Chapter 6

Discussion on the Interrelation of Research Questions and Choice of Different Methodology

In this thesis, we focused on the general question that when and how domain knowledge can guide us for a perfect decision in the operational management of clinical trials. This question follows our hypothesis that different techniques of information gathering and statistical analysis alone are not sufficient to address problems concerning operational and decisional analysis of collected data for the derivation of perfect clinical trial success-prediction rules. The solution to these problems emphasizes, on one hand, an extensive integration of medical knowledge and, on the other, an explicit yet comprehensive modeling of imprecise predictors and prediction rules. The existing methods are using either a deductive (knowledge-driven) approach based on pre-existing expert knowledge and hypothesis testing, or an inductive (data-driven) approach based on the rules induced directly from data using certain algorithms. Thus, there is a need for an integrative framework to combine the deductive approach and inductive approach for operational and decisional making procedure during the conduct of clinical trial. This is where; tools like CPA, MA and IA are extremely useful not only for operational decisional purposes but also to contain material and human resources.

The strategy or logic of the research design for this study is primarily a deductive one. I have examined a particular set of events using a given theoretical model and have derived research questions in the language and terms of that model. If I investigate my questions only to find that the empirical data cannot be accommodated to the framework of the theory (something which is possible, despite the development of the research questions with the theory, because of the flexibility and revisability of the qualitative approach), then it will be clear that available theories are not adequate to describe the situation at hand. In other words, there is an element of theory-testing to the strategy for this research. Crucially, however, this theory-testing is not a straight up-or-down set of judgments that will either validate the overall theory or invalidate it.

My adjustments or additions to the theoretical frame have been offered throughout this thesis, and especially in the conclusions. In the previous chapters I explained and defended the specific theoretical framework to be employed in these investigations. Here it
may be worthwhile to offer a more general rationale for the choice of this particular perspective. A scheme for determining which kinds of research strategy are most appropriate for which kinds of research questions. While one can criticize aspects of his breakdown of questions and strategies, a very useful idea arises from that the kinds of research questions one can ask and fruitfully answers are necessarily bound-up in the methods and theoretical perspectives used.

When it comes to research questions and strategies for answering those questions, it seems we have a ‘chicken-or-the-egg’ situation. Which came first, the research questions or the methodology? In practice, I suspect the theoretical commitments and training of the researcher condition the kinds of questions that might be asked, even as the researcher should be seeking the methodological approach most apt to elucidate the topic at hand (or, as in a famous statement attributed to psychologist Abraham Maslow, if one is adept at using a hammer, everything tends to look like a nail). In my case as a student, the research topic and the epistemological point of view were developed in tandem — each playing against the other during the preliminary research into the topic.

Once the research programme matured, I then tended to develop different rational approaches into which I can feed a set of events and out of which answer of different research questions can be derived or interpreted. However, the development of the questions was not such a clean, stepwise process. Indeed, the best reason to use these rational approaches as an explanatory approach for my empirical study is that the study and the approach were developed together and are therefore intertwined in the research questions. Could other methodological approaches be used? Certainly, but the resulting research questions and answers would not be the same.

Properly conducted clinical trials are crucial to the process of evaluating proposed treatments and preventive strategies with respect to safety, efficacy, and effectiveness. As experiments, the methods must ensure the scientific and statistical credibility of the evidence used to promote the adoption of some new approach. With the involvement of humans as subjects, we must protect the safety of the patients participating in the clinical trial (individual ethics), while ensuring the rapid introduction of optimal treatments (group ethics). Additionally, because economic resources are always limited, we prefer the most efficient designs that satisfy the scientific, statistical, and ethical constraints.

The industry is also heavily regulated globally and performance needs not only to conform to these standards but excellence in quality and performance to add shareholder
value, also needs to be embedded as company culture, as part of the company environment. To align company performance to these objectives as part of the core business of the clinical trial, the need for an effective and rational approaches that coordinates and combines available activity-based best practices as a generic approach for CROs/pharmaceutical industry, is evident. The decision as to what approach to use in this research project was limited by the competitive and secretive of nature of the pharmaceutical industry.

Therefore, the data needed for the analysis are not generally available and a case study was the only option for this research. Historical data available from scientific reports were used because of the lack of a custom developed electronic data-capturing program at research place at the time of the empirical study. The other option, to collect real time data per hard copy, was experimentally tried as a pilot study in the CRO/pharmaceutical industry, but without success. Because of the workload of the personnel, they were reluctant to keep a record of daily activities undertaken. Therefore, historical data were gathered from available scientific reports and source data. The methodology of activity-based management models is well described in literature. Information from these literature sources was used to evaluate best in class management models to construct a rational approach for a pharmaceutical CRO. The literature study also revealed the importance of a customer focus and the effect that non-value adding customer demands have on resources and consequently also on profitability.

