I. Thesis Abstract

This thesis comprises of three different domains of rational approaches in clinical trial management woven together by the idea that Critical Path Analysis, Meta analysis and Interim Analysis which influence organizational operations and decision making strategies in the pharmaceutical industry, i.e. an essential ingredient of clinical trial studies. This is a modular thesis in which three modules of rational approaches to clinical trials have been laid out serially.

In the first module, we described the application of Critical Path Analysis in development of new clinical trial projects to avoid complexity in schedules, enhancement of project control and handling project constraints for optimized decision.

In the second module, we concentrate on how several things be considered while selecting a hypothesis and study design. There should be some specific knowledge to be gained from Meta Analysis of several projects aimed to explore the same clinical trial goals. Some reasons to perform Meta-Analyses are to establish the presence of an effect, determine the magnitude of an effect such that it resolves the differences in a literature if any and determine important moderators of an effect.

At the end and the third module of this thesis examines monitoring of response variables to predict the final outcome through an impartial and statistically valid approach, viz. Interim Analysis. Such interim analysis and monitoring of specially sizeable (and/or risky) trials keep the decision process free of conflict of interest while considering cost, resources and meaningfulness of the overall project. Whenever necessary such interim analysis can also call for potential termination or appropriate modification in sample size, study design and even an early declaration of success.

Given the extraordinary size and complexity of clinical trial today, my research explains a few pivotal rational approaches to plan, analyze and predict the outcomes of a clinical trial that incorporate what is learned during the course of a study or a clinical development program. It also gives us a fine handle on how the project is completed, without compromising its validity or integrity. The goal of these methods is to make better and more timely decisions to allocate all study resources more efficiently, reduce costs and timelines, and better achieve informational goals compared to traditional study and program approaches. Such approaches can also fill the gap by directing the resources towards relevant and optimized clinical trials between unmet medical needs and interventions being tested currently rather than fulfilling only business and profit goals only.
Abstract contd...

Part I: A rational approach to clinical research: Critical Path Analysis
(Investigational Study 1)

Context & Objective

Clinical researches are operating in a strictly regulated environment that can be described by many best practices in management sciences. However, a distinct model for the management of clinical trials still needs exploration and research by virtue of which scope, time, and resources are scientifically managed and predicted. Implementation of such a Critical Path Analysis (CPA) will quantify real-time performance and operational processes of the projects most optimally. This will evaluate the performance and operational processes for possible improvements as well as strategize efforts to get the desired end results.

Methodology, Results & Discussion

Activities of a model clinical trial were listed as 78 different items, which were further merged into 35 major activities. Performing dependence analysis, the latter activities were finalized into 25 items which were then incorporated in activity predecessor table for the purpose of network diagram and CPA. The CPA was carried out considering patients, conduct and outcome. Activities were inclusive; described the trial entirely with accuracy, in chronological and logical sequences. CPA is a procedure for using network analysis to identify those tasks which are on the critical path: i.e. where any delay in the completion of these tasks will lengthen the project timescale, unless action is taken. This approach does not replace an adherence to the requirements contained in all applicable regulations, guidelines or SOPs governing the clinical trials but ensures the proper use of operational and decisional approaches for optimal resource management.

Conclusion

As the need to meet deadlines becomes more and more important to produce good and stable project plans; the CPA is very useful for determining activities that can overcome the project delays. We found that project mutation, i.e. protocol amendments and also other critical activities, had a statistically significant effect on the time factors of a study. Clinical trial resources can only be carried out effectively if a series of accurate resource models can be produced that can provide a range of project execution alternatives. In this way the project may be effectively monitored and realistic schedules can be maintained.
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Part II(A): A rational approach to clinical research: Meta Analysis
(Investigational Study 2)

Comparison of Tumor Response Rate and Toxicities with Polychemotherapy Versus Monochemotherapy in Patients of Metastatic Breast Cancer: - A Meta-Analysis

Background: Polychemotherapy and intermittent monochemotherapy regimens in metastatic breast cancer were examined in a meta analysis that included both tumor response rate and toxicities.

Material and Methods: Randomized controlled studies (conducted during 1990-2008) comparing monochemotherapy and poly-chemotherapy in advanced breast cancer patients were selected from electronic databases. Meta-analysis for response rate and toxicities (nausea and vomiting, toxic death, alopecia and reduced White Cell Count (WCC)) was performed using the Mantel-Haenszel method. The heterogeneity among the trials was assessed through a $\chi^2$ statistic, $I^2$ and visual inspection of the forest plots.

