CYBAGE
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Data Driven Approach to Manage Clinical Trials

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"What gets measured gets managed."
"What doesn't get measured doesn't get managed."

OVERVIEW

Launching new drugs and vaccines into the market requires successful, effective execution and monitoring of clinical trials. Executing clinical trials is a lengthy, expensive endeavor. This relies on a huge volume of data generated from multiple systems such as Clinical Trial Management systems, Drug Supply Management systems, Laboratory Information Management systems, Randomization systems, and Inventory Management systems. These systems together contribute in providing comprehensive information of clinical trials conducted globally.

Dealing with complex questions and having great uncertainty are the characteristics of clinical trials. Organizations performing clinical trials can witness geographically distributed clinical trial operations, evolving regulations, and increasingly complex protocols regulating trials. These organizations are

impelled to make prudent investments for effective, easy access and seamless exchange of data in clinical trials. The aim is to improve their success rate while achieving compliance and cost cutting and addressing slowdown in momentum of clinical trial operations.

This paper discusses how the use of analytics will allow organizations involved in clinical trials to explore multivariate responses more clearly. This will allow them to take proactive and adaptive approaches to decision making and optimize the way they work, while studies are under way.

CURRENT SCENARIO

Organizations conducting clinical trials use multiple disconnected methods to manage clinical trials. These methods comprise the Electronic Data Capture system, Randomization system, Clinical Trial Management system, and Laboratory Information Management system, among others. The data generated from these methods is stored in a proliferation of disparate data silos, which have limited collaboration. This makes it difficult to do cross-query. This leads towards creation of disconnected reports, which cannot provide a comprehensive view of clinical trials.

An increase in the number of trials, protocol complexity, multi-centric nature, and regulations is being witnessed. So, business users find it critical to get multidimensional reports that can be easily generated and allow holistic inspection and user-friendly exploration of multivariate responses, expressed and stored in all kinds of data. Although organizations are data-rich, the current scenario of dispersed data silos causes immature information consumption. So, it becomes difficult to monitor clinical trials and proactively address quality issues.

TRIAL INTELLIGENCE AND TRIAL ANALYTICS

The key behind successful clinical trials is transparency and seamless access of data at all levels. This must be assisted by effective, collaborative workflows to mitigate identified risks. To do so, pharmaceutical industries consider Clinical Trial Intelligence (aka Business Intelligence) as an important tool. This can monitor and track metrics or key performance indicators (KPIs) in the form of reports or dashboards. The crux is to make meaningful use of these metrics to unearth hidden trends and patterns using statistical algorithms. These algorithms correlate to factors that influence the overall quality of trial operations. This crux is called 'Trial Analytics' (aka Business Analytics).

"Trial analytics is the systematic analysis of data into insight for making better decisions by discovering and communicating trends and patterns within the data effectively."

Clinical Trial analytics can be leveraged by retrospective and/or predictive analytical methods. These serve as a viable solution that can address the need of clinical trial monitoring. This solution can enable study teams to react quickly to quality issues.

"Retrospective analytics is backward looking insights on the business - reporting on what happened and what is currently happening."

"Predictive analytics is forward-looking analysis - providing future-looking insights on the business, forecasting what is likely to happen and why it's likely to happen."

TRIAL ANALYTICS AT RESCUE

Using Clinical Trial analytics, following can take place:

- Clinical Trial managers can track milestone progress.
- Sponsors can monitor portfolio performance.
- Site investigators can follow patient timelines and protocols.
- Data monitors can review data collected to date.

Further, Clinical Trial analytics can also be used to visualize noncorrelated data sets along shared dimensions; for example, patient electronic medical records can be overlaid with protocol inclusion and exclusion criteria, to visualize availability of eligible patients. Likewise, the overlaying FDA principle investigator database over the aforesaid results will visualize the availability of probable clinical trial sites and in fact a probable investigator to conduct trials. Similarly, patients' adverse events, concomitant medications, and visits can be overlaid against lab results. Incorporating trial planning and actual patients enrolled can help to identify the sites that are consuming the most resources while producing the least results. This can allow the mangers to optimally utilize Clinical Research Associates (CRA) and avoid recruiting or allocating more CRA to a site. Protocol Compliance charts identifying the study events that are overdue and at risk of being noncompliant can call managers to action.

Here is a table depicting some key trial metrics.

Study Metrics	Site Metrics	Quality Metrics	Data Metrics
• Site activation and recruitment • Enrollment and retention • Subject status distribution • Subject visit progress • Study discontinuations • Protocol deviation trends • Disposition summaries	• Top enrolling investigators • Data entry lag • Data entry compliance • Enrollment and retention • Screen failures • Protocol deviation sites	• Query aging • Query resolution • Outstanding queries • Average days query • Resolution form Source Data Verification (SDV) percent • Form entry and SDV	• Visit status • Data backlog • Data projection • Form status • Laboratory trending • Safety surveillance

In general, many problems faced by Clinical Trial teams are caused by lack of understandable information. When this barrier is removed, performance should improve.

