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GENERAL

TRIAL ANALYTICS – A TOOL FOR CLINICAL TRIAL MANAGEMENT

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Abstract: Prolonged timelines and large expenses associated with clinical trials have prompted a new focus on improving the operational efficiency of clinical trials by use of Clinical Trial Management Systems (CTMS) in order to improve managerial control in trial conduct. However, current CTMS systems are not able to meet the expectations due to various shortcomings like inability of timely reporting and trend visualization within/beyond an organization. To overcome these shortcomings of CTMS, clinical researchers can apply a business intelligence (BI) framework to create Clinical Research Intelligence (CLRI) for optimization of data collection and analytics. This paper proposes the usage of an innovative and collaborative visualization tool (CTA) as CTMS "add-on" to help overwhelm these deficiencies of traditional CTMS, with suitable examples.

Keywords: CTMS, BI, CTA, CTI, Decision Support System, OLAP, KPI

The accent of clinical trials management process is highly critical for any organization performing clinical trials. In the present scenario, organizations spend hundreds of millions of dollars on budgets, time frames that range to decades, and the complexity of these trials has been ever-increasing. There has been a lot of effort duplication and wastage on data management, programming and reprogramming for these trials. Pharmaceutical firms now know the criticality of managing plan accuracy, timeliness, and making better resource allocation decisions. Adding a single day to the planned duration of a clinical trial may cost around $ 1 million. Similarly, losing a day from business market exclusivity due to a delay in submission could cost around $ 10 millions.

Prolonged timelines and large expenses associated with bringing new drugs to the market have prompted a new focus on improving the operational efficiency of clinical trials. As a result, industry sponsors of clinical trials have been increasingly reliant upon a variety of IT-enabled Clinical Trial Management Systems (CTMS) in order to improve managerial control in trial conduct.

A CTMS is a customizable software system used by biotechnology and pharmaceutical industries to manage large amounts of data involved with the operation of a clinical trial. It is widely used to maintain and manage the planning, preparation, performance and reporting of clinical trials, while emphasizing on keeping up-to-date contact information for clinical trial participants and tracking milestones and deadlines e.g., those used for regulatory approvals or issuing progress reports. Currently, all the CTMS do provide clinical trial sponsors with improved oversight of a trial conduct. But, these trials continue to be routinely over-budgeting, suffer from poor communication, lack team awareness, and are found to be unable to forecast and resolve issues quickly.

The problem with the current CTMS is the widely varying requirements of clinical trials managers. Some standard requirements include: budgeting, patient management, compliance to government regulations and compatibility with other data management systems. The complete set of requirement of one manager/sponsor might be completely different from that of another. These shortcomings result in delay and, sometimes, failure of clinical trials. A recent study suggests that improvements in a few key areas can result in a dramatic 60–90% reduction in total cost of a clinical trial (1). Yet, beyond electronic data capture (EDC), no class of tools was proposed as enablers of the same (1). This paper proposes the usage of an innovative and collaborative visualization tool "as a CTMS add-on" to help overwhelm these deficiencies of traditional CTMS.

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OBSTACLES IN SUCCESS OF CLINICAL TRIALS

Apart from the above limitations of traditional CTMS, the success of clinical trials is also hindered by the following obstacles:

- enrollment challenges;
- inconsistent and uninformed planning;
- poor visibility of enrollment trends;
- inability to evaluate effective adjustments to rescue a problem trial;
- poor communications/collaboration across global study teams.

These challenges are explained in detail, below:

Enrollment challenges

Ninety percent of clinical trials don't finish on time because of increased regulatory requirements, complex protocols, and a global patient population that is quite difficult to track. These reasons make the trials' recruitment increasingly difficult to manage, and result in enrollment failures and thus on-time completion. The impact of this is quite significant. Delays in enrollment completion affect timely submissions for regulatory approvals, and subsequently, the product launch. Budget and cost overruns combined with launching delays can cost a company a good amount of fortune.

Inconsistent and uninformed planning

A reliable and feasible enrollment plan is critical to finishing a trial on time. As tools like spreadsheets, business intelligence software, and transactional CTMS require extensive customizations, so, study teams often rely on intuition, good fortune, and choked budgets to meet subject and timeline targets. Also, requirements for enrollment management vary from one manager to another, making it difficult to share best practices or enforce consistent business rules across and among organizations.

