Within-trial prediction for the number of future events

進行中の試験におけるイベント発生数の予測

1. Introduction

In randomized clinical trials, mid-course monitoring of sample size is becoming increasingly commonplace and important. For the studies with a failure time outcome, sample size estimates depend mainly on the proposed effect of treatment on the difference in failure rates, usually measured by the hazard ration, but sample size is also dependent on the number of events that will be observed during follow-up which depends on the overall failure rate. A departure from the estimated failure rate at the design stage may reduce the power unacceptably for a clinically important hazard ration. This might be resolved by making appropriate design modifications (usually increasing the sample size or extending the follow-up time until the enough events are observed). To inform the decision about whether and how to make mid-course correction, predicting the number of events in the future course of the trial is desirable.

Prediction has long been recognized as an important practical aspect of interim monitoring of randomized clinical trials. It is nature and potentially more accurate to make the prediction by using the accumulating data from the trial itself, rather than the results from prior trials with similar design. In addition to the point prediction, for many applications, it is important to provide lower and upper bounds of the prediction (prediction interval) at some specified level of confidence to reflect the uncertainty of prediction.

Prediction can be performed on the basis of either unblinded or blinded data. In the former case, prediction procedures make use of data from the trial including information about treatment assignment. In the later case, information about which treatment group a patient is assigned to is not identified. In the unblinded case, there is considerable concern about inflation of the type I error rate for the trial as a whole and manipulation of the trial data if the unblinded result is disclosed. That is the reason why regulators seem to favor blinded procedures, as FDA (Food and Drug Administration) draft guidance on the topic of sample size re-estimation emphasizes that blinded procedures should 'generally be considered for most studies' [1].

In this paper, we will present 2 separate approaches to predict the number of events for the future course of the trial given the accumulating observed data. Either method will estimate prediction intervals by a straight-forward simulation. Moreover, as an expected blinded sample size re-estimation, we won't estimate the treatment

difference from the ongoing trial data to modify clinically meaningful alternative hypothesis for testing. The incentive of my work comes from a clinical trial setting which will be described in next section.

2. REAL-CAD trial context

REAL-CAD trial is an ongoing randomized, open-labeled, investigator-initiated, large scale clinical trial, of stable coronary artery disease (CAD) patients with hypercholesterolemia, comparing the intensive (Pitavastatin, 4 mg/day) and moderate (Pitavastatin, 2 mg/day) Statin therapy on cardio-cerebrovascular outcomes. The primary endpoint is defined to be a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke and hospitalization for unstable angina [2]. This trial intended to randomly assign 12600 patients in a 1:1 ratio, as it eventually randomized 13054 patients from January 2010 to July 2013. All patients are to be followed up until March 2016 to obtain 1033 primary events, which would give the study a statistical power of 80% at 2-tailed α level of 0.05, assuming a constant overall event rate of 0.025 person-year and an hazard ratio (high/low) throughout follow-up of 0.84. A interim analysis is pre-specified to be conducted when approximately 50% of 1033 required events are reported. Independent Data Monitoring Committee (IDMC) will review interim analysis data and make recommendations about whether to continue, modify or stop the trial.

At the time accrual was complete (August 1, 2013), 193 primary events occurred. From this data, we found that the overall event rate was approximately 0.009 person-year, rather than 0.025 as was proposed. Because the planned sample size is already quite large and accrual of patients was closed, increasing the sample size is not realistic. So we will have to rely on extending follow-up to achieve significance, given that this much lower event rate than expected would last until the end of follow up period. But we also have chance to prove our hypothesis without changing our plan, if overall hazard rate is not constant but getting higher with time, and then 1033 required events are still possible to reach within the planned follow up period. Or since the assumption of constant overall event rate no longer hold and hence, the estimated sample size before the study commenced might not so accurate, a smaller sample size instead of 1033 events may also enable us to detect the treatment difference.

The failure rate used for sample size estimation was based on a few Japan studies in hypercholesterolemia and/or CAD patients and with common lipid-lowering treatment of statin or eicosapentaenoic acid [3, 4, 5, 6, 7]. These studies indicated that the occurrence probability for primary event defined above should be 2~5% per-year.

