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1. Introduction

Response-driven adaptive designs are used in phase III clinical trials with an objective to treat a larger number of patients by the eventual better treatment. The objective of a phase III trial is to compare the performances of two or more competing treatments where the patients often arrive sequentially into the study. Quite often the patients are treated one after another and thus the procedure allows to use the past allocation-and-response history up to any entering patient to determine his/her treatment. Thus, the adaptive designs have their role to play in such a scenario to help us achieve some ethical gain by treating a larger number of patients by the better treatment. At the same time, we also need some significant amount of allocation to the worse treatment as well to enable us to make meaningful inference about the treatment difference in an efficient manner. Adaptive design is all about the trade-off between ethical gain (which is achieved if a larger number of patients are treated by the better treatment) and efficiency of the follow-up inference (which is achieved if the allocation is balanced in a 50:50 way) under equal variance set up.

Quite a few real applications of adaptive designs are there with an increasing frequency in the recent days. Some real applications of adaptive clinical trials for dichotomous responses are due to Professor M. Zelen (in a breast cancer trial, reported by Iglewicz, 1983), Bartlett et al. (1985), Tamura et al. (1994), Ware (1989), Rout et al. (1993), Muller and Schefer (2001). Several adaptive designs are available in literature,

although most of them are suitable for binary treatment responses. Some of the well-known designs are the play-the-winner rule (see Zelen, 1969), the randomized play-the-winner rule (see Wei and Durham, 1978), the success driven design (see Durham, Flournoy and Li, 1998). For such designs, the expected proportion of allocation to the better treatment arm is more than 50%, and this proportion increases with the increase in treatment difference. However, most of these designs are birth processes and accordingly the variability is too high. In fact, the standard deviations of the proportion of allocation for these designs are so high that an allocation which is less than one or two standard deviation(s) from the expectation often leads less than 50% patients to be treated by the better treatment, in case of a two treatment experiment. Recently Ivanova (2003) introduced a new adaptive design for two-treatment allocation, called the drop-the-loser rule, which is a death process. Consequently, the variation is quite low as it is known from the results of stochastic processes that death processes have less variability than the birth processes. Hu and Rosenberger (2003) observed that the drop-the-loser rule has the smallest variability among the available adaptive designs for binary responses.

All the above designs are for binary treatment responses. Certainly the amount of research on adaptive design is very low with more general treatment responses, e.g. continuous treatment responses. The reason is mostly the complexity that arises with such more general responses, the question naturally arises is: how to adapt. The few works available in this context are due to Rosenberger (1993), and Rosenberger and Seshyer (1997). Here we provide a version of the drop-the-loser rule applicable for continuous responses where some of the covariates can take an important role in the responses. Thus, a response with an unfavourable covariate should get much weight in favour of the treatment concerned than the same response with a favourable covariate. In any realistic design, these aspects are to be taken care of. So, for the purpose of application we need a version of the drop-the-loser rule, which is equipped with continuous responses and properly takes care of the covariates of the patients. We provide a covariate-adjusted drop-the-loser rule for continuous treatment responses, which we abbreviate as CCDL. There we consider a linear model for the responses and for the sake of mathematical simplicity we assume normality. We also consider an approach to carry out the proposed

CCDL without having a linear model of responses or when the response model is unknown.