Poor visibility of enrollment trends

Study managers often miss valuable insights and fail to spot potential problems because they lack the tools to quickly identify clinical study enrollment trends. Although, the spreadsheet models can provide some assistance, but have limited ability to aggregate data and predict potential problems in an automated fashion. Instead of foreseeing problems, most study managers rely on contingency planning to address enrollment issues after they take place.

Inability to evaluate effective adjustments to rescue a problem trial

Slow site initiation, high screen failures, seasonal variability, and unproductive sites can all delay recruitment. Even good plans need to be adjusted from time to time. Without the ability to predict, simulate, and model different scenarios, study managers can't effectively adjust the plan to keep enrollment on track. In addition, significant amount of a study manager's time is spent in aggregating data from multiple sources, which can be better spent analyzing the data to make the best decisions. Without simulation and modeling tools, study managers can't view and drill down into the data to diagnose problems or to track progress. Moreover, they may over-invest in activities that contribute to over-enrollment, such as advertising campaigns, new centers, and other costly initiatives.

Poor communications across global study teams

Many global study teams have difficulty in collaborating because they lack timely data communication across numerous countries and centers. This lack of transparency impedes communications across multiple time zones and delays decisions. Not only does the absence of a transparent system reduce staff efficiency and increase enrollment and data clean-up problems, but it also allows companies to repeat costly mistakes. When companies can't track each site's historical performance, they can't identify top performers or weed out underperformers for future trials.

LIMITATIONS OF TRADITIONAL CTMS IN CLINICAL TRIAL MANAGEMENT

The clinical trial stage of drug discovery, generally, has a timeline range of 6–8 years, and involves budgets of hundreds of millions of dollars. The very high rate of failure and delays in completion makes this stage a highly risky affair. Following are the various limitations of traditional CTMS in clinical trial management:

In answering customer business questions

Although the pharmaceutical industry uses expensive CTMS, many business questions essential for the success of clinical trials remains unanswered, e.g.:

- What are the demographics and medical conditions of patients and how are they affecting the results of a clinical trial?
- How does patient compliance affect outcome?
- How to quickly identify candidates for a clinical trial?

- What is the lifetime value of screening and interventions?
- Why are the reasons for a patient's death?
- How quickly can the unknown trends/patterns be identified and drilled down for details?

In patient enrollment

Management of patient enrollment has always been a big limitation for CTMS. An optimal approach for managing patient enrollment must include the following:

- ability to define feasible enrollment plans;
- track progress of enrollment;
- make informed corrections to the plan as and when needed.

This information visualization is inadequate in traditional CTMS without the help of an analytics tool. Moreover there is a priceless need of site selection through intelligent identification of disease zone/population through historical records.

In clinical trial follow-up

After every clinical trial, there exists a very important follow-up stage. Following are the various limitations of traditional CTMS at various substages of clinical trial follow-up:

Planning stage

Every clinical trial begins with a plan. Life sciences companies require use of predictive analytics to forecast and visualize different scenarios so they determine the best course before taking action. Traditional CTMS lacks this feature to provide the predictive analytics to forecast and visualize different scenarios so that the best course of action while planning a clinical trial.

Tracking

A study manager tracks the recruitment progress by gathering data from various source systems (e.g., CTMS) to ensure that the enrollment exercise in on-track. Most of the times, they enter these information manually from the source systems into the spreadsheets to see how the actual enrollment process is progressing against the plan. The disadvantage of this manual system is that the facts and figures are updating every moment, so it is very difficult to get the current picture at any point in time.

Problem diagnosis

Even the best-laid plans can run off-course. If this happens, then study managers must quickly identify the underperforming areas (e.g., countries and site investigators), to correct the plan. This function is also absent in traditional CTMS.

Optimizing

Optimizing the plan is easy only when the system is capable of predicting where recruitment is headed in order to model and implement changes to bring the project back on track. This final step in the clinical trial follow-up process is critical and requires business intelligence (BI) for the success of clinical trial.

Spreadsheet dependency

Custom-designed or commercial CTMS often lack the flexibility and forecasting capability to model the entire enrollment picture across a worldwide development portfolio. Consequently, spreadsheets are used for modeling and forecasting, thus giving rise to the following issues:

- Manual processes introduce substantial control risks.
- The combination of CTMS for collecting actual enrollment and spreadsheets for forecasting or scenario modeling leads to problems of data integrity and information silos.
- Spreadsheets lack enterprise-class functionality such as managed workflow and the ability to push template changes out to hundreds of users simultaneously.
- Keeping multiple systems up to date and synchronized is frustrating, time-consuming and error-prone.
- Spreadsheets create islands of data, making enterprise-wide reporting a challenge.