PATIENT RECRUITMENT AND RETENTION OR ENROLLMENT CHALLENGES

Recruiting patients is one of the vital milestones and also the biggest challenge known in clinical trials. Factors such as patient population epidemiology, protocol inclusion or exclusion criteria, and patient knowledge about clinical trials often affect the ease and speed with which subjects can be found and enrolled. As clinical trial milestones for enrolling subjects are not reached, new sites are initiated to cope up the missing deadlines. This leads towards increased and unexpected costs, while final milestones are often missed, and results cost overruns in common.

Also, the sites tend to over commit in the sites' feasibility surveys and are overly optimistic about their ability to supply patients. In reality, in any specified trial, the majority of sites fail to enroll a single patient, and some of them can enroll to partial capacity.

Introducing predictability into the Trial Recruitment and Retention process can substantially improve patient enrollment success rates and adherence to study timelines. Comprehensive, data-driven analysis with 'what if'´scenarios can be used to establish confidence levels. This can result in defining a baseline forecast. This forecast can predict the probability of enrollment success in a specific timeframe, specified certain variables with a high degree of accuracy.

SCOUT PATIENT AVAILABILITY

The primary step is to estimate the number of eligible patients participating in a specified trial, based on the trial inclusion or exclusion criteria, the treatment guidelines and procedures, and the competitive landscape. To do this, the foremost action is to assess availability of patients based on the population epidemiology by geography.

Leveraging data in Electronic Medical Records (EMRs), pharmacy, or integrated medical claims databases can assist us to determine patients that meet the inclusion or exclusion criteria and also pinpoint where they are located. Clinical trial registries, publications, and subscription databases can assist in performing competitive analysis. Further, applying diagnostic and procedure codes and medication restrictions can refine the resultant population count of potentially eligible patients.

The output so generated can be shown as a heat map, illustrating the dominance of patients in the target population, by location.

Regulatory View
Monitoring Clinical Trial Operations is a regulatory requirement, required by 21 CFR 312.50 and 312.56.

In August 2011, the FDA issued a draft guidance entitled Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring. The guidance "recommends that each sponsor design a monitoring plan that is tailored to the specific human subject protection and data integrity risks of the trial".

SCOUT PRODUCTIVE CLINICAL TRIAL SITES

A productive site is generally defined as a site that can deliver the maximum patients based on its access to target patients, historical performance, capabilities, and resources. Scouting such sites can be achieved by overlaying the Food & Drug Administration's (FDA's) 1,572 databases of clinical investigators on to a patient heat map. The output so generated can highlight those investigators in close proximity to clusters of patients who match the inclusion or exclusion criteria.

In addition, the available historical data of such sites in a company's database can assist to evaluate the site's performance.

FORECASTING ENROLLMENT PROBABILITY

With the help of powerful statistical algorithms, the probability that a particular outcome will occur based on a specified action or set of assumptions can be projected, which is distributed across time.

OPTIMUM RESOURCE UTILIZATION OR INCONSISTENT TRIAL PLANNING

Having sufficient resources to complete a measurable task is the key behind optimum resource utilization. Enterprises generally rope in external contract research organizations to complete a task that can be completed by existing resources if a fluid, data-driven approach is considered at the time of project scheduling. Clinical Research Associates (CRAs) are the ultimate drivers behind site monitoring visits. Traditional monitoring, typically, is based on a calendar schedule or trigger points such as missing deadlines, regardless of clinical data or the risk to patients. Also, the CRA staffing for site monitoring visits is based on the anticipated workload. This leads to a situation that has all the expenses of a site visit, with very less value. Using a Predictive analytics-based approach, sponsors can assess investigator risk and allocate

monitoring resources where they are needed most. For example, accurate patient-enrollment forecasting and accurate patient visit-schedule forecasting. Herein, it becomes straightforward to calculate the monitoring workload at each site. With accurate forecasting, CRAs can schedule site visits to coincide with a full-day's work of monitoring. By aligning the workload with the visits, efficient monitoring visits are the result. Each site visit is maximized in value.

Using the Risk-based monitoring approach, CRAs can focus on sites having maximum risk. Risks can be high Adverse Event (AE) reporting and data quality issues at the site. For sites that have historically good track records of performance and quality, monitoring visits are reduced. The sites with a higher risk profile receive commensurately increased monitoring visits.

CONCLUSION

Pharmaceutical organizations are battling with the evolving regulatory and scientific landscape. In this scenario, Trial analytics provide a ray of hope to gain control of their business processes and streamline the process at multiple points.

Trial analytics at the execution level enables pharmaceuticals companies to focus their efforts where they matter the most—accurate forecasts for planning and risk-based leveraging of resources.

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