Field research in management is generally associated with cross-sectional research, the systematic collection and analysis of data from multiple sites at a point and time; time-series research, collecting and analyzing longitudinal data studies from one or a small number of organizations; case studies, and in depth study of the experiences of a single organization at a single point in time. Field research is mostly descriptive and it helps to develop theories, to explain how the world is and how it maintains itself. Field research can also be used for testing theories. Such theories are generally about stability, equilibrium and optimality. The theories predict that people and organizations behave in certain ways (Kaplan, 1998).\textsuperscript{1-2} The field researcher collects data that can test whether the actual behaviour of individuals and organizations is consistent with the hypotheses in the theory.

The field research method followed for this thesis was one of a case study. The data of a sample of contract research projects/studies from a single organization or pharmaceutical company was collected. The data were collected according to an activity-based methodology, analyzed with a statistical and productivity model, to construct a management model and to
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establish whether the actual behaviour of the CRO was consistent with theory and with the objectives formulated for this research. The study can be defined as an explorative research project with the design classification of a case study with numeric exploratory analyzes of research projects executed at pharmaceutical company.

The data of the research project were divided into primary data and secondary data. The primary data consisted of historical activity and related in respect of clinical study projects contracted to pharmaceutical company. The selected projects were executed over a period of several months. Secondary data were obtained from books, journal articles and information on the Worldwide Web (www), as well as from databases, formal computer-aided searches of electronic databases (PubMed, Medline, TRIPS, CEBM, and Science Direct) were performed by scrutiny of the reference lists of trials, review articles, abstracts and meeting proceedings. Electronic as well as manual search of specific journals. Real-time data were gathered from Final Scientific Research Reports. To assess the activity time and processes, relating to the assessment of the operations and decisions was selected for standardization purposes. Project design, objectives, population for inclusion, and the fact that all the operational divisions are as a rule involved in the execution of these projects, largely standardize these projects which corollary contributed to their selection.

The objectives of Phase II and Phase III projects are generally to prove efficacy and tolerability in patients, and the protocol design, objectives and time-frames differ greatly. The time-frames for the patient studies (Phase II – III) projects are as a rule also much longer: they are usually multi-centered projects over and above the fact that all the business units are usually not involved in the execution of a study. Therefore, the management associated with these aforementioned activities, and the output measures in relation to standardized activities executed during clinical research projects, it will impose a proper distribution of output, which may change the management model and recommendations. The criteria were set to ensure a homogeneous sample of projects with the least accompanying variation in design, which may interfere with the scientific evaluation of the research results.

The operating environment of pharmaceutical industry and the capacity to move new compounds through clinical trials emphasize the need to outline the vision and mission of the CRO in a rational approach to effectively align every activity according to company objectives. A rational approach is an essential plan on how to maintain a competitive advantage and needs to be reformulated continually, because a company that stagnates on
visions of the past will not survive the future. CROs and industry will need an innovative vision to move the present into the future.

The results presented will be used to formulate a rational operational and decisional management model applicable to future business. The rational approaches were constructed with accurate historical data by using as much real time data as was possible – balancing accuracy with effort, and not being too elaborate or excessively detailed. The rational approaches constructed to align effort and efficacy of CRO/Pharmaceutical industry processes was based on activity-based information because this methodology seeks to discover the causal factor, known as the cost driver, which determines the demand for the use of a particular overhead resource, known as an activity.

The definition that a theory is a set of statements that makes explanatory or causal claims about reality was explored to assess the best set of statements with which a model can be constructed for a CRO/Pharmaceutical industry. Therefore, as informative writing in literature confirms, good theories and models provide causal accounts of the world; allow the researcher to make predictive claims under certain conditions; bring conceptual coherence to a domain of science; simplify the reader’s understanding of business in the pharmaceutical, and contract research industry. The theory was confirmed that companies should know their drivers and deliverables, as well as which of their services make or lose money, emphasizing that schedules should preferably be structured not only by rule of thumb but, be based on target timelines.

What we found in our case study that through CPA and PERT we can achieve that project mutation, i.e. protocol amendments and also other critical activities, had a statistically significant effect on the time factors of a study. This emphasis on measures of outcome has no place in a program review. On the contrary, information on outcomes may be valuable even without rigorous evidence that outcomes are actually consequences of the program. Such observations relate especially to evidence of wasteful operation, the avoidable use of expensive or ineffective drugs, overstaffing, delays, the underuse of expensive equipment, superfluous activities.

A clear interrelationship between activities, the shortest and most critical (i.e. optimal path from starting to complete the last activity and deliverables, the best possible resource management and timelines predictions. It may appear that the CPA does not accommodate large variations in timelines and resources. Even it is so there is a sister techniques to overcome this PERT.
A CPA gives the top management a full-proof and analytical estimate of a critical project parameter for a complex CT project. For example, the CPA provides a prediction of the completion date for the entire project. Say, a marketing team of a huge pharmaceutical company is ready to launch a product in a critical cardiovascular area in four years. The consultants are saying that based on a given protocol the CT project will be over in at least 3 yrs and 8 months. This leaves no time for a NDA submission and review by regulatory agencies for a market authorization as the review process would take a minimum of 6 months. However, an accurately done CPA shows that all activities of this trial from start to finish including incorporation in NDA dossier are going to be over in 35 months. The top management, thus, can easily work with the marketing for a possible NDA submission (for a fast or even a regular track approval). This shows that a CPA can open up the real possibility of launching aforesaid product in 4 years.