2. Covariate-adjusted adaptive designs for continuous responses

2.1. The set up

Suppose we have the two competing treatments, say A and B, in a phase III clinical trial. We have a set up where the patients enter into the set up sequentially and each entering patient is treated either by A or by B using some randomisation where the probability of allocating any treatment is adaptively determined according to the state of art based on the data up to that stage. Here we have a set up where the responses are continuous and a covariate vector x affects the responses. For illustration, at this stage, we assume simple linear model of responses where the covariate vector influences the responses in the same way for both the treatments. For many types of treatment responses, a simple transformation of the response variable, e.g. the log of survival time, leads to a linear model of responses. For simplicity, we again assume a normally distributed response structure, although this assumption is not needed for our development and implementation of the technique. Normality, of course, brings some elegance in the mathematics. Suppose we have n patients in the trial. Let T_i be an indicator which takes the value 1 or 0 according as the i th patient is treated by A or B. Consequently, Y_i be the response. Thus we assume that $Y_i \sim N(\mu_A + x_i^T \beta, \sigma^2)$ or $Y_i \sim N(\mu_B + x_i^T \beta, \sigma^2)$ depending on the i th patient is treated by A or B, where x_i is the covariate vector of the i th patient. Note that different σ^2 could be one real possibility. But we decide to describe our design in a simple set up. Such types of extra modifications can be done in our approach without much additional difficulty.

Note that, in our model above, the treatment difference (see Ware, 1989; Wei et al., 1990) is $\mu_A - \mu_B$. Our allocation design should be such that it will allocate a larger number of patients to treatment A if $\mu_A - \mu_B > 0$, and the allocation proportion to treatment A should increase with the increase in the difference $\mu_A - \mu_B$. But we should

note the covariate values of each patient and give appropriate weights to them in the allocation design.

2.2. The BB design

In the BB design, the $(i+1)$st patient is treated by treatment A with probability

$$\Phi\left(\frac{\hat{\mu}_A - \hat{\mu}_B}{\sigma_\Phi}\right),$$

where $\hat{\mu}_{Ai} - \hat{\mu}_{Bi}$ is the covariate-adjusted estimate of $\mu_A - \mu_B$ based on the data up to the first i patients and σ_Φ is a scaling constant.

2.3. Covariate-adjusted drop-the-loser design for continuous responses

It is observed that the DL rule for binary responses allocates with quite low variability. Here we want to propose a more updated rule for continuous responses with covariates taken into consideration, namely the covariate-adjusted continuous drop-the-loser rule (CCDL). Our proposed allocation design is as follows.

We start with an urn having one ball each of type A, B and I, where I is the immigration ball. For the $(i+1)$st entering patient, $i \geq 0$, we draw a ball from the urn, and treat the patient by treatment A or B if the drawn ball is of type A or B. On the other hand, if the drawn ball is of type I, we add one ball each of the types A and B to the urn, replace the I ball, and draw one ball from the urn afresh. We continue this procedure until we get a ball of A or B to treat the patient accordingly. Let the response of the patient be Y_{i+1}, the covariate vector is x_{i+1}, and the indicator of allocation is T_{i+1}. We then replace the drawn ball with a probability $p_{i+1} = p_{i+1}(Y_{i+1}, T_{i+1}, x_{i+1})$, which is also a function of all the accumulated data up to the first $(i+1)$ patients. We then carry out the same procedure for the next entering patient.

The all important problem lies in determining p_{i+1}. For this we proceed as follows. Let $\hat{\beta}_i$ be the estimate of β up to the data of the first i patients. Then we suggest to set p_{i+1} as

$$p_{i+1} = G\left(Y_{i+1} - \hat{\beta}_i^T x_{i+1} - c\right), \tag{2.1}$$

where G is the cumulative distribution function (cdf) of a symmetric random variable. Specifically, we can use the cdf of a normal distribution with variance σ_Φ^2. Thus, (2.1) reduces to

$$p_{i+1} = \Phi\left(\frac{Y_{i+1} - \hat{\beta}_i^T x_{i+1} - c}{\sigma_\Phi}\right). \tag{2.2}$$

Here c is a constant, which is set to make most of the p_i-values not too close to 0 or 1. Thus, a meaningful idea can be to choose c as the prior idea of $(\mu_A + \mu_B)/2$. One can sequentially update c by replacing it by $(\hat{\mu}_{Ai} + \hat{\mu}_{Bi})/2$. The choice of σ_Φ should also be driven by the fact that all the p_i-values should not too close to 0 or 1. Note that a small value of σ_Φ will make the p_i-values too sensitive to the Y_i-values, p_i will be close to 0 or 1 according as $Y_i - \hat{\beta}_{i-1}^T x_i - c < 0$ or > 0. But, on the other hand, a very large value of σ_Φ will make the p_i's close to 0.5, irrespective of the corresponding responses, thus making the adaptive mechanism very week. That is also not desirable. It is the experimenter's task to choose σ_Φ moderately by balancing this trade-off.

