Paper AR01

Analytical Risk-Based Monitoring (ARBM) – How Central Monitors Detect the Ripple in the Dataflow that Hides the Danger On Site

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ABSTRACT

Central monitors analyze the technology-driven, real-time picture of data quality provided by modern analytical risk-based monitoring (ARBM) tools. By focusing on critical data that represent the greatest risk to the study objectives a central monitor is able to view data from different and more holistic perspectives. On-site monitors (CRAs) in contrast often only see the impact of new data on individual subjects at one timepoint in comparison with subjects at one or several similar sites. However, switching between a study-wide, country-, site- or subject-focused perspective and observing data changes in real time can amplify risk signals.

Here we present a case in which central monitoring detected previously overlooked frequent changes of the eligibility status of patients. A further investigation in this signal showed that several sites had problems to confidently calculate a relevant score and therefore continued to change its value. Consequently, armed with this knowledge the study team was able to mitigate the issues and prevent the potential enrolling of not eligible patients and wrong stratification before the end of the recruitment period.

INTRODUCTION

Regulatory authorities as well as the guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) refer to central monitoring as part of a systematic and risk-based approach to monitor clinical trials that uses remote data analysis to identify missing and/or invalid data as well as unusual data patterns to evaluate the study conduct across multiple sites [1,2,3].

In a paper published during the recent COVID-19 pandemic a group of authors from the Association of Clinical Research Organizations (ACRO) describes how many sponsors implemented at least some of the key components of a risk-based monitoring (RBM) approach for their studies to compensate for the restrictions placed on on-site monitoring models by reduced site access [4]. The authors measured the success of these measures by showing that non-COVID-related protocol deviation numbers did not drop significantly when the majority of site visits shifted to an off-site model. Two of the eight RBM key components are centralized monitoring and the use of key risk indicators (KRIs), which are commonly described as the metrics used to assess site performance

As the pandemic accelerated the implementation of RBM, a more recently published study provided first statistical evidence that the monitoring of KRIs via central monitoring is an effective way of detecting data quality issues in clinical trials if the concept is properly implemented and signals are efficiently managed and followed up [5]. The Quality by Design (QbD) Project of the Clinical Trials Transformation Initiative (CTTI) as well as newly published research outline how more study-specific critical to quality factors (CtQs) [6] can be used to improve the construction of a more holistic picture of a clinical trial and to improve QbD by setting quality tolerance limits (QTLs) [7].

Taken together this shows that the work of central monitors is crucial for the implementation of a RBM approach. This paper will outline how central monitors identify, follow up and communicate risk signals in tight collaboration with CRAs using a Crohn's disease (CD) case study that was supported by a central monitor working within ICON's Functional Service Provision (FSP) model.

CROHN'S DISEASE ACTIVITY INDEX (CDAI) AS CTQ IN CROHN'S DISEASE STUDIES

An electronic research of available CD research literature revealed that the most used index was the Crohn's Disease Activity Index (CDAI) [8]. However, the CDAI is a complicated measure that requires several days of evaluation and is calculated based on many datapoints such as clinical tests as well as data that may vary from subject to subject (i.e. abdominal pain). In this case study the CDAI at baseline was used to determine eligibility as well as for subsequent stratification of randomized subjects. As correct determination of eligibility and correct stratification were identified as CtQs for this study, monitoring the centrally available data for the baseline CDAI was a key part of the central monitoring strategy. An algorithm was programmed to monitor these CtQs and to identify and flag any inconsistencies between the patient's eligibility status in the eCRF, stratification in the IXRS system and centrally available key data for the baseline CDAI score (Fig. 1).

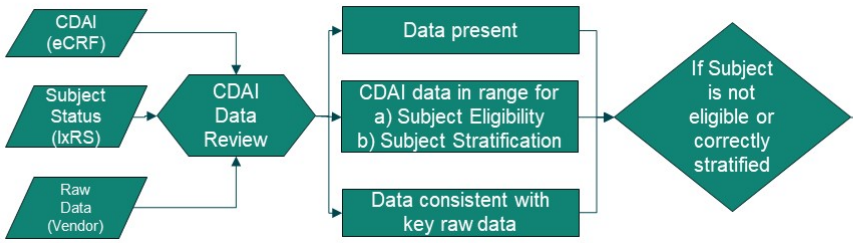

Fig. 1: *Schematic for the electronic comparison of datapoints for baseline CDAI with the patients eligibility status in the eCRF, stratification in the IXRS system and centrally available key vendor data for clinical tests during the central monitoring of a Crohn's disease study. The protocol specified that eligible patients must have a baseline CDAI score of 450 ≥ CDAI (baseline) ≥ 220. Eligible patients were subsequently stratified in two strata (above or below CDAI (baseline) =300).*

IDENTIFICATION OF CENTRAL MONITORING RISK SIGNALS DURING THE MONITORING OF CROHN'S DISEASE STUDIES

During the execution of the study the central review was performed bi-weekly by the central monitoring team to monitor variations in the incoming data flow. Here we show the process that led to the identification of a serious risk signal in principle for a simplified set of patients (Fig. 2). During the initial reviews, central monitoring detected several site- and subject-level issues. In one case the baseline CDAI score for patients was changed after enrollment effecting the eligibility review and resulting in a signal that ineligible patients had been enrolled in the study. The score was corrected after follow-up and intervention by the local team and the site was retrained. Over the course of several reviews central monitoring realized that what seemed initially to be an issue specific to one particular site was a pattern repeated at other sites and in other countries.

