Precision Generalized Phase I-II Designs for Personalized Dose Optimization

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Abstract

A new family of precision Bayesian dose-finding designs, PGen I-II, based on early efficacy, early toxicity, and long-term time to treatment failure is proposed. A PGen I-II design generalizes a Gen I-II design by accounting for patient heterogeneity characterized by patient subgroups. A PGen I-II design makes subgroup-specific decisions, which include dropping an unacceptably toxic or inefficacious dose, randomizing patients among acceptable doses, and identifying a best dose in terms of overall treatment success, which is defined in terms of time to failure over long-term follow up. A piecewise exponential distribution for failure time is assumed, including subgroup-specific effects of response, toxicity, and dose. Latent subgroup variables are used to adaptively cluster subgroups found to have similar dose-outcome distributions, with the model simplified adaptively to borrow strength between subgroups in the same cluster. A simulation study is reported that shows the PGen I-II design is superior to designs that either assume patient homogeneity or conduct separate trials within subgroups.

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