Predicting Timing for the Final Event in a Clinical Trial Using a Nonparametric Bayesian Poisson Process Simulation

Ibrahim Turkoz,[1] Marc Sobel,[2] Brianne Brown,[3] Larry Alphs[3]

[1]Janssen Research and Development, LLC, Titusville, NJ; [2]Statistics Department, Temple University, Philadelphia, PA; [3]Janssen Scientific Affairs, LLC, Titusville, NJ

INTRODUCTION

- Time-to-event outcomes are important clinical measures because they often identify disease outcomes that, if improved upon, have important public health implications
  - Examples of such events include death, relapse, adverse drug reaction, or alternative disease outcomes whose timing is often difficult to estimate
- There are limitations to using time to event as an end point
  - It is difficult to predict the timing of events so that study duration and sample size can be estimated
  - The sample population enrolled in a particular study may deviate from samples used to make initial estimates
- The duration of many time-to-event clinical trials is based on the observation of a predetermined total number of events and is essential for sample size calculations. This knowledge is also critical for resource estimations
- The continuous monitoring of event incidence rates plays a critical role in making timely decisions affecting clinical trials. It is important to determine if initial assumptions apply to the study of interest and to review the likelihood that predetermined operational milestones will be met
- Previous research in this area can be divided into two strategies:
  1. Assume that event times have a particular parametric distribution: This is used to plan the sample size (ie, required number of patients) and the trial's duration
     - These prediction strategies estimate the number of events required to test the null hypothesis assuming a given level and power. The length of the trial is assessed using estimates of accrual rates, time to event, loss to follow-up, accrual time, and length of the continuation period
  2. Use parametric Bayesian models for the survival times and accrual rates
     - Typically, these models assume exponential and Weibull survival times and homogeneous accrual rates.[1,2] Among the models considered were the Bayesian bootstrap
     - The Bayesian bootstrap has two fundamental limitations:
       1. The predictive posterior used to generate future survival times is discrete. This reflects the fundamental property of the bootstrap
       2. The predictive posterior used to generate future survival times does not make use of the unobserved (censored) data
- To better inform operational decisions, we have developed a blinded, nonparametric Bayesian Poisson process simulation to address the limitations of other approaches and confirm initial assumptions for determining the timing of the final events to better inform operational decisions
- As a case study, we used data from a recently completed randomized, double-blind (DB), placebo-controlled, relapse-prevention study (NCT01193153)[3] that examined the safety and efficacy of a long-acting injectable antipsychotic in preventing relapse in patients with schizoaffective disorder

METHODS

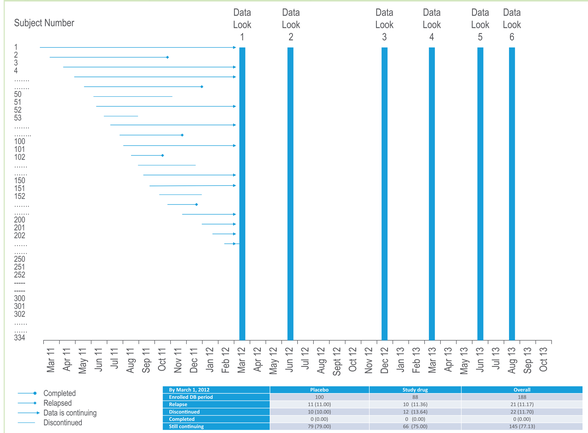
- We employed Bayesian methodology to fit Poisson processes to the observed data. The posterior predictive distribution is used to predict future trial results
  - Bayesian formulations have the advantage that predictions are made in the form of posterior intervals having posterior probability interpretations
- Key assumptions:
  - Future relapses and censored events mirror those already observed; posterior probability constructions provide this logical link between past and future (predicted) events
  - Conditional on the parameters of the model, the behavior of subjects is mutually independent and depends on an underlying inhomogeneous Poisson process
- The current approaches for predicting future events generally rely only on observed relapses
  - We improve on this by making predictions using both observed relapse and censored events
  - Fitted inhomogeneous Poisson processes incorporate the dynamic evolution of both hazard and accrual rates[4-6] and better describe and predict the occurrence of outcomes (both observed and censored)
  - The occurrence of relapse and censored events is characterized by an overall likelihood based on the underlying intensity function

