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Optimizing Clinical Research Operations with Business Analytics

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ABSTRACT

SAS® is widely accepted as the gold standard in determining safety and efficacy for clinical trials, and provides the primary mechanism for preparing data for these traditional clinical research analysis activities. Most traditional SAS users in the pharmaceutical industry, however, are unaware of the broad range of SAS analytics that are widely applied in other industries. This paper will discuss and describe how SAS business and advanced analytics can be used to:

- design better trials
- target patient recruitment
- select the best investigator sites
- improve resource projections
- optimize other operational activities

These operational activities are historically managed through experience and spreadsheets. Experience and spreadsheets rarely provide the quantitative insight to make the best and most informed decisions. The application of business and advanced analytics to clinical trial operations represents a new and improved approach to reducing the cost and time associated with managing clinical research projects.

INTRODUCTION

Bringing a new drug to market is an expensive proposition; the cost is often estimated at $1.2B.[1] This investment includes the entirety of work from discovery in the lab through approval by the national regulatory agencies, and will vary between therapeutic areas, geographies and a myriad of other factors. What does not vary, however, is that the expense is extraordinarily high and that ongoing investments of this magnitude are not sustainable.

The biopharmaceutical industry is in addition undergoing a widespread revolution. By many accounts, the era of the blockbuster drug is rapidly fading. Many high-revenue producing drugs are coming off-patent, and the pipeline to replace these drugs and their associated revenue is not encouraging.

To compound the issues facing the biopharmaceutical industry today, insurers and other payers are carefully evaluating their reimbursement policies in order to ensure that their payments are being well-spent. The US government has allocated over $1B to fund comparative effectiveness research in order to provide tangible evidence regarding which therapies perform better. If one company's drug is found to be less effective than another's, changes in revenue will be significant for both companies.

These related factors are all contributing to the clear message that it is no longer 'business as usual' for the biopharmaceutical industries. Companies must identify ways to work efficiently and effectively in order to ensure that their investment dollars are well-spent.

Of the $1.2B estimated for each research program, several hundred million dollars are allocated just for clinical trials, with the cost for each trial ranging as high tens of millions of dollars, and sometimes even higher. With projects of this size, it is easy to see how management of such projects must be efficient, but most manufacturers apply only basic tools to such management activities.

SAS, with its rich set of advanced analytics tools, provides an ideal means to bring rigor to the decision-making processes and management of clinical research projects. Although SAS has been widely accepted as the gold standard for providing statistical capabilities to determine the safety and efficacy of individual and integrated projects, and SAS is frequently the tool-of-choice in clinical trial data quality and transformation activities, only a limited set of SAS analytical tools have historically been applied during the clinical trials execution process.

As shown in Figure 1, there are several key areas where SAS analytical capabilities can bring significant efficiencies to the clinical research process. Each of the opportunities in Figure 1 describes business processes that are associated with clinical research operational activities. The operational activities typically occur much earlier in the process than the traditional role that SAS has in biostatistics activities, and use limited (if any) analytics-based decision-making efforts. Instead, decisions regarding these areas are most typically made via unmanaged, manually populated spreadsheets, and are guided more by past experiences than hard data.