BUSINESS INTELLIGENCE (BI) IN CLINICAL TRIALS: PRESENT SCENARIO

The BI software market has grown at over 10% per year in recent years (2). The most common domains are sales tracking, marketing, and financial analysis (3). Penetration into the clinical trials space has been limited. Recent industry consolidation has left a few large vendors with entrenched platforms along with many small emerging vendors with niche applications. According to Stephen Few and others, are useless charts and distracting visual features that tend to confuse users (4). Further, chart creation is still only the realm of a privileged few; users still have limited facility to compose visualizations, especially with loosely related data. Hence there is an urgent need of a system that empowers end-users to compose visualizations themselves would break down information silos and allow much faster and more effective analysis and decision making.

CLINICAL TRIAL ANALYTICS (CTA)

Why CTA?

Improving the study execution process is a difficult challenge, as the number of people, processes, and inherent variability involved is quite large. Clinical trial has become a complex process from inventory tracking to enrollment profiling, adverse event analysis, financial tracking, and personnel management; similar in size to a large systems engineering effort. Keys to success of clinical trials include transparency at all levels, smooth coordination of related efforts, and regular early detection of problems. The most disruptive situations occur when activity is diverted from the plan. For instance, enrollment at a few sites might be lagging, and it is unlikely that they will be able to catch up. Another variance from plan would be an unexpectedly high number of adverse events in a specific population. In each case, the range of alternative solutions is wide and requires inputs from across functional boundaries, often a difficult proposition. If data, geographic or procedural barriers prevent fluent communication and information flow among the broader trial team, issues seem to linger for much longer than desired. Likewise, a different set of experts are charged with data monitoring and analysis. While trials are required to adhere to regulations and study protocols, any variances have both cost and data quality implications. Late or missed visits don't just mean schedule delays; the resulting data may be tainted and have regulatory impacts. So, carefully monitoring the incoming data for impending problems acts as will be a key capability. Analytics can help here, but just detecting the presence of anomalies is inadequate. Determining the reason for anomalies requires human brilliance at assembling information fragments and clues across multiple disciplines. Tools like CTA allow broad inspection and intuitive exploration and thus empower analysts beyond statistical and/or reporting packages.

Scope

The CTA solution is designed for clinical research organizations for optimizing the results of clinical trials by reducing cost and duration as well as increasing success rate and safety. Its capability of data integration makes it the right choice for analyses of patients' complex data, response rates, laboratory tests, adverse events, and physical or demographic data. Analysts are enabled to quickly identify unknown trends or patterns in data, drill down for details, find incomplete records, evaluate the quality or significance of information and perform more complex data queries quickly and intuitively.

The unique ability to explore a number of multivariate responses, expressed and stored in all kinds of data, help drug makers evaluate the drugs' safety and efficacy in early phases of development. Clinical trials groups benefit on having the ability to explore complex information in a collaborative and flexible environment.

It is to be noted that CTA is not a replacement of CTMS; rather it is an add-on to CTMS. CTMS is a clinical trial management and documentation tool. On the contrary, CTA will be used as reporting and business intelligence/analytics tool. The various features of the proposed integrated system as opposed to the standard CTMS are highlighted in Table 1.

Intended business users

A CTA system can benefit a wide range of business users. Managers can track milestone progress, sponsors can monitor portfolio performance, site investigators can follow patient timelines and protocols, and data monitors can review data collected to date.

Visualizations created for outlier detection or forecasting will always use current data. Tools and data sets not being correlated, can be viewed along shared dimensions; for example, financial data can be overlaid with enrollment events and visits, to visualize pay-for-performance over a given time interval. Likewise, patient adverse events, concomitant medications, and visits could be overlaid against lab results. Incorporating trial planning and budgeting can help identify which sites are consuming the most resources while producing the least results. Protocol compliance charts identifying which study events are overdue and at risk of being noncompliant, can call managers to action. Many problems faced by clinical trial teams are caused by lack of understandable information. When this barrier is removed, performance should improve.

