Journal of Applied Sciences

ISSN 1812-5654

science alert

ANSInet
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Journal of Applied Sciences 15 (2): 374-376, 2015
ISSN 1812-5654

ansinet
Asian Network for Scientific Information

RESEARCH ARTICLE OPEN ACCESS

DOI: 10.3923/jas.2015.374.376

Bayesian Adaptive Randomization Designs for Clinical Trial

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ARTICLE INFO
Article History:
Received: October 17, 2014
Accepted: December 03, 2014

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ABSTRACT
Bayesian Adaptive Randomization Design (BARD) is widely used in clinical trials, this design allow to adaptively assign patients to the better treatment. The aim of this study is to compare the potential of Simple Bayesian Adaptive Randomization Design (SBARD) with two common designs (Pocock and O'Brien Flemming), in detecting the effect of treatments. The 5,000 simulations are done to evaluate the performance of SBARD and the two common designs under the same clinical scenarios. The operating characteristics of the SBARD and two common designs are presented. We found that, under scenario 4, the SBARD has greater power (0.938) than the Pocock and O'Brien Flemming designs in detecting the difference between control and treatment arms, using small number of total subjects (116 vs., 292, 600). The SBARD design would be one of the simplest design incorporates with the short term outcomes in clinical trial.

Key words: Bayesian adaptive randomization, sequential analysis, monitoring, clinical trial

INTRODUCTION

Traditionally, conventional randomization methods are equally assigned patients into treatments. However, many physicians may find a objectionable balanced randomization because they believe that some patients may be forced to use the inferior treatment until the end of study. Another way to deal with this problem is known as sequential analysis. Group sequential designs are frequently used to evaluate the effect of interventions in human subjects and monitor ethical and financial issues (Emerson *et al*., 2011; Jennison and Turnbull, 2000). The standard group sequential designs are proposed, Pocock and O'Brien Flemming (Emerson *et al*., 2007). The Pocock procedure is primarily of theoretical significance, as this procedure uses the same nominal significance level at each interim while the O'Brien Fleming procedure is more conservative at the first look or early interim but less conservative in the latter and the final looks (Lewis *et al*., 2007). However, both procedures are unpractical for some cases. Over the last 10-20 years, an alternative approach called Bayesian Adaptive Designs (BAD) was proposed. The BAD enable investigators to modify trials in midcourse which including early stopping the trial, adaptively assigning patients to better therapies, adding treatment arms, dropping treatment arms and extending accrual beyond from the origin when the results of the study was not satisfactorily known (Berry, 2006; Berry *et al*., 2010a; Chow and Chang, 2008). The BAD is implemented in many clinical trials develop from both pharmaceutical and the United States Food and Drug Administration (FDA) (Berry *et al*., 2010b). Recently, the US FDA much addresses the advantage of BAD in improving decision making, time and cost saving and using fewer patients. Moreover, in year 2010, the US FDA has been endorsed the guidance for the use of Bayesian statistics and also issued the use of Bayesian adaptive designs as well (Berry *et al*., 2010a; Guidance for Industrial and FDA Staff, 2010).

The studies involving Bayesian adaptive designs have been reviewed. Schmidli *et al*. (2007) used BAD to evaluate the survival endpoints in seamless phase II/III. Zhou *et al*. (2008) proposed an outcome based adaptive randomization trial design for patients with advance stage non small cell lung cancer. Wathen and Thall (2008) presented the new approach deriving an BAD for a randomized group sequential clinical trial based on right-censored event time. Chen and Smith (2009) proposed an adaptive group sequential design using Bayesian Decision Theoretic Approaches (BDTA) in phase II clinical trial. Eickhoff *et al*. (2010) proposed BAD to evaluate both diagnostic and therapeutic implication of biomarkers.

In this study, we focus on the evaluation of the potential of Simple Bayesian Adaptive Randomization Design (SBARD) with two common designs (Pocock and O'Brien Fleming) in detecting the effect of control and treatment arms in the setting of cervical cancer trial phase III where the treatment effect is measured as the difference in binomial proportions.

MATERIALS AND METHODS

Background of randomized clinical trial: A monitoring design was proposed, as a feasibility study in randomized controlled multicenter clinical trials phase III in the patients with Locally Advance Cervical Cancer (LACC) data in Thailand year 2010. For confidentiality consideration, the specific treatments could not be named in the trial. Response rate, one of the short term outcomes was selected to perform the simulation study. Response rate was classified into two categories: (1) Complete Response (CR) and (2) No Complete Response (no CR). The conventional sample size was calculated based on a fixed time and constant hazard ratio to detect the improvement of progression-free survival between two treatments, criterion for significance (alpha) has been set at 0.05, subjects required to have statistical power at 90% are 300 in each group, the total sample size is 600 patients.

