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Driving Quality into Clinical Trials

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ABSTRACT

CluePoints' central monitoring platform offers an automated and unsupervised approach to risk-based monitoring (RBM) to ensure that no stone is left unturned in assessing and improving data quality and, ultimately, enhancing patient safety. This paper explores the value of an integrated approach to comprehensive clinical and operational data analysis.

It demonstrates how analytics and visualization tools can support an RBM strategy by analyzing clinical and operational data to identify the risks which can arise from a range of issues including lack of training, misunderstanding of a protocol, carelessness, negligence or even fraud. It considers the full process, from obtaining data from various sources, through to visualizing, analyzing and transforming results into corrective actions. The paper also discusses how a multidisciplinary study team typically made up of data managers, statisticians, monitors and physicians can work together to improve data quality.

INTRODUCTION

Since the FDA issued its guidance encouraging a risk-based approach to clinical trials monitoring [1], the industry has begun embracing new oversight approaches and is actively embarking on a paradigm shift. The budget for monitoring activity usually represents around 30% of the total clinical trial budget [2] with source data verification (SDV) accounting for a significant proportion of this activity. However, with numerous studies demonstrating inefficiencies with the SDV methodology [3, 4, 5], the new regulatory landscape offers an opportunity for the industry to reduce its use of this approach and leverage analytics to assure high data quality and patient safety.

To ensure its successful implementation, there is a necessity to align current technology with emerging new requirements of an RBM approach in the clinical operations workflow.

Figure 1 provides an overview of the main components of the solution that has been implemented in the CluePoints central monitoring platform. The subsequent sections of this paper explore the principles and challenges for each of the building blocks.

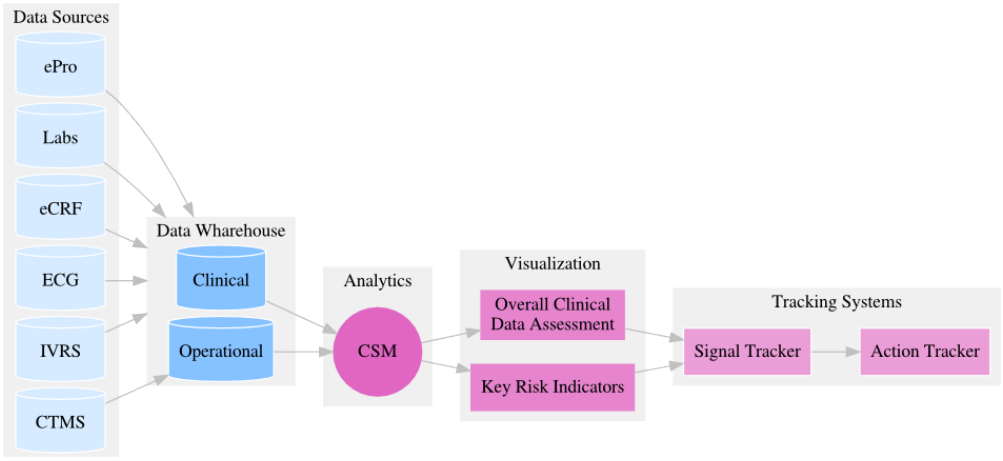

Figure 1: RBM Platform Components

FROM DATA SOURCES TO DATA WAREHOUSE

To perform a comprehensive assessment of data quality there is a need to identify which data are going to be analyzed and in which systems those data reside. CluePoints' Central Statistical Monitoring (CSM) engine requires patient level

data, which typically come from several sources, such as electronic data capture (EDC), interactive voice response systems (IVRS), electronic patient reported outcomes (ePRO), etc. It is essential that the RBM platform is able to accept and analyze data from a number of different sources [6].

Depending on the underlying technology for the data sources, the data can either be manually uploaded to the system via flat files in Clinical Data Acquisition Standards Harmonization (CDASH), Study Data Tabulation Model (SDTM) or any custom format, or alternatively, directly from the source through the use of a web services connector. Nowadays, most EDC systems have web services that expose data in the Clinical Data Interchange Standards Consortium's Operational Data Model (CDISC ODM) format, making the conversion to SDTM datasets straightforward. The ODM standard supports incremental data, receiving only information pertaining to what has changed and not the entire snapshot. This has the advantage of reducing the impact in terms of bandwidth, but on the other hand, does require some logic in order to process the transactions. The use of automated transfers makes it possible to have analysis in near to real-time which opens the door for trend analysis.

A challenge in integrating information from heterogeneous data sources is to ensure correct mapping in the identifiers for the subject, study center and visit. The system needs to have some automated validation checks of data to guarantee it complies with the expected structure.

CENTRAL STATISTICAL MONITORING

The concept behind CSM is that data quality can be assessed with statistical methods [7, 8]. As all centers participating in a given study have the same CRF, the data structure is similar for each, making it possible to compare centers and identify sties whose data are inconsistent with others. CSM uses a large number of statistical tests and scoring algorithms to identify unexpected or unusual patterns in trial data in order to determine its quality, accuracy and integrity. The approach is able to detect these unusual patterns based on the fact that it is extremely difficult to invent plausible information, particularly in highly dimensional multivariate data. Sponsors and CROs are able to determine the quality and integrity of their data throughout the entire trial process, detecting potential fraud and data errors.

One of the other main advantages of adopting a statistical testing approach is that it allows for the assessment of statistical significance, meaning it provides an objective measure of how likely the difference is to happen by the play of chance. The CSM methodology can be applied both for the overall data quality assessment as well as the KRIs.