Technical description

CTA uses tools and techniques for decision support, data extraction, querying, and data mining to gather and analyze data for clinical research for different categories of business analytics (BA) like: Information and knowledge discovery; decision support and intelligent systems and visualization (5, 6). Information and knowledge discovery uses OLAP (on-line analytical processing) *ad-hoc* queries, data mining, text mining, Web mining and search engines. Decision support and intelligent systems include tools and techniques such as decision

Table 1. Comparison of standard CTMS and CTA-CTMS integrated system.

Main Feature	Sub-Feature	Feature in standard CTMS (Yes/No/Partial)	Feature in CTA + CTMS (Yes/No/Partial)
Clinical Trial Monitoring	Ability to define feasible enrolment plans	No	Yes
	Tracking enrolment progress	Partial	Yes
	Make informed corrections to the plan as and when needed	No	Yes
	Modifying enrolment data dynamically	No	Yes
	Identification of under-performing areas	No	Yes
	Optimization of the clinical trial plan	No	Yes
	Modifying enrolment data dynamically	No	Yes
Reporting	Ease of reporting	Partial	Yes
	Flexible reporting	No	Yes
	Spreadsheet dependency	Yes	No
	Real-time reporting	No	Yes
	Drilled-down reporting	No	Yes
	Trend analysis	No	Yes
Data Management	Data monitoring	Partial	Yes
	Data integration from various systems	No	Yes
	Database ETL (extract, transform and load) feature	No	Yes
Business Intelligence	Identification of KPIs	No	Yes
	Monitoring of trial progress	Partial	Yes
	Business forecasting	No	Yes
	Business analytics	No	Yes
	Answering capability for customer business questions	No	Yes

support systems, statistical analysis, data mining and predictive analysis. These tools and techniques can be used for generating a hypothesis as well as data collection and analysis. Further, decision support systems, specifically clinical research decision support systems (CRDSS), can be created for multiple purposes supporting the research goals and initiatives.

Functional description

The stepwise CTA model is shown in Figure 1. It starts with defining business questions/objectives through requirements eliciting (inputs). This step is followed with the creation of clinical trial business intelligence models using dimensions and measures. The final outputs are analytic reports and key performance indicator (KPI) scorecards. These tools provide end-users with predefined and *ad-hoc* reports, help them to measure and monitor progress toward organizational goals, and discover meaningful information about the data. Also, patterns and trends can be identified. When being web-enabled they can be consumed by any client application and platform.

CTA can provide solutions for various problems encountered in traditional CTMS. Some of its functions include:

- Analysis of patients' complex data, response rates, laboratory tests, adverse events, and demo-

graphic or physical data to quickly identify unknown trends or patterns in data, drill down for details, find incomplete records, evaluate information's quality or significance and generally perform even complex data queries quickly and intuitively.

- Correlating clinical findings such as lab values with conditions to discover new approach to diagnosis and treatment.
- Quickly identifying candidates for clinical trials by study of patients' clinical data population to determine study locations.
- Targeting non-compliant population by comparing geo-location-wise distributed study sites to determine the root cause of study failure/delay.
- Determining the frequency of screening procedures to enhance diagnostic values and prevent deaths by finding the risk factors so that high risk patients can be targeted for diagnosis and treatment.
- Interacting with database to find patterns, relationships, and correlations.

APPLICATIONS OF CTA

Study compliance monitoring, performance measurement, quick identification and issue resolution

CTA tools used for remote site monitoring can involve the sites in a collaborative manner and enable them to derive benefits from the data they enter. Empowering sites to actively track their own performance against key metrics allows them to compete against other sites; strong performance can become a strong track record, which can lead to active participation in future trials. Moreover, these tools will encourage site investigator involvement and data perusal leading identification and resolution of issues much early than the team meetings or scheduled monitor site visits.

