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Covariate-Adjusted Response-Adaptive Designs for Semi-Parametric Survival Responses

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Abstract : Covariate-adjusted response-adaptive (CARA) designs use the available responses to skew the treatment allocation in a clinical trial in towards treatment found at an interim stage to be best for a given patient's covariate profile. Extensive research has been done on various aspects of CARA designs with the patient responses assumed to follow a parametric model. However, ranges of application for such designs are limited in real-life clinical trials where the responses infrequently fit a certain parametric form. On the other hand, robust estimates for the covariate-adjusted treatment effects are obtained from the parametric assumption. To balance these two requirements, designs are developed which are free from distributional assumptions about the survival responses, relying only on the assumption of proportional hazards for the two treatment arms. The proposed designs are developed by deriving two types of optimum allocation designs, and also by using a distribution function to link the past allocation, covariate and response histories to the present allocation. The optimal designs are based on biased coin procedures, with a bias towards the better treatment arm. These are the doubly-adaptive biased coin design (DBCD) and the efficient randomized adaptive design (ERADE). The treatment allocation proportions for these designs converge to the expected target values, which are functions of the Cox regression coefficients that are estimated sequentially. These expected target values are derived based on constrained optimization problems and are updated as information accrues with sequential arrival of patients. The design based on the link function is derived using the distribution function of a probit model whose parameters are adjusted based on the covariate profile of the incoming patient. To apply such designs, the treatment allocation probabilities are sequentially modified based on the treatment allocation history, response history, previous patients' covariates and also the covariates of the incoming patient. Given these information, an expression is obtained for the conditional probability of a patient allocation to a treatment arm. Based on simulation studies, it is found that the ERADE is preferable to the DBCD when the main aim is to minimize the variance of the observed allocation proportion and to maximize the power of the Wald test for a treatment difference. However, the former procedure being discrete tends to be slower in converging towards the expected target allocation proportion. The link function based design achieves the highest skewness of patient allocation to the best treatment arm and thus ethically is the best design. Other comparative merits of the proposed designs have been highlighted and their preferred areas of application are discussed. It is concluded that the proposed CARA designs can be considered as suitable alternatives to the traditional balanced randomization designs in survival trials in terms of the power of the Wald test, provided that response data are available during the recruitment phase of the trial to enable adaptations to the designs. Moreover, the proposed designs enable more patients to get treated with the better treatment during the trial thus making the designs more ethically attractive to the patients. An existing clinical trial has been redesigned using these methods.

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