other sites in the study.

CSS findings are presented at the CMWG. Presentations are concise and include a site by site review with an explanation of each finding (graphs and explanation as above included for each finding). In addition, for each finding, possible root causes and suggested follow-up actions are included (examples):

- Potential Root Causes
 - o Subjects have demographic similarities that would result in very similar response to the scale
 - o The administrator of the scale is doing so in a way that differs from a typical administrator
- Suggested Follow-up
 - o Study Physician to review subjects to determine if there is a medical reason explaining these similarities and confirm that all subjects were correctly enrolled and treated
 - o Review the process of scale administration. Identify any issues with specific administrators and provide retraining if needed

CONCLUSIONS

Successful implementation and roll-out of CSS to the organization required a well thought out road-map including the selection of the appropriate staff, robust staff training, efficient communication and transparent process integration. By leveraging the existing infrastructure and processes we have created a scalable model for integration of CSS into the Janssen method for risk-based monitoring and provide an additional layer of data quality oversight.

REFERENCES

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