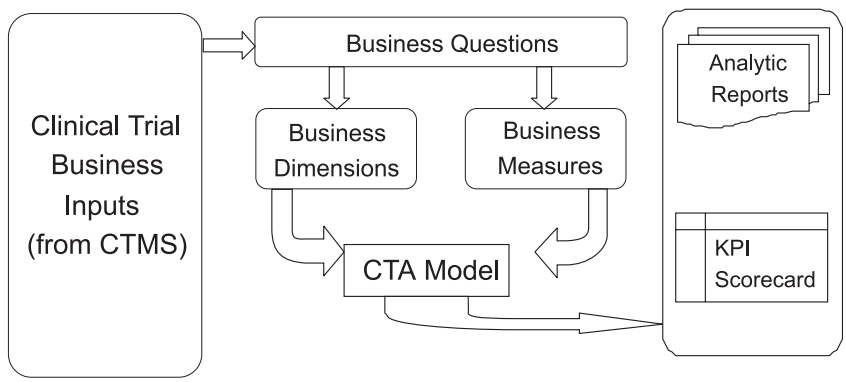

Figure 1. Clinical trial analytics overview

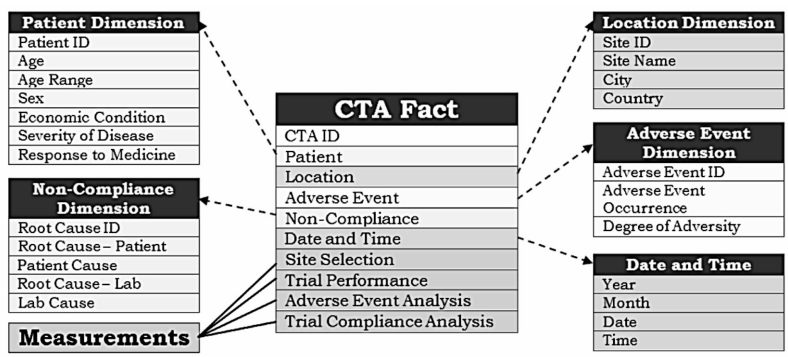

Figure 2. Schematic representation for the clinical trial data model example

Table 2. KPI systems of clinical trial analytics.

KPI name	Measurement components
Site location potential index	Number of diseased patients, their economic condition, age group, sex etc.
Trial compliance index	Number of late visits, recrutment target failure, dosing errors, regulatory complications, delay in completion etc.
Drug adversity measurement	Degree of adversity, number of deaths, time of recovery, number of counter medicines etc.
Drug potential index	Non response-response ratio, degree of recovery, time to recovery etc.

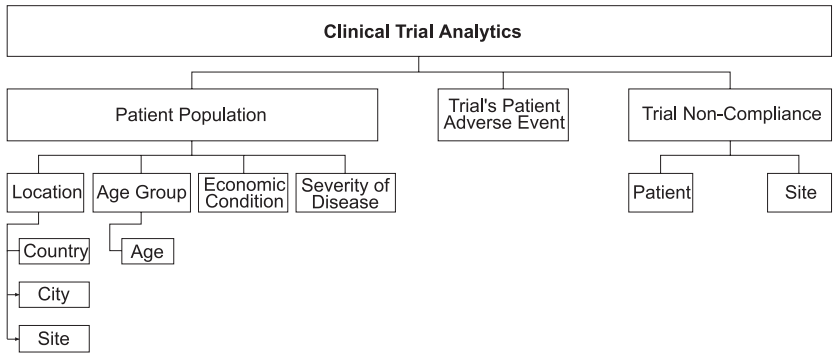

Figure 3. Classification hierarchies of clinical trial data dimensions

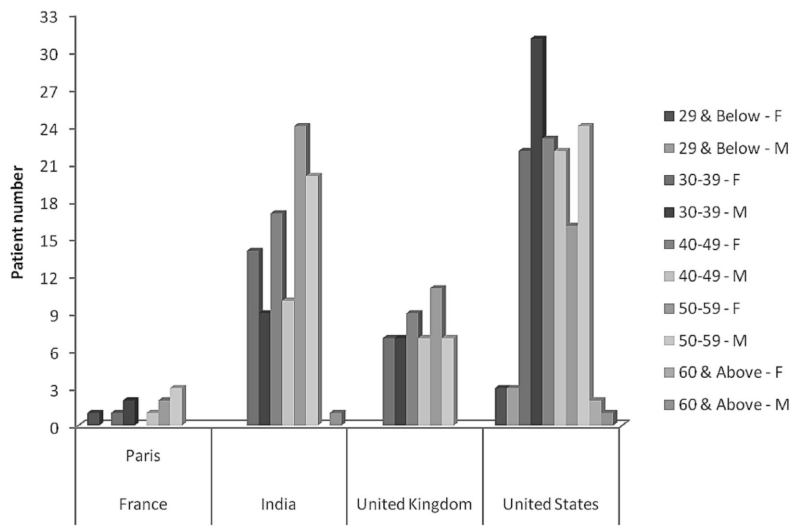

Figure 4. Example of country-wise distribution of patient population for a particular disease