OVERALL DATA QUALITY ASSESSMENT

The underlying principle in the overall quality data assessment is to consider all patient related data with no prior or selection in terms of variables. The CSM engine processes all variables from various data sources at a given time, with between two and ten tests performed per variable. The results are then collated and organized in a matrix with as many rows as centers, and as many columns as combination of tests and variables. For a typical Phase III trial with 200 centers and 400 variables, it is not uncommon to end-up with 1,000,000 p-values. The results from the matrix are then summarized with a scoring algorithm in order to detect sites that are atypical.

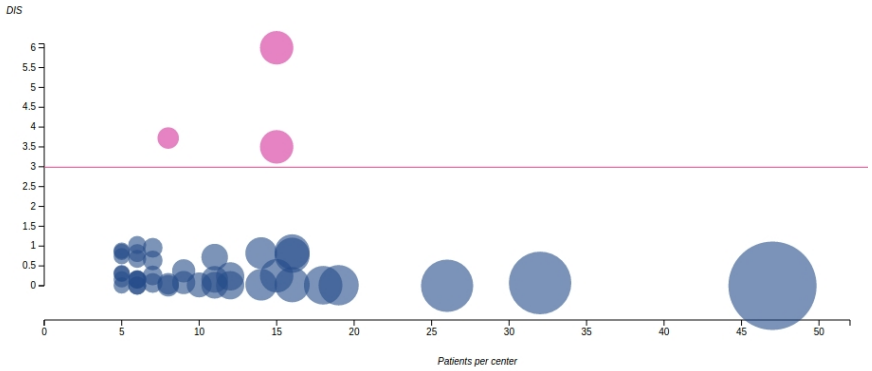

Figure 2: Identification of Atypical Sites

Figure 2 illustrates how center scores can be visualized, with each bubble corresponding to a center and the size of the bubble corresponding to the number of patients connected to the site. The vertical axis is the score, so the higher the bubble, the most atypical the site is.

KEY RISK INDICATORS

The key risk indicators (KRI) analysis focuses on a limited number of metrics, which are chosen to assess different dimensions of the site performance such as quality, timeliness and efficiency [9]. Usually, the study team ends up with a selection of 15 to 25 variables that are key for the study. In addition to generic indicators, such as the rate of adverse events and protocol deviations, which will be used regardless of the therapeutic area, a number of study-specific risk indicators will be added. For each risk indicator there is the need to define thresholds above which the site is identified as inconsistent and requires further scrutiny. Selecting and defining these thresholds can be a challenge for sponsors and CROs as this is often based an empirical evidence and experience, making it subjective. By being based on statistical significance, the CSM engine offers an objective way of defining these thresholds.

center	Country	#Patients	#Medium	#High	Missing pages	Missing pages >	Protocol Deviation	Queries open > 2	Discontin or Lost	# Days Open	Patient Status
202	USA	4	0	2	🔴	🔴	🟢	🟢	⚪	⚪	🟢
80	USA	4	0	1	🟢	🟢	🟢	🔴	🟢	⚪	🟢
124	USA	25	0	1	🟢	🟢	🟢	🔴	⚪	🟢	🟢
147	USA	14	0	1	🟢	🟢	🟢	🔴	🟢	🟢	🟢
69	USA	10	2	0	🟢	🟢	🟢	🟢	⚪	⚪	🟡
123	USA	15	2	0	🟢	🟢	🟢	🟢	🟡	⚪	🟡
199	USA	7	2	0	🟢	🟢	🟡	🟢	🟢	🟢	🟡
23	USA	21	1	0	🟢	🟢	🟢	🟢	🟡	🟢	🟢
30	USA	5	1	0	🟢	🟢	🟢	🟢	🟢	🟡	🟢
33	USA	20	1	0	🟢	🟢	🟢	🟢	⚪	⚪	🟢
38	USA	9	1	0	🟢	🟢	🟢	🟡	🟢	🟢	🟢
52	USA	5	1	0	🟢	🟡	🟢	🟢	🟢	🟢	🟢

Figure 3: KRIs Dashboard

The results from the KRI analysis can be displayed with a dashboard offering traffic light visualization, as illustrated in Figure 3.

TRACKING SYSTEMS

Any centers that are highlighted with the overall Clinical Data Assessment and KRIs need to be tracked and documented. Firstly, any signals (a group of atypical variables and data points which may be explained by a common root cause) need to be documented. For example, a signal could be a high proportion of missing values in many variables in the laboratory domain. Once all atypical results have been assigned to signals, the study team can perform a review of the signals and see which are considered as an issue and require corrective action. An action tracker will then list and monitor all the follow-up steps that are needed in order for the issue to be resolved.

CONCLUSION

The implementation of an RBM approach requires current processes to be adapted and redesigned, in order for sponsors and CROs to realize its full benefits. Analytics and visualization tools can support a RBM strategy by analyzing clinical data to identify risks arising from a lack of training, misunderstanding, carelessness, negligence or even fraud. A multidisciplinary, skilled team, including a central analyst, is also critical to the success of any RBM strategy, with study staff responsible for reviewing the risks, interpreting results and signals from the analytics tool, and also agreeing on the corrective actions that are required.

CluePoints' central monitoring platform offers an automated and unsupervised approach to RBM, ensuring that no stone is left unturned in assessing and improving data quality and, ultimately, improving patient safety.

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