Predicting Accrual in Clinical Trials: Bayesian Posterior Predictive Distribution

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Introduction:
The most common reason why clinical trials fail is that they fall well below their goals for patient accrual. Accrual rates are often developed in an ad hoc fashion. If they are monitored at all, accrual rates are examined using a purely subjective approach. There are not any good quantitative tools for planning and monitoring accrual rates.

With good planning tools, researchers would be able to construct realistic targets for their sample sizes than promising a sample size that could not be delivered in a reasonable time frame and within a limited research budget. With good monitoring tools, researchers would get an early warning when accrual rates are suffering. This would allow them to take appropriate corrective action before too much harm was done.

Notation:
- $T$: Planned trial duration
- $n$: Planned number of patients
- $P$: Prior certainty about accrual
- $t_0$: Start of the trial
- $t_i$: Observed arrival times
- $m$: Current number of patients
- $w_i$: Observed waiting times
- $W_i$: Unobserved future waiting times
- $Exp$: Exponential distribution
- $\theta$: Parameter of $Exp()$
- $IG$: Inverse Gamma distribution
- $k, V$: Parameters of $IG()$

Questions to elicit a prior distribution:
1. How long will it take to accrue $n$ subjects? (This is $T$).
2. On a scale of 1-10, how confident are you in your answer to (1)? (Divide by 10 to get $P$).

We calculated three predictive distributions:

- A) Informative prior at the start of the study ($m=0, P=0.5$);
- B) non-informative prior after 39 patients ($m=39, P=0$);
- C) informative prior after 39 patients ($m=39, P=0.5$).

We can also use this process to obtain a posterior predictive sample size. Let $T$ represent the time point at which the study must end. Compute partial sums $S_j(m+1)$, $S_j(m^2)$, $\ldots$ until the partial sum exceeds $T$. The values $n_j$ which represent the largest values where the partial sums do not exceed $T$, provide a predictive distribution of sample sizes. See Figure 2 for an example.

Future work:
The model we propose is easily extended in a variety of ways:
1. Use of alternatives to the exponential distribution for modeling waiting times.
2. Examination of alternative prior distributions.
3. Use hierarchical models to predict accrual across multiple centers in a multi-center trial.

We hope that the method in this paper encourages investigators to account for these uncertainties when planning and monitoring accrual in a clinical trial.