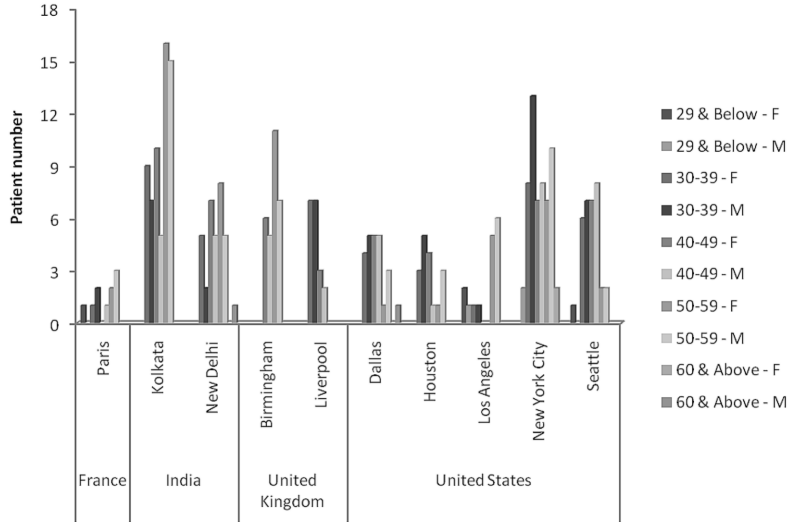

Figure 5. Example of country- and city-wise distribution of patient population for a particular disease

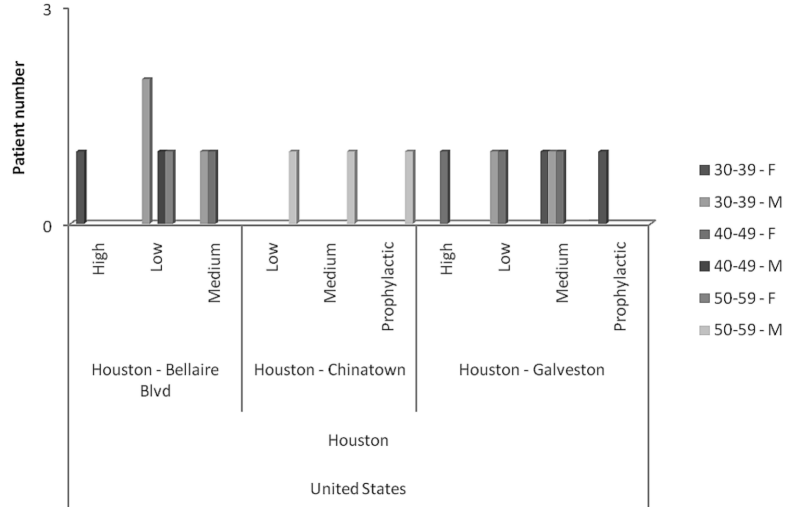

Figure 6. Example of site, economic condition, age group and severity wise distribution of patient population for a particular disease in a specific city

Remote site monitoring

According to Eisenstein, the largest area for improvement of clinical trial management is in the area of remote site monitoring, estimated at 21% of trial costs (3). Monitors have the difficult job of ensuring protocol compliance and data quality, so regular review of trial data is critical. Substantially large costs are incurred with prolonged trial monitoring travels and resolution of data inadequacies. With the CTA tools, this desired information can be captured in periodic standardized reports or data views resulting faster issue resolution.

Freedom from expensive trial amendments

It is a very regretful fact that many original sites close down during the course of a trial. Analysis of investigator performance across trials and assessment of their propensity to drop out of trials, or not able to recruit patient types, can help in ensuring that organizations do not have expensive

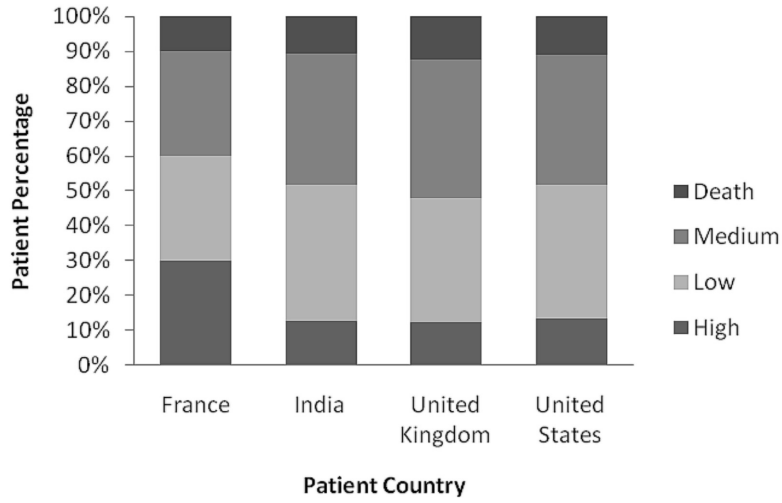

Figure 7. Example of country- and age-group-wise patient severity to a particular disease