In the present set up, our data up to the i th patients comprises the allocation indicators $\{T_1, \Lambda, T_i\}$, the responses $\{Y_1, \Lambda, Y_i\}$ and the covariate vectors $\{x_1, \Lambda, x_i\}$. We denote the following;

$$\bar{Y}_{Ai} = \frac{\sum_{j=1}^{i} T_j Y_j}{\sum_{j=1}^{i} T_j}, \quad \bar{Y}_{Bi} = \frac{\sum_{j=1}^{i} (1-T_j) Y_j}{\sum_{j=1}^{i} (1-T_j)}, \quad \bar{x}_{Ai} = \frac{\sum_{j=1}^{i} T_j x_j}{\sum_{j=1}^{i} T_j}, \quad \bar{x}_{Bi} = \frac{\sum_{j=1}^{i} (1-T_j) x_j}{\sum_{j=1}^{i} (1-T_j)},$$

$$n_{Ai} = \sum_{j=1}^{i} T_j, \quad n_{Bi} = \sum_{j=1}^{i} (1-T_j),$$

$$S_{xx,i} = \sum_{j=1}^{i} T_j (x_j - \bar{x}_{Ai})(x_j - \bar{x}_{Ai})^T + \sum_{j=1}^{i} (1-T_j)(x_j - \bar{x}_{Bi})(x_j - \bar{x}_{Bi})^T,$$

$$S_{xy,i} = \sum_{j=1}^{i} Y_j x_j - n_{Ai} \bar{Y}_{Ai} \bar{x}_{Ai} - n_{Bi} \bar{Y}_{Bi} \bar{x}_{Bi}.$$

The normal equations are

$$\sum_{j=1}^{i}\begin{pmatrix} T_j \\ 1-T_j \\ x_j \end{pmatrix}\begin{pmatrix} T_j & 1-T_j & x_j \end{pmatrix}\begin{pmatrix} \mu_A \\ \mu_B \\ \beta \end{pmatrix} = \sum_{j=1}^{i} Y_j \begin{pmatrix} T_j \\ 1-T_j \\ x_j \end{pmatrix},$$

implying

$$\begin{pmatrix} n_{Ai} & 0 & \sum_{j=1}^{i} T_j x_j^{\,T} \\ 0 & n_{Bi} & \sum_{j=1}^{i} (1-T_j) x_j^{\,T} \\ \sum_{j=1}^{i} T_j x_j & \sum_{j=1}^{i} (1-T_j) x_j & \sum_{j=1}^{i} x_j x_j^{\,T} \end{pmatrix}\begin{pmatrix} \mu_A \\ \mu_B \\ \beta \end{pmatrix} = \begin{pmatrix} n_{Ai}\overline{Y}_{Ai} \\ n_{Bi}\overline{Y}_{Bi} \\ \sum_{j=1}^{i} Y_j x_j \end{pmatrix},$$

and hence

$$\hat{\beta}_i = S_{xx,i}^{-1} S_{xy,i}. \tag{2.3}$$

We use (2.3) and the current patient's response and covariate vector values to obtain the ball replacement probability (2.1) or (2.2). Note that in such a situation, the estimate of the treatment difference, $\mu_A - \mu_B$, is

$$\hat{\mu}_{Ai} - \hat{\mu}_{Bi} = \overline{Y}_{Ai} - \overline{Y}_{Bi} - (\overline{x}_{Ai} - \overline{x}_{Bi})^T \hat{\beta}_i. \tag{2.4}$$