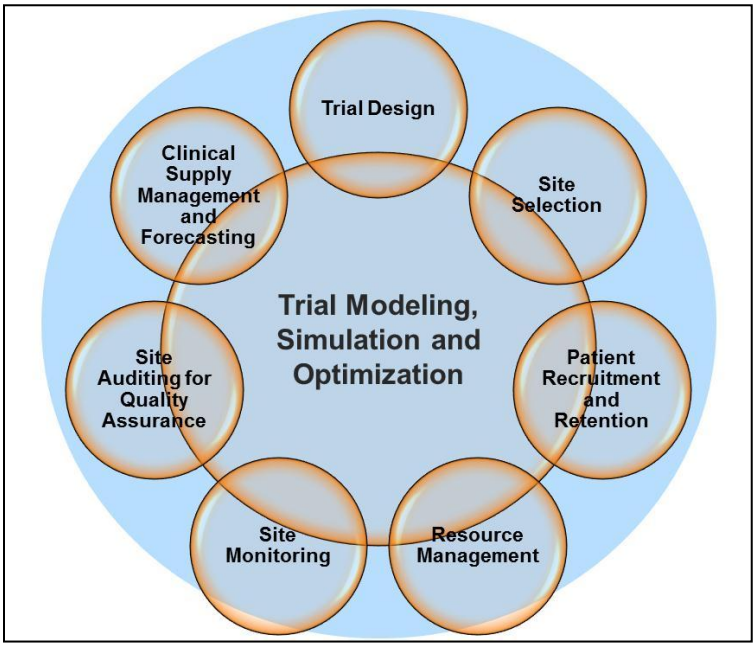

Figure 1. Clinical Trial Optimization Opportunities

In many cases there are direct parallels between these specific clinical trial processes and business processes in other industries where SAS is frequently used to create not only informed, but optimized decisions. This paper addresses each clinical trials analytics opportunity shown in Figure 1, describes the business process involved, identifies how analytics can better solve the problem, and uses examples from other industries where appropriate.

Analytics, however, will not be successful when executed in a vacuum. Organizations must invest in both data preparation so that the analytics can be successfully applied, and personnel that can lead business process initiatives. As with all change, the keys to success are people, process, and technology. This paper provides the foundation on which to successfully change the process and to enable the biopharmaceutical industries to develop new therapies with optimized operational activities.

TRIAL DESIGN

For years, clinical trials have typically been designed using traditional biostatistical techniques. While experimentation, by its very nature, means that not all expected results will be achieved, the business of clinical trials necessitates a more robust approach. A poorly designed trial has many ramifications beyond simply failing to prove the desired endpoints and can bring entire research programs to a halt because expected safety or efficacy is lacking. There are the additional considerations of cost, ethical treatment of patients, and wasted resources.

Trials can be more successfully designed by applying analytics to historical data in order to assess the likelihood of the trial's success in terms of both operational and statistical outcomes. In some cases, a trial might be designed optimally for demonstrating safety or efficacy, but be impossible to execute due to restrictive inclusion/exclusion criteria. Similarly, a trial might be easy to execute, but impossible to meet its scientific objective.

While all trials are designed with some level of scientific and operational rigor, life sciences research organizations are now beginning to more broadly apply simulations to the design process. With simulations, various different designs are defined, and then a series of trials are simulated with advanced analytical software. These simulations are used to assess various parameters including different dosing regimens, patient retention, completion results, and patient enrollment.

Importantly, one key outcome of the simulation process can be a statistical assessment regarding the use of an adaptively designed trial. Adaptive trials have the potential to transform the clinical trial process by allowing predefined changes to the ongoing trial based on accumulating data during the trial conduct. This type of adaptive approach enables several potential trials to be combined into a single trial, thereby reducing the lag between trials as well as reducing the number of trials required for approval. This adaptive approach, which has been available for many years but has recently gained momentum in industry and with the FDA, is not without risk. Through the simulation process, it is possible to determine the best approach in moving a research project forward and to reduce the risk associated with exploring adaptive trials

SITE SELECTION

There are many critical aspects of a clinical trial, but perhaps the most critical in terms of successful trial execution and operations is site selection. Site selection provides the foundation to meet the project's timeline regarding patient recruitment, and ultimately the final delivery dates for the trial study report. In short, sites that are not able to recruit sufficient patients will seriously impact the ability to complete the trial on time and will become a sinkhole for trial budgets. The average sponsor cost to open and close an investigator site, regardless of whether any patients are enrolled, is estimated at $50,000, and 80% of sites enrolled one or fewer patients in Phase II/III in 2008/2009.

The effects are further compounded when additional sites need to be opened at $50,000 each to make up for the patient recruitment shortfall associated with the previously selected sites.

Beyond the direct relationship between successful sites and patient recruitment milestones, sites also indirectly affect the trial's goals through cost and quality issues. Sites that collect poor-quality data requiring additional monitoring visits and disproportionate numbers of data queries will increase the expense of the trial through additional labor costs, while potentially interfering with the ability to accurately calculate the outcome of the trial due to data quality issues.

In addition, sites are frequently selected because their physicians are identified as 'key opinion leaders' and are considered important to the pharmaceutical company sponsoring the trial. These key opinion leaders are perceived to influence how other physicians would treat similar patients and represent the first step toward marketing a drug under investigation.