Clinical Trial Example

- The performance of the Poisson process was examined using the event rates from a randomized, double-blind (DB), relapse-prevention study (NCT01193153)[3] of patients with schizoaffective disorder
- The study had a total of 334 subjects
- Prediction need: timing of the 95th relapse
- Design
  - 1:1 randomization ratio of treatment:placebo
  - Duration 15 months
  - Recruitment period of 18 months
  - A priori expected relapse rate for treatment was 30%
  - A priori expected relapse rate for placebo was 50%
- The first subject entered the trial on March 23, 2011. The data points are used for purposes of simulation and inference
- We have examined predictive analytical results using six different data looks
- The observed relapses and discontinuations for data look 1 in March 2012 of the schizoaffective disorder trial are shown in **Figure 1**. There was a total of 188 patients enrolled; 21 patients relapsed prior to the first look and 22 discontinued. This resulted in a total of 145 patients who continued; enrollment has not yet completed

An electronic version of the poster can be viewed by scanning the QR code. The QR code is intended to provide scientific information for individual reference. The PDF should not be altered or reproduced in any way. These are electronic reproductions of posters presented at the International Society for CNS Clinical Trials and Methodology (ISCTM) 2016 Autumn Conference; September 26–27, 2016; Philadelphia, PA. All copyrights remain those of the copyright holder. This page will not be available after October 27, 2016.
http://bit.ly/2c99tki (This URL is case sensitive.)

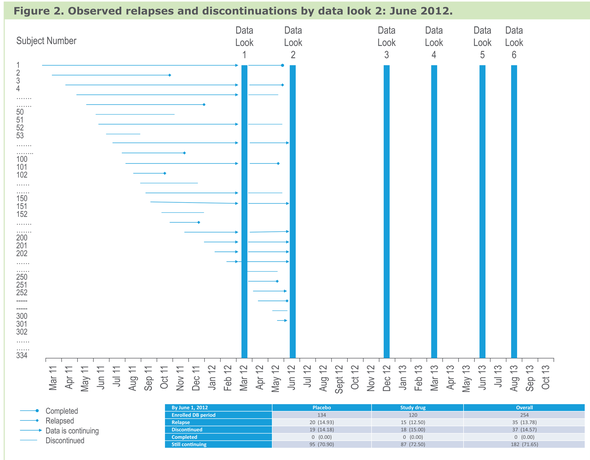
Figure 1. Observed relapses and discontinuations by data look 1: March 2012.



By March 1, 2012	Placebo	Study drug	Overall
Enrolled DB period	100	88	188
Relapse	11 (11.00)	10 (11.36)	21 (11.17)
Discontinued	10 (10.00)	12 (13.64)	22 (11.70)
Completed	0 (0.00)	0 (0.00)	0 (0.00)
Still continuing	79 (79.00)	66 (75.00)	145 (77.13)

- Data look 2 occurred 90 days after data look 1, in June 2012 (when enrollment was still not completed). There were 254 patients, 35 relapses, and 37 discontinuations (**Figure 2**)
- The predictive analyses will be based on these two time points for illustrative purposes

Figure 2. Observed relapses and discontinuations by data look 2: June 2012.



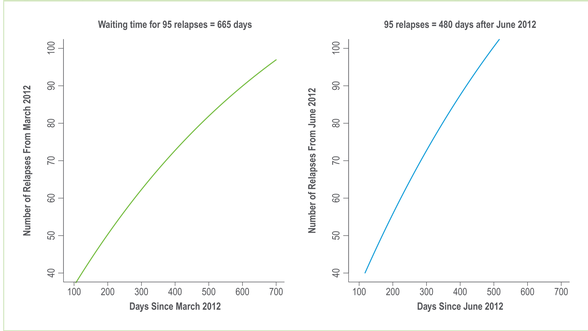
By June 1, 2012	Placebo	Study drug	Overall
Enrolled DB period	134	120	254
Relapse	20 (14.93)	15 (12.50)	35 (13.78)
Discontinued	19 (14.18)	18 (15.00)	37 (14.57)
Completed	0 (0.00)	0 (0.00)	0 (0.00)
Still continuing	95 (70.90)	87 (72.50)	182 (71.65)

RESULTS

The Naive Approach

- Assume a constant relapse rate of a. We use a naive approach to calculate the expected time until 95 relapses have occurred conditional on the data prior to data look 1 and data look 2 (**Figure 3**)
- In Figure 3, the number of relapses based on March 2012 data (the left-hand panel) overestimates the true value. The panel on the right (based on June 2012 data) underestimates the true prediction
- Limitations of naive approach:
  1. Ignores issues arising from staggered entry
  2. Fails to use the information available from censored data
  3. Fails to take into account the evolution of hazard rates
  4. Fails to provide sufficient model flexibility
  5. Fails to provide a useful margin of error

Figure 3. Expected number of relapses since March 2012 and June 2012 using naive approach.



