Paper AR07

Real-World Examples of eCOA Compliance and Audit Trail Review Using Advanced Statistical Methodology

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ABSTRACT

eCOA data represents a larger proportion of clinical data than ever before, and regulatory guidance is dictating the need for systematic audit trail reviews. This data is historically difficult for on-site monitors to review, as a centralized monitoring approach is needed to adequately contextualize the data. In this session, the author will discuss traditional statistical monitoring techniques which allow study teams to review audit trail data. In this paper we will also explore newer techniques and functionality that support this review, including real-world practical examples of issues found at investigative sites. This paper will show how analytical review can support data quality using novel techniques and drive regulatory compliance.

INTRODUCTION

According to a 2023 report from ISR, sponsor organizations are expecting electronic Clinical Outcome Assessments (eCOA) to make up 53% of all COAs collected, and plan to use eCOA in 64% of their trials through 2025 [1]. The Tufts Center for the Study of Drug Development reported that sponsor companies have rapidly increased the use of digital endpoints, with the use of these endpoints doubling every 3 years since 2015. As of mid-2024, more than half of digital endpoints are used to support secondary clinical trial outcomes [2].

At the same time, there has been an increasing regulatory focus on audit trail review of these types of clinical systems; the recently released ICH E6 (R3) requires that audit trails and logs are decipherable and can facilitate analysis, and that review should be a planned activity adapted to an individual trial [3]. The EMA released their guideline on computerized systems and electronic data, which stated that sponsors should conduct regular reviews of audit trails to identify and investigate suspicious activities, ensure data integrity, and to detect and prevent data breaches [4]. Both recent guidelines recommend taking a risk-based approach.

The aim of this paper is to outline traditional statistical monitoring techniques that can support this type of analysis, as well as to explore newer techniques that can highlight data inconsistencies and atypical site behavior while demonstrating increased regulatory compliance.

PART I: TRENDS IN DATA STRUCTURE IMPACTING CLINICAL MONITORING

According to the Society for Clinical Data Management, approximately 70% of clinical trial data is now captured outside of EDC systems. This paper will focus on eCOA and ePRO devices, however, this high percentage can also include decentralized trials (DCT) and real-world evidence (RWE), which also produce audit trail metadata.

According to an SCDM paper, many data systems available cannot even implement multiple Schedules of Visits and Procedures that are required for today's more complex study designs and clinical trial landscapes [5]. As such, much data from ePRO and eCOA sources is "unlinked" to the traditional "schedule of assessment" grid that is typical of protocols and protocol synopses of previous decades. That decoupling creates challenges from a technical standpoint, but also from a monitoring perspective.

CLINICAL MONITORING OF EPRO/ECOA DATA

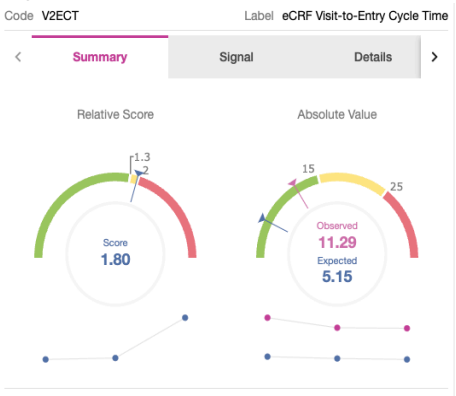
Historically, many clinical trials have leveraged paper diaries, which patients have used to report clinical trial outcomes, adverse event data, and to facilitate daily collection of subject statuses. These paper diaries, distributed at one patient visit, and reviewed at the next visit, have historically been challenging to monitor. While the patient-reported data is often critical to meeting a trial's primary and secondary endpoints, patient non-compliance with paper diaries has been an issue for decades [6]; the rise of electronic patient diary data should be seen as a positive development for clinical research efficiency.

Monitoring of a patient's paper diary by a site monitor is relatively straightforward in practice; the monitor would assess if the diary was completed, and all adverse event/endpoint data was assessed by the site staff appropriately. Missing diaries would often be recorded as missing data unlikely to be retrieved. This process outlines several gaps in the potential validity of the data- whether they are unreported recall information, issues with contemporaneousness, or some other data quality issue. These items can be assessed using ePRO/eCOAs audit trail data.