Despite the multiple means of affecting the research program (time, cost, and quality), very little effort is made to identity and select the optimal research sites. Instead, pharmaceutical companies primarily rely on past recruitment performance (that is, how many patients did the site recruit previously?) as well as site questionnaire responses that indicate an estimate by the site of their own ability to recruit appropriate patients. These basic measures, the latter of which is frequently a biased guess by the investigative site, are very limited in their ability to identify the 'best' site because 'best' is not typically quantified as part of the selection process.

Instead, the optimal site will be determined by assessing a variety of data points (recruitment history, queries, re-queries calculated thought-leadership, and so on) weighting these factors appropriately, and quantitatively determining which sites are indeed 'best'. Clearly, a low-cost site that cannot recruit patients will have little value; similarly, a site that recruits many patients but collects low-quality data at high costs is limited in value as well.

SAS has been applying analytics to solve business problems such as these for years, primarily through our solutions for supplier intelligence, which enable comprehensive sourcing capabilities. Just as it is not enough to select the lowest cost supplier, it is similarly insufficient to select the best historic recruiter. A comprehensive solution enables research organizations to apply analytics-based decisions in selecting the best research sites.

PATIENT RECRUITMENT AND RETENTION

Patient recruitment is widely recognized as the single biggest bottleneck of the clinical trials process. In a Centerwatch 2007 survey, fewer than 7% of US sites reported meeting their enrollment timelines. As patient enrollment timelines slide, additional sites might be initiated, creating increased and unexpected costs. Final delivery milestones are frequently missed and cost overruns are common.

Confounding the problem of delayed patient recruitment is the common practice of over-recruitment to address patient retention concerns. For a given clinical trial, an assessment is made to determine the number of patients required to meet the trial's statistical endpoints. Because the trial manager expects some number of patients to fail to complete the trial (ideally, a quantitative assessment based on previous trials), the overall patient recruitment goal is inflated to account for these non-completing patients. In effect, research companies are compounding a recognized problem of missed patient recruitment goals by adding additional patients to these existing goals, all but ensuring delays in determining the outcomes of the trials.

Applying patient retention processes will result in more patients completing the trial, and reduce the number of required patients to be enrolled in order for statistical validity of the trial outcomes to be achieved. This type of retention activity is widely practiced in other industries, where the focus is on customer retention. In these industries, companies look for trends in their existing customers' behaviors (for example, fewer clicks on retailing Web sites or diminished use of a long-distance calling plan), and then intervene (perhaps by offering a targeted discount) to retain the customers' business. In clinical trials, interventions might take the form of increased contact from the investigator, or other similar activities, in order to retain the patient's participation in the clinical trial.

The parallels between customer retention and patient retention are quite clear. It costs far less to retain a customer or patient, than it does to recruit a new customer or patient. By applying patient retention techniques using existing and common tools available to other industries (http://www.sas.com/industry/fsi/retention/index.html), patient recruitment efforts can be managed more effectively.

RESOURCE MANAGEMENT

At its core, resource management is about having sufficient resources available to complete a measurable task. This can be thought of the various skilled position players on a baseball team, or the number of CRAs assigned to a clinical trial. Without the proper number of resources, coupled with the proper set of skills, work simply cannot be completed as desired. In a baseball game, the same 9 positions are required for 9 innings every game and a limited bench of replacement resources is always available. Clinical trials, however, are different and require a more fluid

approach to resource staffing. This fluid approach must take into account the planned project schedule, other competing projects, and it must accommodate the frequent changes that occur during the clinical execution process.

The most compelling area to look at regarding resource management has to do with CRA staffing and site monitoring visits. Most research organizations plan their staffing needs around a linear work timeline that includes tasks such as site selection, site initiation, patient recruitment, and so on. However, the work rarely occurs in this type of linear fashion, and its forecasted completion is directly related to the previous discussions regarding site selection and patient recruitment.

If CRA staffing for site monitoring visits is to be based on anticipated workload, it becomes critically important for that workload to be accurately forecast. Instead, organizations typically rely on an approach of 'x' patients per month for recruitment, when historical models almost always indicate that patient enrollment is not nearly linear. Based on this false assumption, it becomes impossible to optimally staff and train the necessary CRA resources because the anticipated enrollment, which will be the ultimate driver for site visits, will lag the linearly forecasted enrollment. If we look at a basic example as shown in Figure 2, the number of idle CRAs initially assigned to a project continues to grow as enrollment begins lagging. This idle CRA workload represents wasted resources that could have otherwise been allocated to other projects. Although it is possible to re-assign resources, there are significant switching costs involved as CRAs must be fully trained on any new project in accordance with organizational standard operating procedures. A more analytics-based approach to this resourcing problem would include the use of accurate forecasting analytical tools to better anticipate model-based patient recruitment.