Modeling the Entry of Subjects Into the Trial Using Temporal Poisson Processes: Functional Approaches

- To accommodate a time-varying accrual rate, accrual times were modeled using temporal Poisson processes
  - Prior work has focused on modeling accrual using generalized linear models with Poisson links[7]
  - Bayesian modeling of temporal Poisson processes has focused on both parametric and nonparametric modeling.[8-10] We take an open model view that accepts that no specific temporal process exactly reflects predicted subject relapses. The likelihood of the (Poisson) temporal process for relapse times $(t_1,\ldots,t_m)$ and intensity function $\theta(t)$ takes the form:

$$(t_1,\ldots,t_m) \sim \prod_{i=1}^{m} \theta(t_i) \exp\left\{-\int_0^t \theta(s)ds\right\}$$

  - Instead, we assume a model-averaging setup in which each of a number of spline models is used according to its posterior probability[11]
- We assume that the intensity function has the functional form where the dot $(\cdot)$ stands for a time, j is an index for the spline functions used, k is the number of splines of the first and second type, and q is a fixed positive exponent:

$$\log(\theta(\cdot)) = \sum_{j=1}^{k} a_j (\cdot - \delta_j)_+^q + \sum_{j=k+1}^{2k} a_j (\cdot - \delta_j)_-^q;$$

$$(\tau_1 - \tau_2)_\pm^q = \begin{cases} (\tau_1 - \tau_2)^q I(\tau_1 > \tau_2) & \text{and if} \quad j = +\\ (\tau_2 - \tau_1)^q I(\tau_1 < \tau_2) & \text{and if} \quad j = - \end{cases}$$

- For linear coefficients a_j and knots δ_j (j=1,…,2k). The resulting temporal Poisson process provides the sampling mechanism used to predict future relapses

The Direct Approach

- In the direct approach, the observed relapse events were assumed to follow a Poisson process with intensity function
- It seems that the legend for **Figure 4** contains predictions of the time required to obtain 55, 65, 75, and 95 relapses using the direct approach
- **Table 1** shows observed data points using the March 2013 data points to check prediction accuracy
- The number of relapses as of March 2013 is postdated relative to March 2012. Using March 2012 data we compare what we predict for March 2013 with the reality. We postdate the 55th, 65th, 75th, and 95th relapses by the time difference (of 365 days) between March 2012 and March 2013. The prediction intervals, although large, cover the postdated results
  - The 55th relapse occurred about 412 – 365 = 47 days since March 2012. A 95% prediction interval is 25–107
  - The 65th relapse occurred about 447 – 365 = 82 days since March 2012. A 95% prediction interval is 69–179
  - The 75th relapse occurred about 488 – 365 = 123 days since March 2012. A 95% prediction interval is 111–233
  - The 95th relapse did not occur using March 2013 data check. A 95% prediction interval is 246–383

Figure 4. Output from March 2012 based on the last 50 of 500 simulations.

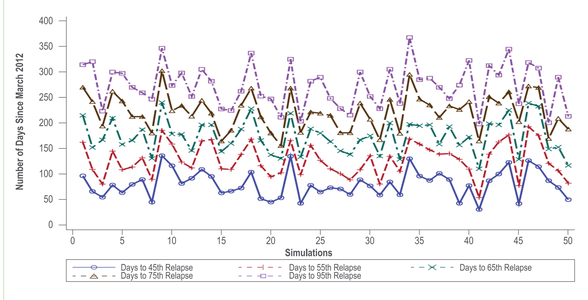
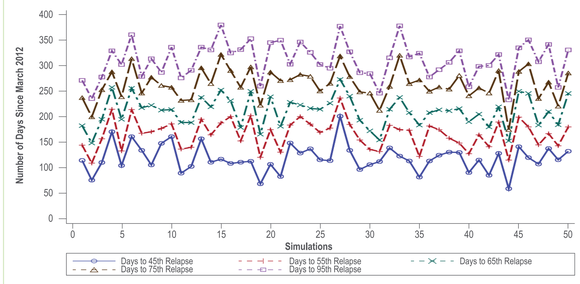