ESTABLISHED AUDIT TRAIL REVIEW METHODS

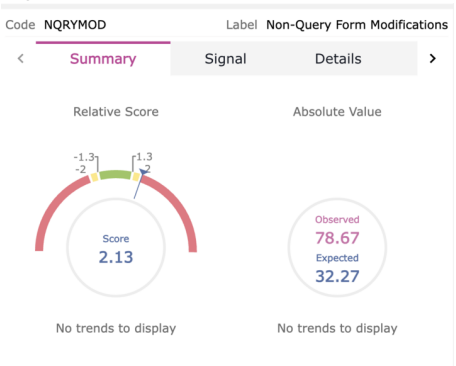
Audit trail review, as a concept, is not new. Stan W. Woolen first coined the ALCOA acronym in the early 1990s while serving in the FDA's Office of Enforcement [7]. 21 CFR 58.130 (e) also notes that data shall be recorded "directly, *promptly*, and legibly", and this has been codified for decades. These guidelines dictate that the manner in which data is collected contributes directly to the quality of that data, and infers that it is important to establish the auditability of ALCOA. Given that ePRO/eCOA technology has been adopted and growing at the rates described above, the focus on contemporaneousness when applied to data quality has also been possible through systematic reviews. The methods of these reviews could be rudimentary Missing Pages Reports (available from eCRF providers for decades) or through Key Risk Indicators (KRIs) focusing on various aspects of a trial. These KRIs could focus on trial operational aspects like Visit to Entry Cycle Times or Query Turnaround Time (Figure 1).

Figure 1:



Similarly, it is also possible today to create KRIs on eCOA/ePRO data entry delay; ePRO and eCOA reporting delay beyond a certain time period (typically 48-72 hours) may constitute "recall" data, which no longer would be considered contemporaneous by some sponsor companies. Another particular area of focus could also be records where there are high levels of data changes (Figure 2).

Figure 2:

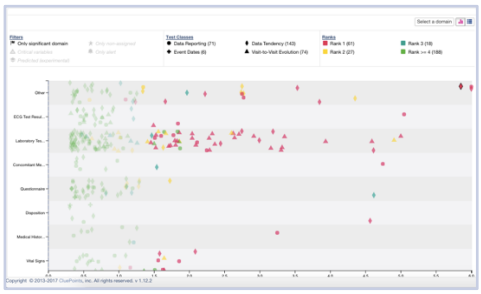


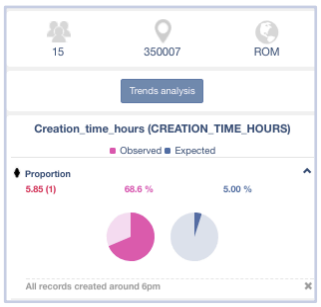
STATISTICAL ANALYSIS

Statistical monitoring methods can also be leveraged for audit trail review. Standard deviations can be used when applied to the above-referenced KRIs to show that a site is atypical compared to others on the study. Statistical approaches can also be applied to timestamp data within the audit trail metadata. Unusual groupings of ePRO/eCOA

entry or update times can indicate impropriety, a lack of understanding of the protocol, or incorrect instructions given to the patient. These techniques have been leveraged in the past and are best visualized using statistical software fit-for-purpose. Figure 3 represents an example using these techniques that show a site that has an atypically high percentage of ePRO records clustered within the 6PM hour

Figure 3:





PART 2: ADVANCES IN AUDIT TRAIL REVIEW TECHNIQUES

The decoupling of clinical data from the visit-based schedule of assessments has presented challenges within clinical trial design. Tools meant to analyze visit-based data, EDC-type reporting, and cycle times were not historically equipped to analyze data that was collected continuously via ePRO/eCOA.

Technological advances have now empowered sponsor companies to evaluate the audit trail data of ePRO/eCOA metadata and completion. One such example, CluePoints' Time Similarity Test (TST) analyzes audit trail timestamps to identify patters indicating potential data fabrication of protocol non-compliance. This test leverages statistical analysis within sites, identifying the probability of patients randomly completing ePRO/eCOA diaries at similar times. This type of test can be analyzed multiple times throughout the same study, enabling study teams to identify trends and inconsistencies early to correct potential errors in data capture. Figures 4 and 5 below show anomalies in eCOA completion as clusters of patients were completing diaries correlated to their start-date on the study.