The initial event rate of 2.5% per-year was supposed to be fairly appropriate for REAL-CAD study until the first event investigation (September 2012) in which less than half of the expected primary events were reported. Meanwhile, LIVES Extension [8], CIRCLE [9], COMPACT-CAD [10] and JAPAN-ACS [11] studies revealed more and more Japanese evidence about the study drug – pitavastatin, the latest potent statin launched in Japan since September 2003 [12] and the USA since June 2010 [13]. These results, not available at the initial design stage, suggested that pitavastatin may exhibit a more favorable long-term effective profile on lipids than other statin, through a mechanism involving a larger increase in HDL-C, a greater reduction on triglycerides and an equivalent LDL-C lowering. This may constitute one of the important reasons for the much lower event rate in REAL-CAD trial. Besides pitavastatin's outstanding comprehensive effect on plasma lipids, another possible reason worth pointing out is the rate of patients who ever underwent coronary revascularization (PCI or CABG) before entering the study is over 80% in REAL-CAD, as compared to a rate of almost 50% in other studies like TNT study [14].

With the context described above, to aid decisions to modify study designs or not, firstly we have to be focused on a straight-forward, but accurate prediction of regarding events to be observed in the future.

3. Data

Because we can't access the REAL-CAD patient-level data when this paper is submitted, to demonstrate our methods, we use the real data from another study called N-SAS BC 05 [15], which is also an ongoing clinical trial with time-to-event as the primary outcome. From November 2007 to December 2012, N-SAS BC 05 study enrolled 1697 patients and reached the 85th primary event up to 18 November 2013. This study is to be stopped at December 2017, leading to a maximum follow up period of 11 years.

4. Methods

The objective is to predict at the future time t (in this paper, 2014/11/18, 2015/11/18, 2016/11/18 and 2017/12/31. But it can be user-defined.), how many events will occur, that is, how many patients who are alive at current time t_0 (November 18, 2013) are expected to fail between t0 and t, given the current data.

Following this objective, we consider the methods proposed by Ying GS, Bagiella E, Heitjan DF, et al. [16, 17], originally for the unblind setting. The parametric method like Method A which place the assumption that the survival function is under a parametric survival time distribution and prior trial survival data are relevant with

distribution assumption, can be utilized. Method A can make the prediction simpler, more convenient and potentially efficient. But there is concern that the predictions may be inaccurate if the true underlying distributions differ from those assumed. To address this concern, the second method – Method B, which is a nonparametric method that combines Kaplan-Meier survival curve point estimation, bayesian bootstrap interval and exponential tail, is also proposed. Convergence of the two methods will add confidence to the predictions.

Let s_i be the failure or censoring time of subject i and let $Y_i(t)$ take value 1 if patient i is under observation and at risk of failure at time t_0, and 0 otherwise. Define $E(t_0, t)$ to be the conditional expectation, given the data up to t_0, of number of events that will have been observed by time . Define $Q(t_0, t)$ to be the conditional expectation, given the data up to t_0, of number of events to occur between t_0 and t. $D(t_0)$ represents the number of events that have occurred by time t_0. Bagiella and Heitjan [18] showed that the conditional expectation of the number of events by time t among subjects at risk at time t_0 is

$$Q(t_0, t) = \sum_{i=1}^{N(t_0)} Y_i(t_0) \frac{F(t) - F(t_0)}{1 - F(t_0)} \quad (1)$$

Thus,

$$E(t_0, t) = D(t_0) + Q(t_0, t) \quad (2)$$

Method A: Bayesian Weibull prediction based on prior survival knowledge combined with current survival data

Unlike the exponential, the two-parameter Weibull distribution [19] describes the hazard function increased or decreased over time. Thus, the Weibull, which includes the exponential as a special case, can offer a promising compromise position between the exponential and nonparametric approaches.