Clearly the above covariate-adjusted rule is the usual drop-the-loser rule (Durham and Ivanova, 2001; Ivanova, 2003) with the unconditional probability of replacing the ball as

$$p_{i+1}^{*} = E\left[\Phi\left(\frac{Y_{i+1} - \hat{\beta}_i^{\,T} x_{i+1} - c}{\sigma_\Phi}\right)\right], \tag{2.5}$$

which depends on x_{i+1} if that is assumed to be non-stochastic. If, on the other hand, we assume a stochastic covariate vector X with a distribution function H, then the expectation in p_{i+1}^{*} in (2.4) is also taken over the distribution of X. We denote it by $p_{A,i+1}^{*}$ or $p_{B,i+1}^{*}$ according as the patient is treated by A or B. Quite naturally, the exact expression becomes complicated.

3. Conclusions

In this report we introduced drop-the-loser type designs for continuous responses with covariates. These designs yield adaptive allocation for continuous responses with smaller variability. The present work assumes a very simple structure where there is no delayed responses, no staggered entry. With the presence of all these practical logistics the method will be much more complicated and we need to adjust the rules sensibly to carry out response-adaptive allocation. The details are under study.

References

1. Bartlett, R. H., Roloff, D. W., Cornell, R. G., Andrews, A. F., Dillon, P. W. and Zwischenberger, J. B. (1985). Extracorporeal circulation in neonatal respiratory failure: A prospective randomized trial. Pediatrics 76, 479-487.

2. Durham, S, Fluornoy, N. and Li, W. (1998). A sequential design for maximizing the probability of a favourable response. *The Canadian Journal of Statistics* 26, 479-495.

3. Durham, S.D. and Ivanova, A. (2001). Drop-the-loser. Technical Report. University of North Carolina.

4. Hu, F. and Rosenberger, W. F. (2003). Optimality, Variability, Power: Evaluating Response-Adaptive Randomization Procedures for Treatment Comparisons. *Journal of the American Statistical Association*, in press.

5. Iglewicz, B. (1983). Alternative designs: sequential, multi-stage, decision theory and adaptive designs. In Cancer Clinical Trials : Methods and Practice, eds. M. E. Buyse, J. Staquet and R. J. Sylvester, pp. 312-334. Oxford University Press.

6. Ivanova, A. (2003). A play-the-winner-type urn design with reduced variability. *Metrika* 58, 1-13.

7. Müller, H.-H. and Schäfer, H. (2001). Adaptive Group Sequential Designs for Clinical Trials: Combining the Advantages of Adaptive and of Classical Group Sequential Approaches. *Biometrics* 57, 886–891.

8. Rosenberger, W. F. (1993). Asymptotic Inference With Response-Adaptive Treatment Allocation Designs. *The Annals of Statistics* 21, 2098-2107

9. Rosenberger, W. F. and Seshaiyer, P. (1997). Adaptive Survival Trials. *Journal of Biopharmaceutical Statistics* 7, 617-624.

10. Rout, C. C., Rocke, D. A., Levin, J., Gouws, E., Reddy, D. (1993). A reevaluation of the role of crystalloid preload in the prevention of hypotension associated with spinal anesthesia for elective cesarean section. Anesthesiology 79, 262-269.

11. Tamura, R. N., Faries, D. E., Andersen, J. S. and Heiligenstein, J. H. (1994). A case study of an adaptive clinical trials in the treatment of out-patients with depressive disorder. J. Amer. Statist. Assoc. 89, 768-776.

12. Ware, J. H. (1989). Investigating therapies of potentially great benefit: ECMO. Statistical Science 4, 298-340.

13. Wei, L. J. and Durham, S. (1978). The randomized play-the-winner rule in medical trials. J. Am. Statist. Assoc. 73, 838-843.

14. Wei, L.J., Smythe, R.T., Lin, D.Y. and Park, T.S. (1990). Statistical inference with datadependent treatment allocation rules. J. Amer. Statist. Assoc. 85, 156 -162.

15. Zelen, M. (1969). Play-the-winner rule and the controlled clinical trial. J. Am. Statist. Assoc. 64, 131-146.