Figure 4 (Atypical Site)

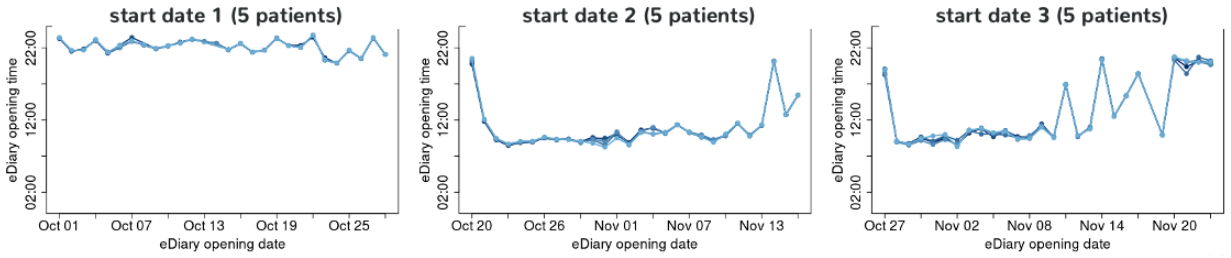


Figure 5 (typical site)

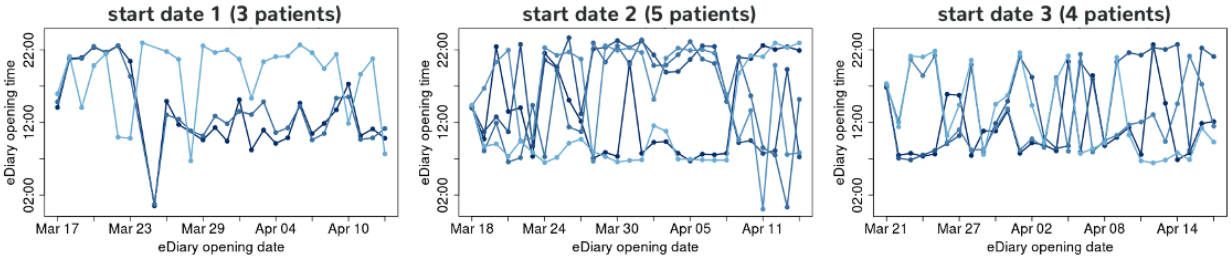
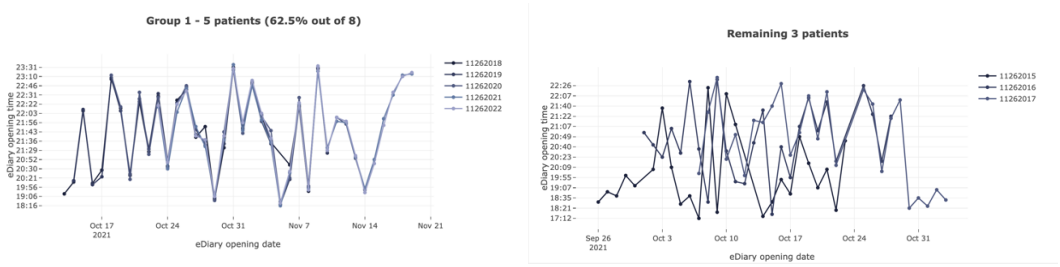


Figure 6 below represents 5 patients at a site that had nearly identical eCOA completion times relative to each other, and how this patient behavior is different than other patients at the same site.

Figure 6:



PART 3: AUDIT TRAIL REVIEW CHALLENGES AND BEST PRACTICES

Audit trail review, while not a new concept, does present significant challenges given the evolving eClinical landscape. As more data is shifted into an electronic capture system, more audit trail data is produced. There is ongoing debate as to how much metadata needs to be collected and analyzed [8] as not every keystroke needs to be logged; this underscores the regulatory recommendation for a risk-based approach noted above.

A different challenge also emerges as the complexity of clinical trials increase; vendor management. According to the Tufts CSDD, the total number of procedures performed in a clinical trial has increased 67% between 2009 and 2020; more procedures equate to more non-eCRF vendor data, more data transfers, more specification documents, and overall operational complexity in managing this electronic data [9]. In an ACDM Q&A, "prospective audit trail review should form part of the Data Management Plans or other documentation" and "[sponsors] need to determine the appropriate level of ATR and provide CROs/Vendors with an ATR Plan" [10]. This planning and vendor buy-in is critical, as it is not possible to review an audit trail if it is not provided in data transfers.

CONCLUSION

As the eClinical landscape continues to evolve alongside the increasing complexity of clinical trials, oversight of complex data sources will grow in importance. Ensuring high quality data through audit trail review, and that data is consistent, will be a priority for data management activities moving forward. Finally, early informal polls of sponsor companies indicate that many sponsor companies are early in their audit trail review journeys. Simply put, starting out small is the best way to build this capability in the coming years, and audit trail review maturity will come with systematic process and cross-functional buy-in. Sponsors cannot let perfect be the enemy of good when it comes to audit trail review, and sponsors must also collaborate with their CROs and vendors to grow their capabilities over time.

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