Introduction

- In multi-regional trials, the underlying overall and region-specific accrual rates often do not hold constant over time. Also, different regions could have different start-up times, which combined with initial jump in accrual within each region often leads to a discontinuous overall accrual rate. These issues associated with multi-regional trials have not been adequately investigated.

- We clarify the implication of the multi-regional nature on modeling and prediction of accrual in clinical trials and investigate a Bayesian approach for accrual modeling and prediction. This approach models region-specific accrual using a nonhomogeneous Poisson process (NHPP) and allows the underlying Poisson rate in each region to vary over time. The proposed approach can accommodate staggered start-up times and different start-up accrual rates across regions/centers.

- Our numerical studies show that the proposed method improves accuracy and precision of accrual prediction compared to an existing NHPP model that does not model region-specific accrual.

Methods

\[
\Pr(N = n | \lambda) = \prod_{j=1}^{J} \left( \frac{\lambda_j^{n_j}}{n_j!} \right) e^{-\lambda_j},
\]

\[
\lambda_j = \beta_j^T \phi(T - t_{j0}),
\]

\[
f(\theta | \beta, \Gamma) \propto \prod_{j=1}^{J} \Gamma_j^{\frac{n_j}{2}} \exp \left\{ -\frac{1}{2} \sum_{j=1}^{J} (\beta_j - \nu_j)^T \Gamma_j^{-1} (\beta_j - \nu_j) \right\}
\]

Data Example

- Cancer trial: randomized Phase 3 study of adjuvant treatments of colorectal cancer.

- Subjects: a total of 1794 Stage 3 patients were planned to be enrolled from 32 countries.

- We conduct a retrospective enrollment prediction at two interim looks with 40% and 70% of patients enrolled and consider grouping all countries into two and three regions as well.

- Task: predicting the time when at least a total of 1794 patients are enrolled across all regions.

Simulation Results

Table 1: Comparison of root mean squared errors (RMSE), mean coverage rates (CR), and mean width of the 95% posterior credible interval (CI) of the proposed method (NHPP) and the original NHPP method (NHPPS), as well as the probability of the proposed method having tighter 95% CI than NHPPS (Prob.), i.e., Pr(\text{prob.}) based on 3000 simulated trials with J = 2, 5 or 30 regions, when participating regions have different start-up times.

<table>
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<th>\text{NHPPS}</th>
<th>\text{Prob.}</th>
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Data Analysis Results

- The proposed approach accommodates different start-up times and accrual rates across regions/centers and allows for discontinuity in the overall accrual rate, compared to the existing methods.

- In numerical studies, the proposed method is shown to improve precision of accrual prediction compared to the NHPPS approach that does not model region-specific accrual rates. In practice, this translates into improved accuracy and precision and hence improved decision making on resource allocation.

- The flexible B-spline model for region-specific accrual rates provides good prediction in the simulation studies as well as the real data example.

- The proposed method would allow a research team to identify potential enrollment problems with certain regions using prediction results from individual regions and enable the research team to use a more targeted approach, such as addressing detected deficiency in recruitment in certain regions or adding satellite regions to increase enrollment.

References