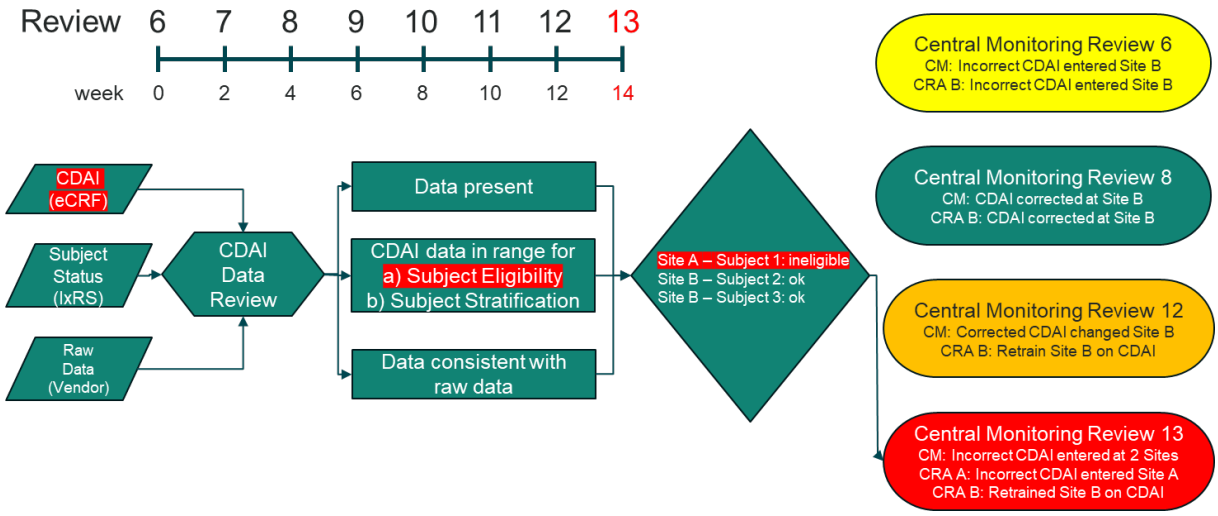

Fig. 2: *Overview of the outcome of the electronic central monitoring reviews during the execution of the case study.*

ANALYSIS AND COMMUNICATION OF CENTRAL MONITORING RISK SIGNALS IN CROHN'S DISEASE STUDIES

A more detailed analysis of the initial signal presented in Fig. 2 indicated that the issue was not missing or incorrectly entered raw data available from the vendor database that was changed. Therefore the central monitoring team performed checks on selected sites that showed multiple signals. These checks revealed that some sites indeed displayed problems to confidently calculate the CDAI score as site staff changed the value for the baseline CDAI datapoint multiple times including values that would have caused a compliance issues with the patient's eligibility and/or stratification status (Fig. 3).