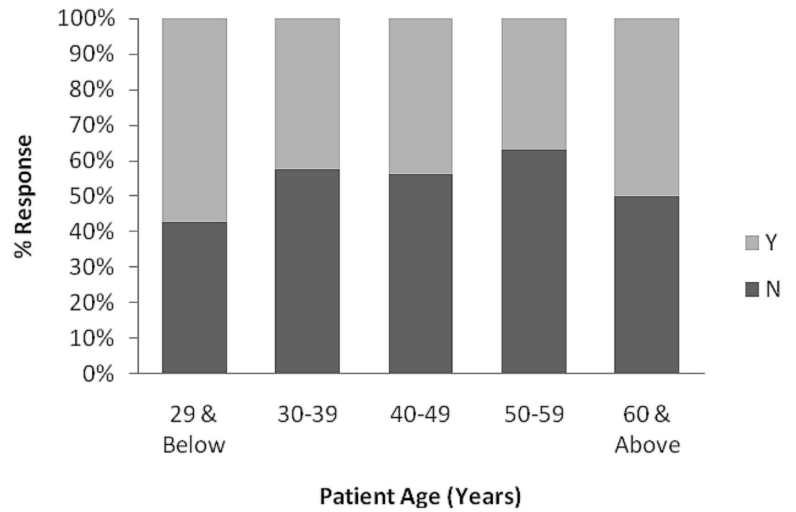

Figure 8. Example of age-group-wise patient response to a particular disease

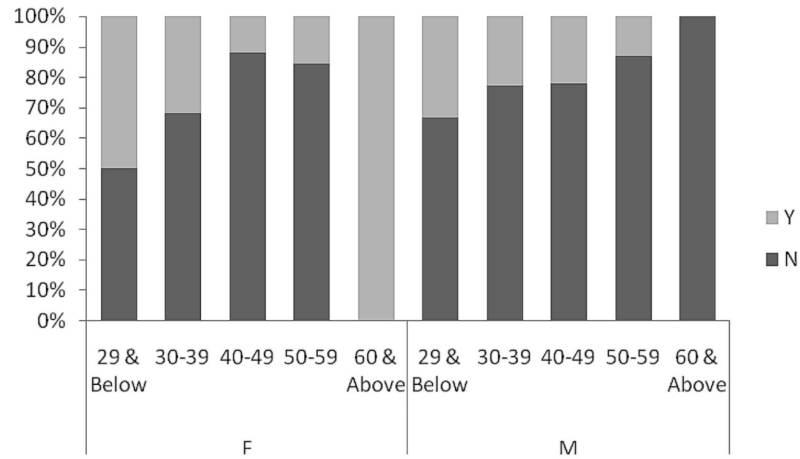

Figure 9. Example of adverse event report (sex-wise

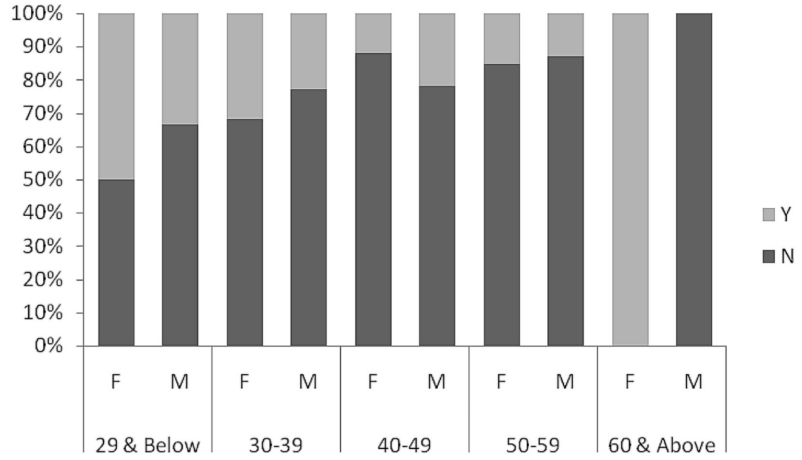

Figure 10. Example of adverse event report (age-group-wise)

