WHITEPAPER

Adaptive Decision Making via Real-Time Harmonization of People, Process and Platform

(Seek, Model, and Adapt Series)

The life sciences industry environment surrounded by the competitive pressures, unpredictability of outcome, and regulatory reforms demands an increased focus on detecting leading indicators of change, and further identifying and quantifying impacts of newly emerging scenarios, rather than relying over black-boxed indicators of performance. In this way, business demands a transformational strategy by making a move from a world of "sense and respond" to one that is focused on "seek and act."

CTRenaissance, an integrated clinical development platform, is built ground-up based on two value added information technology models that catch attention — One that uses the Internet to integrate and externalizing the enterprise, and second that empowers you to go beyond externalization to actively seek new scenarios that may impact design strategy or operations.

By Maulik Shah, MaxisIT | ClinAsia

For instance, the Draft Guidance for Adaptive Clinical Trials, published by the FDA, addresses the apprehension in the pharmaceutical industry by simplifying regulatory issues and setting realistic expectations, as well as outlining standards and requirements that can be attained through a suitable infrastructure. Adaptive Clinical Trials offers huge benefits because of its inherent strong control of a study, which becomes even more powerful with harmonized processes in an integrated computing environment. However, this new approach requires a business transformation and an enterprise-wide architectural alignment – an exit from the traditional mindset clinical trials. People, processes, and technology must become truly synergistic in order to reap the benefits offered by Adaptive Clinical Trials, thereby minimizing potential risks or, even worse, biased actions jeopardizing success. Thus, each decision must be supported by strong evidence indicating Why, What, Who, When, and even How.

A holistic infrastructure requires true harmonization and complete integration, that is, one that can deliver built-in integrity including real-time metrics. This whitepaper will also provide a 360 degree view into the key issues surrounding Adaptive Design and the need for a scalable infrastructure for conducting Adaptive Clinical Trials that imbues a timely decision-making process. Other aspects covered are: providing insight on standardization & Integration; dashboards to monitor, assess, and adapt; built-in controls (firewalls) to ensure Integrity; and decision-making process & structure.

Industry Challenges

Pharmaceutical and life sciences organization face following challenges on a routine bases:

- Inability to perform integrated decision making without compromising on cross-functional dependency, interlinking, and transcending effects of each decision's across the functional domains;
- Lack of single-source view of clinical trial data in real-time and a solution to monitor the evolving trends;
- Inefficient and non-streamlined process for study design often takes longer turn-around-time in designs' planning, setup, monitoring and optimization (in case of adaptive clinical trials) or making go/no-go decisions or even track any bottleneck at the site level, enrollment level, drug-supply level or at data management level or analysis level. Overall process depends more on individual or departmental approach, which costs more and even causes loss of revenue or investments via delayed decision making;
- Departmental or domain specific solutions can support necessary optimization at one level, but does not provide the solution that spans across the domains.

Ultimately resulting into an inefficient course of action and decision-making relies on aged information.

Scenario

Specifically speaking, mid-course decision-making capabilities in adaptive trials represent the major problem domain. Current infrastructure landscape lacks timely availability of cross-functional, interwoven aspect of information that can allow agile decision-making; often the decisions lack confidence as they lack enough insight on its impact across the functional areas. Delay in business critical decision-making causes either loss of revenue or loss of investment or both.

(Current) Multi-stage process goes through various manual touch-points and disparate systems. The entire process would involve multiple organizations *(Software Vendors, CROs, LAB, Contractors, Independent Committees etc.)* various tools, inconsistent data formats and individualistic approaches causing loss of focus from the desired information and its meaning.

Convincing results with correct statistical inference, highest level of confidentiality and assured consistency between the stages of the study are primary requirements for validity and integrity of adaptive designs. Successful execution of adaptive trials depends on in-depth planning, availability of clean data, constant monitoring, rapid analysis, secured review, and efficient decision-making.

Senior management at most of the organizations and also the study teams clearly realize that the potential benefits of adaptive trials are substantial. Adaptive Clinical Trials are complex in nature and raise certain operational challenges due to its iterative nature than a sequential process. Constant monitoring and frequent decision-making at an accelerated cycle times are critical for realizing the benefits.