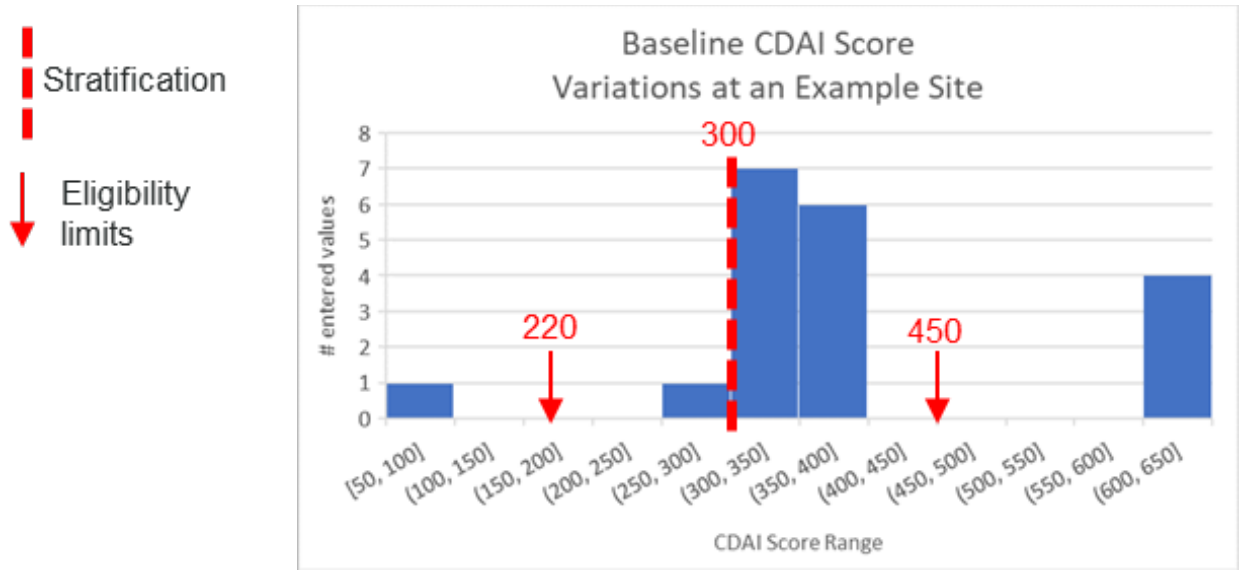

Fig. 3: *Spot check performed by the central monitoring one example site to analyze the root cause of signals for a changing eligibility and stratification status of subjects in the electronic central monitoring reviews.*

To further understand the signal, central monitoring staff examined the audit trails of the baseline CDAI score on study level for all enrolled patients before 30% of the recruitment goal was reached. Thus, we detected that the initially entered value had been changed in 61% of baseline CDAI scores (Fig. 4). Furthermore, the analysis revealed that this happened in 44% of the cases on multiple dates for the same datapoint and subject. The change impacted stratification in 11% of the cases but no ineligible patients were enrolled. This led to the conclusion that numerous sites lacked the ability to confidently calculate the CDAI score. The problem was communicated directly to the global study lead and addressed by raising 20 issues triggering a check of entered and changed scores and a retraining of site staff.

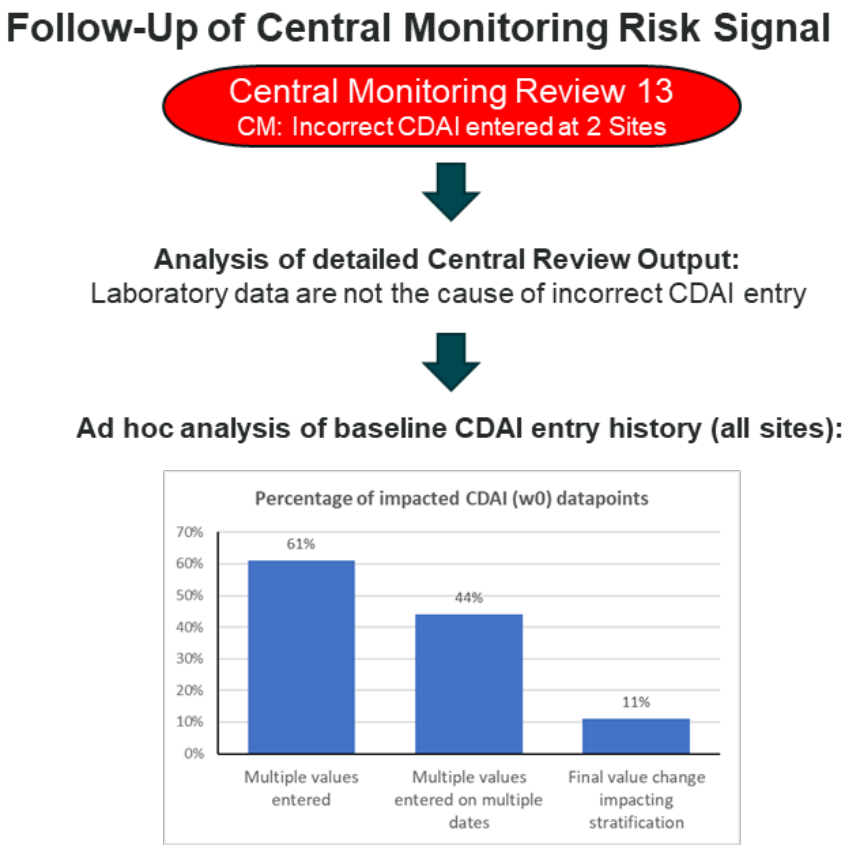

Fig. 4 *Identification of the root cause of an electronic central monitoring review risk signal through an ad hoc follow-up analysis of eCRF audit trails.*

CONCLUSION

15 of 28 sites in six different countries struggled to correctly calculate the CDAI score, which was critical for the determination of eligibility and stratification. Three protocol deviations for stratification issues were raised. However, this issue has been identified comparatively early in the enrollment period (before approx. 30% of the recruitment target was reached) and successfully mitigated before it had an even more severe impact. This has been achieved through the use of the available technology by the central monitoring team. The use of a data visualization dashboard enabled central monitors to switch between a study-, country-, site- and subject-level view for a holistic picture of available CtQ data. This allowed for early detection of a potentially study-wide risk signal and the development of a further study-wide analysis. Once the risk was clearly identified the study team was able to target the sites that required mitigation.

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