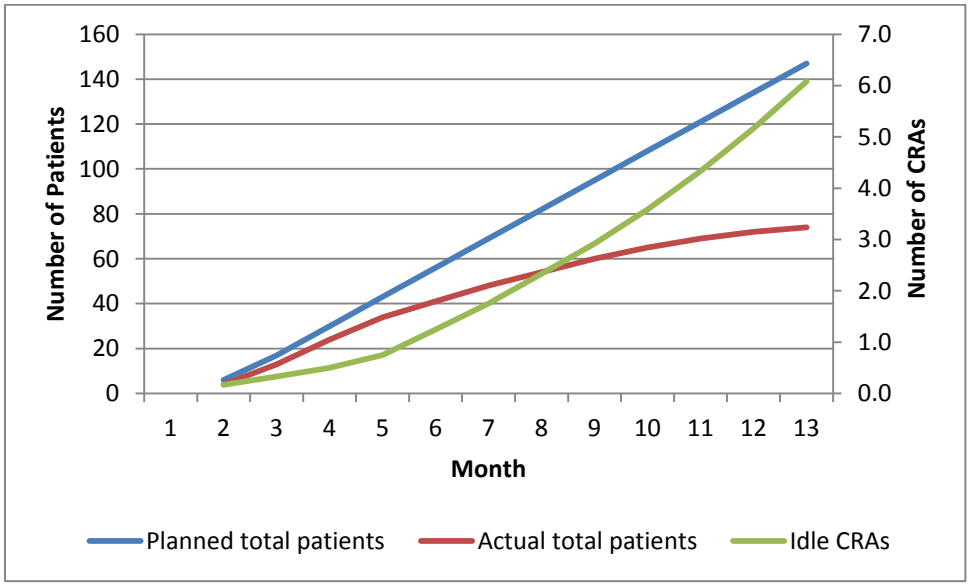

Figure 2 Planned Versus Actual Patient Enrollment

In many ways, this is similar to the resourcing issues associated with how airlines schedule their reserve flight crews. In this situation, the airlines position (and pay) reserve crews that can step in when the scheduled crew is grounded due to weather delays, illness, or other issues. Where most airlines base their reserve staffing upon a simple percentage of resources, America West Airlines (now part of the US Airways Group) is using advanced forecasting analytics (http://www.sas.com/success/awa.html) to determine the level of staffing that is actually required. With this approach, monthly forecasts at America West were never off by 1 resource per month, and a similar strategy can be deployed with regard to CRA (or for that matter, other departmental) resources.

SITE MONITORING

The monitoring of data and processes at the investigator site is a critical aspect of clinical trials, and in many cases, the costliest aspect of the trial. Historically, site monitoring has been managed on a calendar basis, with CRAs visiting sites without direct regard to the workload that is associated with that visit. Frequently, a site will be visited when it has a comparatively small number of patients or when little has changed since the last visit or simply because such a visit is due based on the calendar. This simplistic approach creates a situation that has all the expense of a site visit with little of the value. And, in fact, it wastes resources that would be better put to use ensuring quality elsewhere within the clinical trial.

Two trends regarding site monitoring in clinical trials are emerging. The first is applying the techniques described earlier regarding resourcing to accurately forecast patient enrollment. Beyond the need to have the right number of

CRAs resourced to a trial on an ongoing basis, there is the additional value in having the CRA conduct site monitoring visits when there is sufficient data at the site to justify the expense of the visit. Through accurate patient enrollment forecasting, coupled with forecasted patient visit schedules, it becomes a straightforward process to calculate the monitoring workload accumulating at each investigator site. With this forecast in place, CRAs can schedule their site visits to coincide with a full-day's work of monitoring. By aligning the workload with the visits, this will create efficient monitoring visits, where each site visit will be maximized in terms of value.

There is an emerging trend in clinical trials to focus on risk-based monitoring. With this approach, CRAs focus on sites with greatest risk, while providing less monitoring coverage for those areas of minimal risk. In this case, 'greatest risk' refers to the likelihood that data quality issues at the site will impede/interfere/impact the successful conclusion of the trial, and potentially the entire research program. For sites that have historically good track records regarding performance and quality, monitoring visits would be reduced, while sites with a higher risk profile will receive commensurately increased monitoring efforts.

