Health Research Economics of Randomized Clinical Trials: Model-Based Risk Management

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1 Abstract

When a randomized clinical trial (RCT) runs behind schedule or over-budget, the scientific value of the endeavor is jeopardized, putting at risk significant financial and human resources. Answering the NIH’s call for “health research economics,” we construct a multi-level model for risk management of RCTs. Extending a previously described probabilistic model of RCT recruitment with cost accounting forecasting\textsuperscript{1,2}, we construct a risk management layer to provide decision support.

When an RCT runs behind schedule or over-budget, we model 3 classes of risk management (RM) strategies the investigator may employ, 1) RM1: opening a new recruitment site, 2) RM2: additional recruitment efforts for current sites, and 3) RM3: closing a subset of existing sites. At any given time, one may exercise none, all, or a subset of these strategies to strike a balance between risk and benefit.

Instead of static decision rules, this probabilistic model provides dynamic decision support for RCT risk management. Using an uncertainty-based evolutionary multiobjective optimization framework\textsuperscript{3}, we implement an evolutionary algorithm-based optimization with embedded Monte Carlo. With full probability characterizations of the risks, our algorithm proposes strategies that protect against catastrophic down-sides.

Target schedule, recruitment, and budget are provided by the user. At a given time, the recruitment pattern of each site is probabilistically modeled. Forecast of future recruitment in the full probabilistic distribution is performed using Monte Carlo technique. The cost accounting model specific to each site is overlaid on the recruitment model. Finally a risk analysis model combines the above and defines multiple objectives that mathematically encode the trade-off between cost and recruitment. Finally, a genetic algorithm is employed to generate optimal strategies.

2 Introduction

Dr. Francis Collins, the Director of the National Institutes of Health, has called for and allocated Federal research funding directed at a new field of scientific studies of how we conduct studies. Coined “health research economics”\textsuperscript{4}, this effort stems from Dr. Collins’s unparalleled success as the Director of the Human Genome Project to complete the draft sequencing effort below budget and ahead of schedule\textsuperscript{5}.

Randomized clinical trials (RCTs) are considered the gold standard of evidence-based medicine\textsuperscript{6}. By assigning qualifying subjects on a random basis into intervention or control groups, conceptually RCTs generate “equivalent” groups at the outset. This allows researchers to make causal statements on any outcome differences between the intervention and the control groups\textsuperscript{7}. The rigor of RCTs
logistics—from subject inclusion/exclusion, record keeping, blinding, allocation concealment—comes at a significant cost. The infrastructure required, from equipment to staff, is typically specialized and costly.

The scientific value of a RCT derives from a combination of the quality of the scientific question, the design of the experiment, its logistical control, and its statistical power. In turn, statistical power is driven by patient recruitment and retention. The individual trial subject constitutes the most elemental unit of human experimentation. In contrast to experiments in the physical sciences, RCT patient recruitment comes with significant uncertainty. In fact the failure to manage this risk is at the root of many RCT closures (ref). Currently, this uncertainty in the conduct of RCTs is typically managed with back-of-the-envelope calculations of the mean. For instance, if the recruitment rate of a particular trial had been 3 per month over the past 12 months, then over the next 6 months we may expect 18 new recruited patients. Yet while this calculation may accurately forecast the expected value of future patient recruitment, it fails to take into account the variability and volatility of the actual number of patient recruitment. Termed the “fallacy of the expected value”\(^8\), this oversight in risk management can be detrimental to the successful completion of the RCT.

In this work, we summarize our work to-date on probabilistic modeling of RCT recruitment, and develop a risk management framework to provide decision support for investigators and sponsors.

We first expand our previous work on probabilistic modeling of patient recruitment, where the discrete probability distribution, the negative binomial, was fitted onto a clinical trial recruitment time series data\(^1\). While for the purpose of short-term forecasting with short time horizon a time-series model such as Poisson autoregressive model may be beneficial\(^9\), for long-term forecasts as considered in this work we will limit ourselves to a marginal distribution model. We presented our findings in the form of an intuitive chart where probabilistic patient recruitment is displayed alongside the statistical power (Figure 1).