Table 1. Observed Data Points From March 2013 Data

By March 2013	Placebo	Study Drug	Overall
Enrolled DB period	170	164	334
Relapse	54 (31.76)	24 (14.63)	78 (23.35)
Discontinued	43 (25.29)	37 (22.56)	80 (23.95)
Completed	29 (17.06)	31 (18.90)	60 (17.96)
Still continuing	44 (25.88)	72 (43.90)	116 (34.73)

- The predictions of the time required to obtain relapses since June 2012 are presented in **Figure 5**
- The number of relapses as of March 2013 are postdated relative to June 2012. Using June 2012 data we compare what we predict for March 2013 with the reality
- We postdate the 55th, 65th, 75th, and 95th relapses by the time difference (of 365 days) between June 2012 and March 2013
- The prediction intervals show substantial coverage improvement over those made using the March 2012 data
  - The 55th relapse occurred about 412 – 270 = 142 days since June 2012. A 95% prediction interval is 72–167
  - The 65th relapse occurred about 447 – 270 = 157 days since June 2012. A 95% prediction interval is 118–215
  - The 75th relapse occurred about 488 – 270 = 218 days since June 2012. A 95% prediction interval is 206–320
  - The 95th relapse did not occur using March 2013 data check. A 95% prediction interval is 241–378
- **The prediction interval (241, 378) is our best guess regarding the number of days until the 95th relapse from June 2012**

Figure 5. Output from June 2012 based on the last 50 of 500 simulations.



The Indirect Approach

Indirect approach to prediction: In the indirect approach we assume an (unknown) probability that each given subject will eventually relapse over the course of the entire trial. The probability that a subject relapses after time T_k but prior to time t given that he/she relapses takes the form:

$$P(t \mid n, T_k, \theta, relapse) = \left(\frac{\int_{T_k}^{t} \theta(w)dw}{\int_{0}^{t} \theta(w)dw} \right)$$

Where θ denotes intensity function

Results from the indirect approach are not provided.

CONCLUSIONS

- **Blinded, nonparametric Bayesian Poisson process models are shown to be superior to their parametric and/or non-Bayesian counterparts**
- **These simulations exploit both observed and censored times to relapse for purposes of prediction**
- **These simulations address the limitations of alternative approaches that include (a) issues associated with staggered entry, (b) failure to make proper use of information arising from censored data, (c) the evolution of hazard and accrual rates, and (d) failure to provide model flexibility**

REFERENCES

1. Bagiella E, Heitjan DF. *Stat Med*. 2001;20:2055-2063.
2. Ying GS et al. *Clin Trials*. 2004;1:352-361.
3. Fu DJ et al. *J Clin Psychiatry*. 2015;76:253-262.
4. Snyder DL, Miller MI. *Random Point Processes in Time and Space*. Wiley and Sons; 1975.
5. Taddy M, Kottas A. *Bayesian Anal*. 2012;7:335-362.
6. Streit RL. *Poisson Point Processes: Imaging, Tracking, and Sensing*. Springer; 2010.
7. Zhang X, Long Q. *Biom J*. 2012;54:735-749.
8. Heikkinen J, Arjas E. *Biometrics*. 1999;55:738-745.
9. Adams RP et al. In: Proceedings of the 26th International Conference on Machine Learning. http://faculty.chicagobooth.edu/workshops/econometrics/past/pdf/Adams2.pdf. 2009. Accessed September 9, 2016.
10. Baddeley A et al. *Spatial Point Patterns: Methodology and Applications With R*. Chapman and Hall; 2015.
11. Denison DGT et al. *Bayesian Methods for Nonlinear Classification and Regression*. Wiley; 2002.

Acknowledgments

I. Turkoz is an employee of Janssen Research and Development, LLC, and is a Johnson & Johnson stockholder. M. Sobel has nothing to disclose. B. Brown and L. Alphs are employees of Janssen Scientific Affairs, LLC, and are Johnson & Johnson stockholders. Writing and editorial support were provided by Lynn Brown, PhD (ApotheCom, Yardley, PA). This support was provided by Janssen Scientific Affairs, LLC.

Supported by Janssen Scientific Affairs, LLC

Presented at International Society for CNS Clinical Trials and Methodology Autumn Conference; September 26–27, 2016; Philadelphia PA