It is important to note that FDA is largely silent on the details associated with site monitoring efforts. In essence, it is up to individual companies to determine the right level of monitoring that is necessary to meet quality expectations, and it makes sense to concentrate those efforts where risk is higher. By reviewing past performance at investigator sites, and building analytical models that indicate the characteristics of sites that are most at risk for data quality issues, it becomes straightforward to implement a risk-based monitoring approach. Further, it becomes practical to deploy risk-based monitoring such that the efforts to target monitoring are fully optimized, and meet a pre-determined quantitative risk profile for the trial as a whole.

SITE AUDITING

In many ways, site auditing by both life sciences quality assurance teams and regulatory authorities is a simple extension of risk-based monitoring as described in the previous section. Audits are designed to confirm that sites are performing in accordance with Good Clinical Practices and industry regulations, and it makes sense, again, to focus on where the risk is highest. This is a similar approach taken by the Internal Revenue Service in the United States, whereby audits are targeted where the risk is highest. In some cases, automated audits (like edit checks in clinical trials) are used to identify data discrepancies. However, more sophisticated and time-consuming investigations would largely be wasted on the average taxpayer. Instead, a risk profile is used to determine where these efforts should be directed.

Currently, site audits are targeted on only the most basic of information. This might include findings identified during scheduled monitoring visits, large numbers of patients and similar factors. True risk-based site auditing would implement more robust analytical models based on historical performance rather than the unsophisticated methods used today.

CLINICAL SUPPLY MANAGEMENT AND FORECASTING

As we build more analytically driven business processes, and specifically, as industry deploys adaptive trials at an increasing pace, one of the key issues that must be addressed is clinical supply management. For every clinical trial, the dosing material must be manufactured, packaged, blinded appropriately, and distributed. This process is vitally important to ensuring that the various treatments are available for sites to provide to patients and to be available in the correct distribution to accommodate the expected distribution of patients at each site.

For traditional clinical trials, this process is initially straightforward as drug is shipped based on spreadsheet-driven enrollment projections. These projections, however, vary in their accuracy. Either more drug must be distributed to account for fluctuations in the projection, or sites must return unused drug for re-distribution to other sites as necessary and appropriate or dispose of any unused drug. More accurate enrollment projections, as described earlier in this paper, will enable more accurate clinical supply forecasting and prevent both over-distribution of study medication as well as re-supply and waste issues. For longer term trials, 'just-in-time' distributions that are closely aligned with forecasted enrollment and visit dates provide an excellent means to optimize drug distribution.

Adaptive trials, on the other hand, present a different set of challenges. These trials typically define different dosing levels in the trial, and might require investigators to switch to a new level based on analytical results as described in the protocol. Because these dosing assignments are determined only when the trial is in-process, it requires a different approach regarding clinical supply. The clinical supply team must be able to model and forecast which doses are needed at which site within some confidence level in order to optimize the availability of the right dose at each investigator site. The only other alternatives are to ship multiple dose packages to each site in anticipation of the various dosing possibilities or to simply react when dosing regimens are changed. Neither of these options is appealing, as the former requires significant expense to 'oversupply' each site, while the latter risks delays in supply distribution.

CONCLUSION

As the life sciences research industries wrestle with the evolving business and scientific landscape, analytics provide the means to gain control of their business processes. There is little doubt that the clinical trial process can be executed more efficiently, and it is possible to streamline the process at multiple points in the trial's execution.

The greatest potential area for leveraging analytics is in applying simulations to trial design and then executing the trial based on that optimal design. Far too many promising therapies are subjected to unsuccessful trials and represent wasted resources and delayed approvals. Those trials that are conducted must be designed to have the highest likelihood of scientific and economic success. When simulation indicates an adaptive design should be chosen, the value of analytics is further multiplied as the application of adaptive trials frequently results in the need to conduct fewer trials, further reducing costs and accelerating time to approval.

At the execution level, analytics enable research companies to focus their efforts where they matter most – accurate forecasts for planning purposes and risk-based leveraging of resources. It cannot be business as usual if the life sciences research industry wants to add to their long history of successes.

REFERENCES

[1] http://csdd.tufts.edu/research/research_milestones

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