Results: Analysis of eligible studies reveals statistical significant difference in response rate (OR 0.72, 95% CI 0.65-0.79), nausea and vomiting (OR 0.80, 95% CI 0.67-0.59), Alopecia (OR 0.75, 95% CI 0.64-0.88) and reduced WCC (OR 0.55, 95% CI 0.48-0.62) which favors polychemotherapy except toxic death (OR 0.87, 95% CI 0.58-1.29). There was marked evidence of heterogeneity in all end points except toxic death.

Conclusions: This meta analysis shows the superiority of efficacy but not of safety of polychemotherapy over that of a single agent. However, the choice of treatment should be based on the response to the therapy, toxicity, patient preference, presence of metastases or imminent complications requiring aggressive and rapid tumor control.
Part II(B): A rational approach to clinical research: Meta Analysis (Investigational Study 3)

Clinical Outcome of Patients of Acute Coronary Syndrome at 7 and 30 days Undergoing Percutaneous Coronary Interventions and Treated with Bivalirudin and Heparin

Background: Recent data suggest that Bivalirudin provides ischemic protection superior to Heparin, and comparable to Heparin plus glycoprotein IIb/IIIa inhibitors, with significantly fewer bleeding complications. Whether this advantage persists in large population has not been fully defined.

Objective: This study systematically evaluates clinical outcomes of treatment with Bivalirudin vs Heparin in patients of acute coronary syndrome undergoing Percutaneous coronary interventions (PCI).

Methods: We analyzed prospective, randomized controlled trials via electronic searches that have reported clinical outcomes at 7 and 30 days. The outcomes were major bleeding, net clinical outcomes and Major Adverse Cardiac Events – MACE. Data from individual trials were combined by a meta analysis method of Mantel-Haenszel calculate a relative risk (RR) and 95% confidence interval (95%CI) across the studies. The heterogeneity across the trials was assessed through χ² statistic, I² and visual inspection of the forest plots.

Results: This meta-analysis involved a total of 30,088 patients (Bivalirudin, n=15,105; Heparin, n=14,983). Compared with Heparin, Bivalirudin was associated with a lower risk of major bleeding (RR 0.38; 95%CI 0.29-0.48 at 7 days and RR 0.67;95%CI 0.60-0.75 at 30 days), net clinical outcomes (RR 0.56; 95%CI 0.47-0.66 at 7 days and RR 0.89; 95%CI 0.83-0.96 at 30 days) and MACE (RR 0.78; 95%CI 0.63-0.96 at 7 days). There was no significant difference in case of MACE at 30 days (RR 1.02; 95%CI 0.93-1.11). Heterogeneity was observed across the trials that reported major bleeding (χ²=14.71, 5 df, p=0.01, I²=66%) at 30 days, but not at 7 days for reported major bleeding, and also for net clinical outcomes and MACE both at 7 days and 30 days.

Conclusion: This analysis further supports that Bivalirudin provides significant improvement in net clinical outcomes and MACE with a significant reduction of bleeding complications.
Abstract contd...

Part III: A rational approach to clinical research: Interim Analysis (Investigational Study 4)

This examines monitoring of response variables to predict the final outcome through an impartial and statistically valid approach. Interim analysis and monitoring of especially sizeable trials keep the decision process free of conflict of interest while considering cost, resources and meaningfulness of the overall project. Whenever necessary such interim analysis can also call for potential termination or appropriate modification in sample size, study design and even an early declaration of success. Given the extraordinary size and complexity today, this rational approach help to analyze and predict the outcomes of a clinical trial that incorporate what is learned during the course of a study or a clinical development program. Such approach can also fill the gap by directing the resources towards relevant and optimized clinical trials between unmet medical needs and interventions being tested currently rather than fulfilling only business and profit goals only.

Concluding remarks on this thesis:-

This thesis presents at least three unique methods to plan, design, analyze and synthesize the modern clinical trials. All these methods namely the Critical Path Analysis (CPA), Meta-Analysis (MA) and Interim Analysis (IA) are rational unbiased and objective methods which provide tremendous insight into the various stages of the entirety of clinical trials. We have demonstrated in this thesis that CPA provides highly accurate and valuable information about a prospective clinical trial program such that trial is accomplished in a critically time, scope and budget. Similarly the MA gives systematic review information on a drug-efficacy, safety, quality or any other chosen aspects. This information can serve as the foundation of evidence based medicine which perhaps other type of review cannot. Finally, the IA of a portion of large or complex clinical trial gives an opportunity to modify the trial or to continue it without any modification or even to terminate it without any negative ethical or scientific implications.