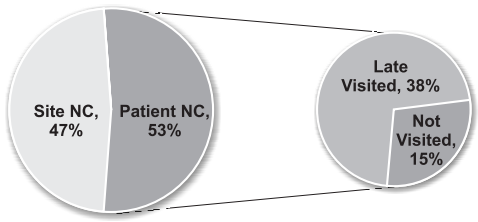

Figure 11. Clinical trial non-compliance analysis with drilled patient causes

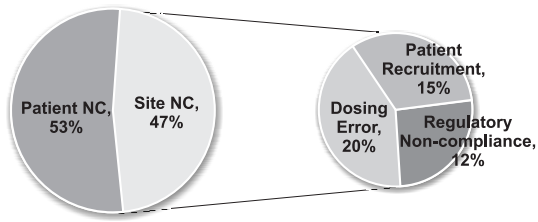

Figure 12. Clinical trial non-compliance analysis with drilled site causes

trial amendments. CTA is capable of resolving these issues by identifying the right patients; map their concentration across geographies and sites where they would be best recruited and even forecast the expected volume of patients and its impact on the trial cycle time, using historical data on patient epidemiology and knowledge of medical claims.

Applying collaborative visualization to clinical trials

Using CTA, it is possible to integrate all relevant data into a single environment where no queries are needed to select and view data. Moreover, the data is always up-to-date, and charts continuously change based on new or altered data. Users can browse at different levels of granularity and directly select and move data among charts, tables, and reports to track important metrics and information concepts. Users can share live visualizations with specific team members or to everyone involved in the study. Yet, data security filters prevent unauthorized access to either data or visualizations.

Clinical trial enrollment forecasting

Patient enrollment is an ongoing challenge for life sciences organizations. Failure to enroll adequate numbers of patients is a primary reason why some clinical trials fail. The ability to collect and model enrollment trends and make decisions to shut down or set up additional sites is key to managing a global development portfolio as study designs become more complex and resources become more scarce. CTA empowers sponsors and contact research organizations (CRO) with robust forecasting and enrollment analytics that involve collaboration among managers, analysts and the individual investigator sites.

EXAMPLE OF BI MODELING USING CLINICAL TRIAL ANALYTICS

Let us view an example of schematically created clinical trial model (Figure 2), which enables creation of clinical trial analytics for further reporting. This model contains clinical trial fact table, dimensional elements (such as patient, location, adverse

event, trial non compliance and time), and hierarchies (explained separately in Figure 3). It also incorporates business logic through relationships for carrying various measurements such as site selection, trial performance, adverse event analysis and trial non compliance analysis. The final outputs are: creation of the front-end analysis applications such as KPI (key performance indicator) systems, balance scorecards, reporting systems, and data mining solutions. Examples of some of the visual analytic reports are given in the following figures (Figures 4–12). We have also indicated some relevant KPI's and their description in Table 2.

CONCLUSION

Gains from popular clinical trial software tools are achieving diminishing returns, and industry consolidation is shrinking the toolmakers' innovation pipelines. Connecting all clinical trials stakeholders through shared understanding of integrated data will help align their incentives and encourage collaboration and prompt issue resolution. Both cost avoidance and value creation can be derived from such a collaborative visualization system. Decreased travel costs, shorter reporting time, and lower query and issue resolution time are common outcomes. Users are empowered to create understandable, usable, and appealing visualizations to capture and share their ideas. Employing a collaborative visualization system leverages existing IT projects and assets to create an integrated data environment capable of growing with your portfolio, while increasing your effectiveness and efficiency at managing clinical trials.
Business intelligence has become essential in most clinical research based organizations. BI is not constrained to individual departments or organizations; rather it is essential at the clinical trial level. This paper analyzed the need for clinical trial BI and presented the development methodology that incorporate iterative and cross-functional CTA approach. The introduced CTA model promotes an approach for clinical trial modeling and BI design according to real business requirements. It reduces the clinical trial life cycle and increases its efficiency by better monitoring, communication and real time measures. Clinical trial BI reveals opportunities to reduce costs and time, stimulate revenue growth, and enables companies to understand the entire clinical trial process from the global organizational perspective.

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