Suppose we have a sample $\{t\}$ following an Weibull distribution with the scale parameters of λ and the shape parameter of α. We can compute the cumulative hazard function - $F(t)$ using the maximum likelihood parameters estimated from the data up to t_0, as $F(t)=1-\exp(-(t/\lambda)^{\alpha})$. Meantime the likelihood function in terms of α and λ is as follows [20]:

[Formula to be inserted]

Taking advantage of prior survival information, a multivariate normal with mean equal to numbers proposed at the design stage are used for intercept and β as our priors. Meanwhile, to explore the sensitivity of predictions to the prior, non-informative diffuse priors are also applied.

Informative moderate priors (time unit of month):

intercept ~ normal(mean= -4.2, sd = 0.20); corresponding to an event rate of 0.015 person-year ranged from about 0.010 to 0.022.

α ~gamma(shape =4, scale =0.25); corresponding to a shape parameter of 1 (exponential survival) ranged from about 0 to 2.

Non-informative diffuse priors:

intercept ~ normal(mean= 0, var=10000);

α ~gamma(shape = 0.001, inverse scale = 0.001);

Once the priors are specified, we can resort MCMC (Markov Chain Monte Carlo) to get a list of posterior sampled values of (intercept, α). Specifically, to simulate the values of the numbers of events at *t*, the following steps are executed:

(i) Take the next element from the list of sampled values of (intercept, α). The scale parameter λ can be estimated as exp(-intercept).

(ii) Conditional on the time spent so far and treatment arm, impute event times for currently censored subjects given the sampled Weibull parameters.

(iii) Calculate the failure subjects whose expected event time exceeds *t*.

By repeating steps (i)–(iii) 1000 times, we obtain a list of values representing a set of 1000 draws from the predictive distribution of number of events at T*, while the 5 and 95 quartiles of this list give the limits of a 90% prediction interval for the predictive number of events.

Method B: Nonparametric prediction in combination with Kaplan-Meier survival curve point estimation, bayesian bootstrap interval and exponential tail

In contrast to the Weibull parametric distribution, with Method B, $F(t)$ in Equation (1) can be estimated nonparametrically by the Kaplan-Meier survival estimator with $F(t)=1-S(t)$, where $S(t)$ is survival function. The densities $f(t)$ from the data up to t_0, can be estimated as the change of $S(t)$ during small time interval divided by the length of that time interval.

To generate the prediction interval, the following steps are performed:

(i) Creat a Bayesian bootstrap sample from the data available by t_0.

(ii) Make Kaplan-Meier curves for the times to event in the bootstrapped data.

(iii) Generate event times for subjects alive and on study at t_0, conditional on survival time exceeding the time already observed.

(iv) Calculate the failure subjects whose expected event time exceeds *t*.

By repeating steps (i)–(iv) 1000 times, we obtain a list of 1000 $E(t_0, t)$. Then the

predictive interval is calculated from the 5 and 95 quartiles of this list.

A potential problem with Kaplan-Meier estimator is that it is not well defined for time points exceeding the largest failure time. A solution to this problem is to append an exponential tail that declines to zero. Again using the maximum likelihood parameters estimated from the data up to t_0, $F(t)$ for time points exceeding the largest failure time are estimated by $F(t)=1-exp(-\lambda t)$.

5. Results

As shown in slides.

6. Discussion

Ongoing

7. Conclusion

Ongoing

8. Acknowledgement

This thesis is submitted to School of Public Health as partial fulfillment of the requirements for the MASTER degree of PUBLIC HEALTH (MPH) at The University of Tokyo. The work presented here has been carried out at the Department of Biostatistics, since autumn 2012.

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【References】

1） Food and Drug Administration (FDA). Guidance for industry - Adaptive design clinical trials for drugs and biologics. Draft guidance, 2010. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm201790.pdf [Accessed 8 November 2013].