![Figure 1 Power-Recruitment Plot](image)

**Figure 1** Power-Recruitment Plot, which displayed on a common axis the expected patient recruitment as well as the corresponding statistical power

Taking the patient recruitment model which allows us to forecast future patient enrollment, we overlay a cost accounting model as described previously\(^2\). This allows for the forecasting of patient recruitment at individual sites as well as the associated costs and cost-per-patient. A visual dashboard was created that generates on-line overview of the status of the RCT (Figure 1).
Here, we extend the model to dynamic risk management (RM) and decision support. Like many complex real-world situations\(^{10}\), in RCT risk management there are several conflicting objectives. A balance has to be found between minimizing cost and maximizing scientific value, not unlike in radiation therapy treatment planning where tumor irradiation is to be maximized while minimizing healthy tissue exposure\(^{11}\). Unlike the optimization of a single objective, the simultaneous consideration of multiple objectives precludes a unique globally optimal solution. In fact there will be a set of solutions that none of which dominate any other. This set of solutions is termed the *Pareto-optimal set*, which mathematically represents good trade-off solutions\(^{12}\). Traditional optimization algorithms designed to hone in on a single optimum perform poorly in this class of problems. In this study we employ the evolutionary algorithm Non-dominated Sorting Genetic Algorithm II (NSGA-II)\(^{13}\).

In brief, at a given time \(t\), the model assesses on-line the probabilistic pattern of patient recruitment. The design variables are the following: RM1) opening a new trial site, 2) RM2: closing an existing cost-ineffective site, or 3) RM3: additional recruitment efforts (marketing & incentive adjustments) for \(k\) existing sites. While the model is able to produce an optimization, the value of this model lies more in providing a decision support infrastructure for the investigator and sponsor. The objective variables are 1) the total cost projected and 2) the 5% lower bound of projected subject recruitment at the end of the study.

### 3 Methods

Methods for modeling the patient recruitment process and for incorporating the cost accounting model are described previously\(^{12}\) and will be detailed in a forthcoming publication (in preparation).

#### 3.1 Recruitment Model

Let \(T\) be the scheduled time of trial completion. At a given time \(t\), \(T > t > 0\), let there be \(n_t\) enrolling sites. Each site \(s\) out of \(n_t\) has been observed up to time \(t\) to recruit \(\{r_{s,j}\}_{j=a_s}^t\) patients where \(r_{s,j} = 0, 1, 2, ...\) represent a time series variable of the number of recruited patients, \(a_s\) represents the time at which the site became active. Marginally, each site \(s\) is fitted with negative binomial distribution \(NB(\mu_s, \kappa_s)\) with moment estimators. The negative binomial distribution is chosen as an over-dispersed Poisson, or alternatively as the marginal approximation to a Poisson
autoregressive model. Response to marketing effort, per site, is modeled as a change in $\mu_s$ into the interval up to $[\mu_s, 1.8\mu_s]$ depending on the amount of resources devoted. Together this enables a projection of the total number of subjects recruited per site in terms of the mean, and more importantly in terms of the variability. As demonstrated previously, this allows for the estimation of the “probability of trial success” where success is defined as the total recruitment $R_T = \sum_s \sum_{j=a_s}^T r_{s,j}$ reaching a recruitment goal given by the user. In the context of the risk analysis, we also develop a measure analogous to value-at-risk (VaR), the 5%ile of the random variable $R_T$.

In the example case provided for illustration, total time scheduled for the RCT is taken to be 36 months, with time at analysis of $t_a = 24$. Target recruitment is 300, $n_t$ is to be 3, representing a multi-center trial with 3 active enrolling centers. At analysis time, 165 subjects have already been recruited across the 3 sites. The sites are modeled as academic medical centers of different sizes and recruitment characteristics (in mean and variance in an over-dispersed Poisson model). The mean at each of the sites is in turn modifiable by the site-specific amount of recruitment/marketing resources. In a back-of-the-envelope analysis, there is an expectation to enroll another 82.5 additional subjects for a total of 247.5. This is below the target recruitment total of 300, jeopardizing the scientific value of the endeavor.

3.2 Cost Accounting Model

For each site $s$, there is an associated one-time initiation cost of $I_s$, variable cost per unit time of $V_s$, variable cost per patient of $P_s$, closure cost of $C_s$, and marketing cost $M_s$. In this model, the response in recruitment is modeled as a linear function of $M_s$. The parameters are assumed to be fixed in this implementation and given by subject matter experts. For simplicity, time-value of money is ignored in this analysis, however the net present value can be incorporated using nominal interest rates published by the Office of Management and Budget\textsuperscript{14}.

For the purpose of risk analysis, sunk cost is not considered. Only costs incurred at or after time $t$ are considered as they would otherwise not provide any differential information on any of the risk management plans.