Simple Bayesian Adaptive Randomization Design (SBARD): Assuming p_i is success rate, x_i is number of success and n_i is the total number of subjects in each treatment ($trt_i i$ = 1 is control arm, 2 is treatment arm) and patients enroll over the period of five years. Based on standard binomial distribution, we have X_i~binomial (n_i, p_i) with beta prior distribution for p_i.

To illustrate that how Bayesian adaptive randomization work, we first study a Simple Bayesian Adaptive Randomization Design (SBARD) case of testing binary response (success rate) between two treatments. Patients are assigned to receive either treatment, using an adaptive procedure that based on assignment probabilities. The simulation study will be conducted to evaluate the posterior probabilities following the study of Wathen and Thall (2008) as follows:

$$\pi = \frac{P(p_1 \rangle p_2 \mid X)^{\lambda}}{P(p_1 \rangle p_2 \mid X)\lambda + P(1-p) \rangle p_2 \mid X)^{\lambda}} \quad (1)$$

where, π is posterior probability, l is tuning parameter.

The next cohort of patients is assigned to arm 2 (treatment arm) with probability π, to arm 1 (control arm) with probability 1-π. When l = ∞, the posterior probability of patient assignment to arm 2 (treatment arm) will be enter to "play the winner rule", in which the next patient will be assigned to the current winner treatment based on the available data and no randomization involved. The larger λ is the more imbalance randomization will be.

A decision rule can be set to compare response rate between control and treatment arms with many choice for the randomize ratios. The decision rules at the end of trial, consider probability (p_1>p_2)> 0.975, conclude control is better otherwise (p_2>p_1)>0.975, conclude treatment is better. At interim phase of three looks, each look is consider probability (p_1>p_2)>0.999, stop the trial early, conclude control is better otherwise (p_2>p_1)>0.999 stop the trial early, conclude treatment is better.

The performance of the SBARD is evaluated by comparing on the average number of subjects and probabilities to be select in each arm with two common designs (Pocock and O'Brien Flemming) under four category of response rate scenarios.

RESULTS

We generated 5,000 simulations to evaluate the performance of SBARD with two common designs under four scenarios. The operating characteristics of the SBARD and common designs are shown in Table 1. In scenario 3, treatment arm has higher chance to be selected (p = 0.865), SBARD requires 45 subjects in control arm and 132 subjects in treatment arm to reach a conclusion and SBARD requires smaller total sample size than Pocock and O'Brien Flemming designs (177 vs., 528,466). However, in scenario 4, treatment arm has the highest chance to be selected (p = 0.938) comparing with the other scenarios, SBARD requires

Table 1: Operating characteristics of two response rates of treatments between Simple Bayesian Adaptive Randomization Design (SBARD), Pocock and O'Brien Flemming designs

			SBARD				
Scenarios/arms	Category response rates	Sample size ratio (SBARD)	Mean No. of patients	Chance to be select	Chance to be select early stopping	Pocock design (mean No. of patients)	O'Brien fleming design (mean No. of patients)
Scenario 1							
Control	0.50	1:1	166	0.098	0.298	60,633	53,158
Treatment	0.50		172	0.096	0.285	60,633	53,158
Scenario 2							
Control	0.50	1:2.7	76	0.031	0.727	601	543
Treatment	0.60		204	0.641	0.068	601	543
Scenario 3							
Control	0.50	1:2.9	45	0.014	0.935	264	233
Treatment	0.65		132	0.865	0.027	264	233
Scenario 4							
Control	0.50	1:2.5	30	0.012	0.980	146	300
Treatment	0.70		86	0.938	0.019	146	300

30 subjects in control arm and 86 subjects in treatment arm to reach a conclusion, under this scenario the SBARD also requires smaller total sample size than Pocock and O'Brien Flemming designs (116 vs., 292, 600) to detect the difference between control and treatment arms.

DISCUSSION

In order to use the Pocock and O'Brien Flemming designs to monitor clinical trials, there is an increasing need to evaluate the benefit of treatment which is concerning on cost, time simultaneously. Many authors have proposed the advantage of Bayesian Adaptive Randomization Design (BARD) to deal with these problems and have encouraged the use of BARD in phase II trials or phase II/III trials (Schmidli *et al*., 2007; Chow and Chang, 2008; Wathen and Thall, 2008; Zhou *et al*., 2008; Chen and Smith, 2009). Our SBARD is the model-based design that uses the short term response information to perform adaptive randomization in clinical trial phase III in the setting of feasibility study. SBARD is efficient than Pocock and O'Brien Flemming designs, that it assigns more patients to the superior treatment. The SBARD would be one of the simplest design incorporates with the short term response. Future study, we may include the long term outcomes, such as survival outcomes to perform SBARD in clinical trial phase III.

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