2） REAL-CAD trial HP http://csp.or.jp/ld/real-cad/ [Accessed 18 November 2013].
3） Mabuchi H, Kita T, Matsuzaki M, Matsuzawa Y, Nakaya N, Oikawa S, et al. Large scale cohort study of the relationship between serum cholesterol concentration and coronary events with low-dose dose simvastatin therapy in Japanese patients with hypercholesterolemia and coronary heart disease: secondary prevetion cohort study of the Japan Lipid Intervention Trial (J-LIT). Circ J 2002; 66(12):1096-100.
4） Yokoyama M, Origasa H, Matsuzaki, Matsuzawa Y, Saito Ishikawa, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet 2007; 369(9567):1090-8.
5） Japanese Coronary Artery Disease (JCAD) Study Investigators. Current status of the background of patients with coronary artery disease in Japan. Circ J 2006; 70(10):1256-62.
6） Sakamoto T, Kojima S, Ogawa H, Shimomura H, Kimura K, Ogata Y, et al. Effects of early statin treatment on symptomatic heart failure and ischemic events after acute myocardial infarction in Japanese. Am J Cardiol 2006;97(8):1165 -71.
7） Furukawa Y, Taniguchi R, Ehara N, Ozasa N, Haruna Y, Saito N, et al. Better survival with statin administration after revascularization therapy in Japanese patients with coronary artery disease: perspectives from the CREDO-Kyoto registry. Circ J 2008; 72(12):1937-45.
8） Teramoto T, Urashima M, Shimano H, Yokote Koutaro, Saito Y, et al. A Large Scale Survey on Cardio-Cerebrovascular Events During Pitavastatin （LIVALO Tablet） Therapy in Japanese Patients with Hypercholesterolemia -LIVALO Effectiveness and Safety Study Extension （LIVES Study Extension）-. Jpn Pharmacol Ther（薬理と治療）vol. 39 no. 9 2011.
9） Maruyama T, Takada M, Nishibori Y, Fujita K, Miki K, et al. Comparison of Preventive Effect on Cardiovascular Events With Different Statins – The CIRCLE Study –. Circ J. 2011;75(8):1951-9. Epub 2011 Jun 15.
１０） Kurogi K, Sugiyama S, Sakamoto K, Tayama S, Nakamura S, et al. Comparison of pitavastatin with atorvastatin in increasing HDL-cholesterol and adiponectin in patients with dyslipidemia and coronary artery disease: the COMPACT-CAD study. J Cardiol. 2013

Aug;62(2):87-94.

１１） Hiro T, Kimura T, Morimoto T, Miyauchi K, Nakagawa Y, et al. Effect of intensive statin therapy on regression of coronary atherosclerosis in patients with acute coronary syndrome: a multicenter randomized trial evaluated by volumetric intravascular ultrasound using pitavastatin versus atorvastatin (JAPAN-ACS [Japan assessment of pitavastatin and atorvastatin in acute coronary syndrome] study). J Am Coll Cardiol. 2009 Jul 21;54(4):293-302

１２） 独立行政法人医薬品医療機器総合機構（PMDA）-新薬の承認に関する情報 http://www.info.pmda.go.jp/shinyaku/P200300016/left.html [Accessed 8 November 2013].

１３） Food and Drug Administration (FDA) Approved Drug Products. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm [Accessed 8 November 2013].

１４） Waters DD, LaRosa JC, Barter P, Fruchart JC, Gotto AM Jr, et al. Effects of high-dose atorvastatin on cerebrovascular events in patients with stable coronary disease in the TNT (treating to new targets) study. J Am Coll Cardiol. 2006 Nov 7;48(9):1793-9.

１５） http://www.csp.or.jp/cspor/kenkyuu/nsasbc_05.html [Accessed 18 November 2013].

１６） Ying GS, Heitjan DF. Weibull prediction of event times in clinical trials. Pharmaceutical Statistics 2008 Apr-Jun; 7(2):107-20.

１７） Ying GS, Heitjan DF, Chen TT. Nonparametric prediction of event times in randomized clinical trials. Clin Trials. 2004;1(4):352-61.

１８） Weibull WA. A statistical distribution of wide applicability. Journal of Applied Mechanics 1951; 18:293–297.

１９） Bagiella E, Heitjan DF. Predicting analysis times in randomized clinical trials. Statistics in Medicine. 2001 Jul 30; 20(14):2055-63.

２０） SAS/STAT(R) 9.2 User's Guide, Second Edition http://support.sas.com/documentation/cdl/en/statug/63033/HTML/default/viewer.htm#titlepage.htm [Accessed 8 November 2013].