Modeling and Prediction of Accrual in Multi-Regional Clinical Trials

Yi Deng[1] , Xiaoxi Zhang[2] and Qi Long[1]

[1]Department of Biostatistics and Bioinformatics, Emory University;

[2]Pfizer Inc.

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

$$\Pr(\mathbf{N}=\mathbf{n}|\boldsymbol{\lambda})=\prod_{j=1}^{J}\prod_{t=1}^{T}\frac{e^{-\lambda_{jt}}\lambda_{jt}^{\,n_{jt}}}{n_{jt}!}$$

$$\lambda_{jt}=\beta_j^T\phi((t-t_j^0)_+)$$

$$f(\boldsymbol{\beta}|\boldsymbol{\nu},\boldsymbol{\Gamma})\propto\prod_{j=1}^{J}|\boldsymbol{\Gamma}|^{-\frac{J}{2}}\exp\left\{-.5\sum_{j=1}^{J}(\beta_j-\boldsymbol{\nu})^T\boldsymbol{\Gamma}^{-1}(\beta_j-\boldsymbol{\nu})\right\}$$

j: index of regions; t: index of time;
N_{jt}: the number of patients enrolled in region j on day t, denote its realization in the current trial by n_{jt}
λ_{jt}: the underlying Poisson rate of region j at time t.
$\phi(\cdot)$: the B-spline basis function.
t_j^0: the start-up time for region j.
β_j: the B-spline coefficients for region j.
We assume $\beta_j \sim MVN(\boldsymbol{\nu},\boldsymbol{\Gamma})$

Simulation Results

Table 1: Comparison of root mean squared errors (rMSPE), mean coverage rates (CR), and mean width of the 95% posterior CI ($\bar{w}$) of the proposed method (NHPPM) and the original NHPP method (NHPPS), as well as the probability of the proposed method having tighter 95% CI than NHPPS (Prob.), i.e., $\Pr(w_1 > w_2)$, based on 1000 simulated trials with $J = 2$, 5 or 30 regions, when participating regions have different start-up times.

Settings				Summary Measures			
d_j	ρ	pct.	Method	rMSPE	CR	w	Prob.
0	0.1	0.4	NHPPS	8.71	0.99	49.44	
			NHPPM, J=2	7.72	0.94	29.15	1.00
			NHPPM, J=5	5.02	0.98	22.27	1.00
			NHPPM, J=30	3.84	0.97	15.73	1.00
		0.7	NHPPS	4.74	0.99	23.68	
			NHPPM, J=2	3.28	0.99	15.54	1.00
			NHPPM, J=5	2.78	0.98	12.68	1.00
			NHPPM, J=30	2.58	0.97	10.44	1.00
	0.3	0.4	NHPPS	17.97	0.96	74.88	
			NHPPM, J=2	11.69	0.96	49.91	0.99
			NHPPM, J=5	9.41	0.96	38.24	1.00
			NHPPM, J=30	5.55	0.99	23.70	1.00
		0.7	NHPPS	8.12	0.95	32.34	
			NHPPM, J=2	5.27	0.98	24.00	0.98
			NHPPM, J=5	3.84	0.99	18.34	1.00
			NHPPM, J=30	2.81	0.99	12.94	1.00
0.5	0.1	0.4	NHPPS	8.53	1.00	50.80	
			NHPPM, J=2	6.80	0.98	34.11	1.00
			NHPPM, J=5	4.47	0.99	23.39	1.00
			NHPPM, J=30	3.90	0.97	15.74	1.00
		0.7	NHPPS	4.45	1.00	24.19	
			NHPPM, J=2	3.28	1.00	17.41	1.00
			NHPPM, J=5	2.84	0.99	13.21	1.00
			NHPPM, J=30	2.59	0.97	10.47	1.00
	0.3	0.4	NHPPS	18.73	0.96	80.27	
			NHPPM, J=2	13.37	0.97	59.99	0.98
			NHPPM, J=5	9.61	0.98	42.67	1.00
			NHPPM, J=30	5.68	0.99	24.49	1.00
		0.7	NHPPS	7.92	0.97	33.99	
			NHPPM, J=2	5.78	0.98	26.76	0.97
			NHPPM, J=5	4.23	0.98	19.86	1.00
			NHPPM, J=30	2.78	0.99	13.25	1.00

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.

Data Analysis Results

Table : Data Example: 95% posterior CIs of the predicted accrual duration (τ) and $w = T_U - T_L$ which is the width of the 95% posterior CI, using the proposed method (NHPPM) versus the original NHPP method (NHPPS).

Real data		NHPPS		NHPPM					
				Two regions		Three regions		Thirty-two regions	
cv	pct.	CI	w	CI	w	CI	w	CI	w
0.1	40%	[594, 660]*	66	[547, 587]	40	[550, 584]	34	[552,578]	26
	70%	[578, 611]*	33	[552, 574]	22	[552, 570]	18	[552,568]*	16
0.3	40%	[533, 593]	60	[528, 585]	57	[526, 583]	57	[570,609]	39
	70%	[553, 589]	36	[549, 581]	32	[546, 576]	30	[559,580]	21
0.5	40%	[525, 594]	69	[522, 582]	60	[518, 567]*	49	[581,628]*	47
	70%	[548, 591]	43	[552, 587]	35	[549, 579]	30	[560,586]	26

*: denotes the 95% posterior CI does not cover the true value ($\tau = 570$).

Conclusions

- 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

[1] Deng, Y., Zhang, X. and Long, Q., (2014) Bayesian modeling and prediction of patient accrual in multi-regional clinical trials. Statistical Methods in Medical Research, in press.

[2] Zhang X, Long Q. Stochastic modeling and prediction for accrual in clinical trials. Statistics in Medicine, 2010, 29(6): 649-658.