Ability to derive such benefits depends on timely availability of domain specific information. Authenticity of the decisions taken depends on the quality of information and also knowing the transcending impact of such decisions across the other functional domains. For example, if we were to make adjustments to one or more operational parameters (reduce Screen Fail rate, e.g.), then having knowledge of how that impacts to drug supply and IA trigger dates, would allow us to make informed, more convincing and scientifically acceptable decisions without causing the loss of integrity.

Various business scenarios, such as listed under, require adaptive cross-functional decision-making; and often catches management's attention due to its non-existence in the current infrastructure landscape.

Let's say at 6 months in a trial following adaptive design, observed event rate is lower than planned, which would cause interim analysis being delayed by 3 months.
What can we do to pull the interim analysis back to plan?

> *Can we add sites? How many sites do we need to add and in which geography? Also if we add new sites, will we have enough drug supply to support the demand?*

Or in another scenario, let's say the observed variance is higher than expected; to counter that we can increase the sample size.

> *If we increased the sample size, what would be the implication to enrollment timelines? Or what will be the impact on drug supply? Or what would be the impact on the expected interim analysis timelines?*

Let's also consider other <u>scenarios involving enrollment, drug supply and interim analysis during mid-course</u> decision making:

Need to define next interim analyses schedule/s: when and how many?

> *This requires quick information availability of current enrollment rate, event rate and forecasting when enough patients will be enrolled and enough events would have occurred?*
>
> *After knowing that from various source systems and manually produced reports, team decides to increase sample size or increase sites or may modify inclusion/exclusion criteria to boost enrollment and then eventually affect the interim analysis timelines. What about drug supply now?*

Need to add or drop a dose: when and which dose?

> *This requires information on current enrollment rate, response data and variability and then predicting the probability of that future data could produce significant results.*
>
> *As a result we may get a range from best possible to worst possible case for future data. In case of adapting to that decision, one may definitely want to know the impact on sample size and even drug supply*

Or certain <u>operation information quest</u>:

> How close are we to triggering an Interim Analysis? ……when will the remaining Interim Analyses for this study (if any) be triggered?
>
> Which studies amongst a group are either ahead of schedule or behind the schedule or on track for enrollment? ……how many patients are expected to be on any specific study in the future date?
>
> What interim analyses are upcoming for this group of studies, and when are they expected to be triggered? ……when will the Interim Analyses be triggered for this study?

Pharmaceutical and Life Sciences industry management realizes a serious need of getting answers to such questions and maintaining the availability of such information at finger-tips to enable faster, accurate and informed decisions. Also knowing the need, ability of accessing cross-functional data, rapid statistical analysis, building displays and even performing predictive scenario modeling are inevitable. Current processes would rather delay and potentially cause loss of integrity with such imperceptive decision-making.

The decision making process must consider its implications among several inter-related functions. Today, forecasting and operational decision-making require excessive manual processing at functional domain level, and also at cross-functional decision making level causing huge turn-around-time.

Moreover this cross-functional decision making requires aggregated data, relationships and dependencies among the cross-functional domains. The data must be analyzed quickly and within the premises of the inter-related functions to proactively identify the implications of potential decisions.

In order to address the above issues and much more, MaxisIT, a pioneer in providing integrated clinical development solutions has come up with an innovative and an intuitive solution – *eAdaptive under CTRenaissance® suite.*

eAdaptive offers ability to perform cross-functional scenarios planning, proactive decision making and model various mid-course corrections utilizing rapid, (pre-built) analytical models. Solution offers role-based and interactive information portal to seek, model and adapt based on various decision support analysis including trend, root-cause, comparative, predictive and forecasting at levels ranging from a trial to a group of trials to program to portfolio to therapeutic area.

eAdaptive helps ***seek Critical Path Opportunities*** early in the trial phase and helps optimize decisions supporting predictive and forecasting modeling techniques in a clinical trial scenario. This solution enables 360^0 review and analysis of a study or a group of studies from the top-down perspective, starting at the therapeutic area to a portfolio level to patient level and cross-functional perspectives, ranging from financial, enrollment, drug supply, interim analysis, clinical reporting to submission timelines. It is aimed to address the need of analyzing the effect of planned adaptive design, reviewing the forecasting of the same design, optimizing current design and also reviewing its potential impact at the same time. Thus, eAdaptive is a pioneering solution in the areas of strong decision support system required during the execution of adaptive clinical trials.

