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Review

Real-time prediction of clinical trial enrollment and event counts: A review

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ABSTRACT

Clinical trial planning involves the specification of a projected duration of enrollment and follow-up needed to achieve the targeted study power. If pre-trial estimates of enrollment and event rates are inaccurate, projections can be faulty, leading potentially to inadequate power or other mis-allocation of resources. Recent years have witnessed the development of methods that use the accumulating data from the trial itself to create improved predictions in real time. We review these methods, taking as a case study REMATCH, a trial that compared a left-ventricular assist device to optimal medical management in the treatment of end-stage heart failure. REMATCH provided the motivation and test bed for the first real-time clinical trial prediction model. Our review summarizes developments to date and points to unresolved issues and open research opportunities.

Contents

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1. Introduction

The first stage of planning a clinical trial involves the selection of the patient population, treatments and outcomes. Attention next turns to determining the trial's size and duration. One specifies a null hypothesis and the test by which to evaluate it, and the test's desired error rates under the null and a designated alternative hypothesis. These features then dictate a target sample size or number of events. Using best guesses of accrual and event rates, one can calculate how long the trial will need to enroll and follow subjects, and when to conduct planned interim analyses. These considerations together determine trial costs [19].

In many trials we find to our chagrin that the realized enrollment and event rates differ from those projected at baseline, often sufficiently to overthrow trial plans. This concern has in recent years stimulated the creation of statistical methods that use data from the unfolding trial itself to rationally update trial projections in real time. Such methods became practical as rapid data collection procedures enabled the construction of accurate interim trial databases. The purpose of this article is to review the statistical literature on these prediction methods.

1.1. Example: REMATCH

Ying and Heitjan [49] described the application of real-time prediction in the REMATCH trial [36]. This was a randomized trial of a left-ventricular assist device *vs.* optimal medical management in the treatment of end-stage heart failure, sponsored jointly by Thoratec Corporation (the device's manufacturer) and the US National Heart, Lung & Blood Institute (NHLBI). As the trial began, the NHLBI empanelled a data and safety monitoring board (DSMB), which held an organizational meeting in December 1998, seven months after the opening of enrollment. The NHLBI wished to have the DSMB meet again in the Spring of 1999. Statisticians in the REMATCH coordinating center were concerned that the trial would not have met its first interim analysis goal — the 23rd death from any cause — by the time of the proposed meeting, creating the need for yet another meeting soon after. The key question was when the trial would have accumulated enough events to make a DSMB meeting worthwhile. Although the statisticians could generate event-time predictions using pre-trial data, by early 1999 it was clear that baseline enrollment and mortality rate estimates were badly in error, and that therefore predictions based only on these data would be unreliable.

It occurred to the REMATCH statistical team to use the accumulating data from the study itself to predict when landmark events such as the 23rd death would take place. Fortunately in REMATCH, unlike many trials up to that time, it was possible to populate the central study database in nearly real time. Each REMATCH clinical center had a customized, dedicated laptop computer in which study staff would enter data during subject clinic visits. The coordinating center, at Columbia University in New York City, ran a weekly upload of all the data from each center. A data manager would process the data and pass them to a study statistician as a set of ascii files. The resulting database, although not guaranteed to be 100% complete or accurate, at least would include a large majority of scheduled forms — most importantly the randomization and mortality forms, which received special attention. With these data in hand, the study team created a statistical model and software for predicting future event times, which they then applied routinely throughout the course of REMATCH. They later published the method as [6], and the REMATCH prediction results as [49].

We return to our discussion of this example in Section 5 below.

1.2. Purpose of the review

The literature on clinical trial prediction is mainly concerned with two targets: Counts of accrual, and counts of events. Barnard et al. [8] reviewed methods for predicting enrollment counts, and Zhang et al. [53] reviewed methods for predicting enrollment and events. In this article we cover both areas, providing a more comprehensive and up-to-date list of citations and, we intend, a more critical evaluation of the methods. We begin by discussing the aims of prediction, then turn to methods for prediction of enrollment, then to methods for prediction of events. We conclude with some discussion of the current state of research.

2. Prediction: what and why

A popular target of clinical trial prediction is the number $N(t)$ of subjects enrolled by some time t in the future. Similarly, one can predict the time $T_N(N^*)$ at which the trial will have enrolled a target count of N^* subjects. These quantities are of interest in particular for trials in which the outcome is a binary or uncensored continuous variable, so that knowing the enrollment determines the power, and knowing the time when the enrollment reaches a landmark value determines the time of a planned interim or final analysis. When the primary outcome is the time to some event, such as death or disease progression, one may wish to predict the number of events occurring by time t, which we denote $D(t)$, or the time to occurrence of the D^*th event, which we denote $T_D(D^*)$. In REMATCH [49], the problem was to predict the times of occurrence of the deaths that would trigger planned interim analyses. These analyses were to take place after the dates of occurrence of the 23rd, 46th, 69th and 92nd events, in our notation $T_D(23)$, $T_D(46)$, $T_D(69)$, and $T_D(92)$.

The typical use of prediction is to identify the timing of future events in order to make efficient logistical preparations. If realized enrollment or event rates differ from those used in pre-trial planning, one may wish to create predictions under various scenarios about the duration of accrual and follow-up and the number of centers to engage, in order to achieve the trial's goals in the most efficient way. *Post hoc* analyses of sequences of predictions can illuminate the reasons that a trial departed from its baseline projections, as well as the timing and potential causes of shocks that occurred during the trial.

Several of the prediction methods that we review involve simulating the entire future course of the trial, conditionally on the data set as it exists at some interim point. Such methods, although potentially laborious to implement, allow one to predict any outcome of interest. For example, Ying and Heitjan [49] demonstrated the prediction of end-of-trial estimates of treatment effect and of the statistical significance of the trial. The latter is equivalent to a computation of predictive power [41,44], or the Bayesian probability that the trial will ultimately reach significance. One can readily adapt such methods to generate the conditional power [19].