3.3 Risk Analysis Model

In this work, to facilitate visualization, we limit the multiobjective function to 2 dimensions to illustrate the trade-off between monetary value with scientific value. Monetary value is measured in dollars, which is a combination of fixed costs associated with opening or closing a clinical trial site, and the variable costs associated with keeping a trial site open (variable in time) and with enrolling patients (variable in recruitment). Scientific value is measured by the 5% lower bound of projected total number of subjects recruited at the end of the trial. The use of the 5% lower bound provides a conservative estimate of the worst-case scenario. This is analogous to the value-at-risk measure widely used in the financial industry\textsuperscript{15}.

The evolutionary algorithm Non-dominated Sorting Genetic Algorithm II (NSGA-II)\textsuperscript{13} is employed to discover the Pareto set. This algorithm is notable for being elitist, diversity-preserving, and for its emphasis on non-dominated solutions\textsuperscript{3}. The parameters used are: 100 generations of population 100, with crossover probability of 0.7, crossover distribution index of 20, mutation probability of 0.2, and mutation distribution index of 20.
3.4 Decision Support

As seen in Figure 3, our model projects with, without any risk management plan, at target completion time the RCT will be both over-budget and under-recruit, jeopardizing the scientific value overall and risking deriving little value from the costly project.

The points on the Pareto front that lie between the target outcome and the actual projected outcome represent reasonable strategies to restructure the RCT to better approximate the cost and recruitment goals, simultaneously.

4 Results

The multiobjective optimization procedure generates a set of Pareto-optimal solutions (blue, Figure 3). This represents a mathematical characterization of the intuitive idea that the more one spends on a clinical trial, the more recruitment we can get, but after a certain point the marginal cost of additional recruitment becomes prohibitively expensive.

Points in the region of space left of the Pareto front are considered “feasible”. Considering the totality of the design variables which included 4 binary and 3 continuous variables, the total amount of combinatorial complex of the feasible space is large. However unless a risk management strategy also lies on the Pareto-front, they are not considered optimal. That is, with the multiobjective optimization procedure, we have reduced the problem of choosing an optimal strategy in N-dimensional space into one of choosing from the large but manageable set of strategies on the Pareto-front. The next step is to choose amongst these strategies. However, as defined, none of these strategies dominate any other.

![Figure 3](https://example.com/figure3.png)

**Figure 3** Pareto-front of optimal risk management solutions to an example dataset. X-axis is the projected 5%ile of total recruitment (a measure analogous with value-at-risk in the financial industry). Y-axis is the projected additional cost from current time to completion. Blue: Pareto-optimal solutions. Red: Projected balance between cost and worst-case recruitment (note this does not lie on the Pareto front but is close to it). Dark red: Current balance of cost-versus-recruitment at time \( t \). Gold: Target total recruitment and target budget.

As noted, points on the Pareto front that lie between the target outcome and the actual projected outcome represent reasonable strategies to restructure the RCT to better approximate the
cost and recruitment goals, simultaneously. Each of these strategies will incur less cost while providing a larger final recruitment count compared against making no structural adjustments.

<table>
<thead>
<tr>
<th>Start a New Site</th>
<th>RM2: Additional Recruitment Efforts</th>
<th>RM3: Closure of individual Sites</th>
<th>Projected Outcomes</th>
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<td>Site 2</td>
<td>Site 3</td>
</tr>
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</table>

Table 1 Risk management strategies on the Pareto front lying in the rectangle between the projected outcome without any risk management and the targeted outcome

These 7 such risk management strategies are tabulated in Table 1. As can be seen, the investigator or sponsor should consider closing Site 3 (a small academic medical center in this example), incurring a one-time closure charge, and re-allocate funds towards increased recruitment efforts at Site 1 (a large academic medical center in this example).

5 Conclusion

In this work we have constructed, step-wise, a probabilistic model of patient recruitment in RCTs, an overlying cost accounting model, and finally a risk analysis framework that enables an uncertainty-based multiobjective optimization decision support for clinical trial sponsors and investigators.

Time-value of money is ignored in this analysis given the low real interest rates (Dec 2010, OMB). Additional costs of RCT delays not accounted for in this model, including delay of FDA filing, prolonged time-to-market, shortened product lifecycle, will individually and as a group be favorable to the dominance of proposed risk management strategies.

With this work we have constructed a general platform for risk management in RCTs. On-going work includes the addition of other types of risks in RCTs, partitioned framework to better model the risk aversion of researchers, and risk management strategies such as regulatory risk.

6 Acknowledgements

We thank Kazuko Shem, MD and Jerry Wright, MS at Santa Clara Valley Medical Center, as well as Charles Koo, PhD at Stanford University for assistance with the development of the probabilistic and cost accounting models as previously described.
7 References