Solution Benefits

Overall information availability for cross-functional decision making process can be significantly reduced with minimum manual intervention. Moreover, such decisions allow optimal utilization of resources, early identification of potential risk or opportunity and overall time and cost benefits without losing validity or integrity of the design. Decisions linked at clinical portfolio, program, and trial levels can reduce: cycle time, number of patients per trial, and grant costs.

Proactive monitoring will help, e.g., identify variance or dropout rate to further adjust the sample size. It also identifies (via cross-functional impact analysis) a need to perform randomization. Built-in interim analysis capability will allow timely decisions to either stop trial or arm due to unexpected efficacy or futility or even be able to combine phases in case of an opportunity.

In case of any midcourse corrections, knowing the requirements for such correction in a timely manner is equally important as its implementation. Likewise, knowing the ineffective treatment arm in a timely manner and controlling the enrollment at that arm and vice versa are very important for overall trial efficiencies and costs management. Also, knowing the unsuccessful trials early on is very important to safeguard the patients and also the investments.

Innovative Technology

Adaptive designs allow necessary adaptation during the course of trial and offer great benefits. Deciding on a change, an adaptation, within the trial causes transcending effects within the interlinked functional areas, which are either not known or not measured effectively in timely manner. Such cross-functional impact can help identify various opportunities and also raise caution on negatively impacted aspects.

"Knowing the unknowns is important in an accurate and informed decision making but knowing the unknowns in a timely manner with an optimal use of resources helps maintain integrity of decisions and achieve desired benefits"

Industry has either looked into this aspects or started to adopt manual solutions or has just realized the need of one unified solution.

CTRenaissance® eAdaptive shows a path forward in adaptive clinical research via its integrated ability to monitor, analyze, and take cross-functional decisions during mid-course corrections. Using rapid pre-built analytical models, it allows reusability and makes reviewing and analysis process faster – time lag from data availability to analysis is reduced drastically and effectiveness, power, of each decision is preserved. It accelerates overall turn-around-time of taking important decisions like removing an ineffective arm to ensure patient safety and also to seize an opportunity to combine phases in case of effective results. It bridges the cross-functional domains such as enrollment, drug supply and interim statistical review – delivering an ability of knowing how each decision impacts all functional areas would increase the accuracy of the decision and confidence of decision maker.

About CTRenaissance®

CTRenaissance® is a configurable, homogenous computing platform that allows options to leverage existing investments in existing infrastructure by integrating and exchanging data in multiple standards such as CDISC, HL7 and even proprietary standards. Based on metadata driven structured content management and business intelligence technological domains, *CTRenaissance®* enables the protocol driven execution of clinical development activities from designing monitoring, analyzing, reporting, and including submission so that the majority of the more mundane tasks and manual interventions are automated, thereby allowing end-users to conduct the trial unencumbered. *CTRenaissance®* provides data and process driven standardization building a layer of abstraction on an existing fragmented landscape and siloed functional views. Its unique approach allows multiple partners and stake holders to collaborate and innovate under one unified and regulatory compliant platform.

CTRenaissance® On-Demand is an integrated and affordable clinical development solutions' suite built from the ground up to meet with the immediate and long-term evolving needs of life sciences organizations with productivity and compliance at its core. It offers a unified view of clinical development operations across the development processes enabling the cross-functional and interdependent stakeholders to make timelier and informed decisions. Simple to use, yet very powerful, *CTRenaissance®* On-Demand empowers business users with the critical timelines to make the right decisions with confidence.

About MaxisIT®

MaxisIT is an integrated technology and services provider in the areas of clinical research and development. MaxisIT offers a unique blend of both clinical trial domain and core technology expertise with thorough understanding of industry data and regulatory compliance standards. With a world class infrastructure and a vibrant work force at our US and India offices, we at MaxisIT believe that innovation and quality takes precedence over other things with emphasis laid on providing clients with the right solution at the right time, automating their business processes, reducing costs and enhancing their overall business value.

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