Similar example can be given for budget, human resources, site and principal investigator resources and the scope of the trial itself (primary endpoints, generalizability of the findings etc).

Clinical trial design and protocols, which outline the trial methodology, are becoming increasingly complex, involving more assessments, exploratory endpoints, biomarkers, biopsies, etc., and increasing the administrative burden of trials. A study of over 10,000 industry-sponsored clinical trials found that the quantity and frequency of trial-related procedures (e.g., laboratory tests, patient questionnaires) per protocol has increased by 6.5 percent and 8.7 percent per year, respectively, during the time period between 1999 and 2005. A separate study of 57 Phase 1–Phase 3, industry-created research protocols found that the average total number of protocol-required procedures increased from 90 for the time period between 1999 and 2002 to 150 for the time period between 2003 and 2005; the average number of inclusion criteria increased from 10 in 1999 to 26 in 2005, and the average case report form expanded from 55 pages in 1999–2002 to 180 in 2003–2006.

Industry sponsors generally do not involve site investigators in the protocol design process. As a result, the required procedures outlined in the protocol might not be easy to smoothly integrate into clinical practice at the sites. A better planning and conferring with site investigators during the protocol design phase can help trials to avoid hitting foreseeable logistical snags.

Janet Woodcock, director of CDER, identified the separation between clinical research and clinical practice as one of the most serious problems with the current clinical research enterprise. The problem is a multi-faceted one that also serves to reinforce many of
the barriers discussed earlier, such as shortages of investigators and patients, high costs, and lengthy timelines.

One aspect of this problem is the lack of involvement of community physicians in the clinical research process. Most health systems and clinical practice sites do not include research as part of their mission;\textsuperscript{33-34} thus, there are fewer physician referrals of patients to clinical research studies and fewer investigators available to conduct the research than there might be otherwise. This also means that research findings are less likely to be adopted by such physicians in their regular practice.\textsuperscript{33} Many health care professionals do not receive training in research methods and have difficulty in understanding research results and therefore applying meta-analysis informative results are better for them to understand the evidence based medicine approach.

The separation between clinical research and clinical care also produces data collection inefficiencies, as some of the data that are routinely collected in the course of clinical trials overlap with data collected for the purposes of clinical care. Integration of clinical care and clinical research datasets would eliminate redundancies in data collection, help researchers to identify potential study participants, and offer other efficiency gains. However, at present, such integration is hindered by the lack of standard nomenclature and blend of incompatible paper and electronic data collection systems used in clinical care/billing and clinical research.\textsuperscript{33-36}

Simulation of clinical trials has evolved over the past two decades from simple instructive game to “full” simulation models yielding pharmacologically sound, realistic trial outcomes. We used the simulated data in our fourth investigational study i.e. Interim Analysis. The need to make drug development more efficient and informative and the awareness that many industries make extensive use of simulation in product development have advanced considerably the use of simulation of clinical trials in pharmaceutical product development over the past decade.\textsuperscript{37}

Our findings suggest that clinicians should view the results of such trials with skepticism. Clinical trials stopped early for benefit are becoming more common; often fail to adequately report relevant information about the decision to stop early, and show implausibly large treatment effects, particularly when the number of events is small.

In our research of performance measurement tools for parallel and distributed program activities, we have developed approaches for automatically guiding the researcher to performance problems in their application in the management. These are examples of such
techniques such as the Critical Path Analysis, Meta analysis and Interim Analysis throughout the conduct of a clinical trial project.

In considering the conclusions that may be drawn based on our evaluation of barrier mitigation strategies, it is important to recognize that establishing clear links between barriers and specific model parameters and their ex-post magnitudes requires extensive research, and our analysis was constrained by the limited availability of this type of information. Nevertheless, our results can help to inform the discussion surrounding possible barrier mitigation strategies and their relative impacts on drug development costs and returns. Our results are summarized in the main texts of the thesis.

Our approaches like CPA, MA and IA improves the efficiency which can help to shorten timelines and increase expected outcome to the pharmaceutical companies. These strategies also reduce the cash outlay needed for the clinical studies. Therefore, holding everything constant, these options may be more appealing as strategies to stimulate drug development, especially early on in the clinical research process.

To complete this discussion of research strategies and theoretical commitments, I will make it explicit (though it is likely clear enough to the reader already) that even the most senior and insightful observers in our field continue to perpetuate the false idea that the opposite of relativism is realism, and therefore tend to conflate realism with absolutism. Suffice it to say that this thesis will use different approaches which treat the decision-making process and drug approval actions.

References


