OPTIMAL DESIGNS FOR CLINICAL TRIALS WITH SECOND-ORDER POLYNOMIAL TREATMENT EFFECTS

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The effect of adding intermediate measures on the efficiency of treatment effect estimation is considered for a second-order polynomial treatment effect, equidistant time-points, different covariance structures and two optimality criteria, assuming either a fixed sample size or a fixed budget. The benefit of adding intermediate measures (at the expense of subjects) depends strongly on the assumed covariance structure and is hardly affected by the two used optimality criteria (D_s or c). For a fixed sample size, the increase in efficiency by adding intermediate measures is large for a compound symmetric structure and small for a first-order auto-regressive structure. For a first-order autoregressive structure with measurement error, the results depend on the covariance parameter values. For a fixed budget and linear cost function, the design with only three measures per subject is often highly efficient. If the structure resembles compound symmetry and the cost per subject is eight or more times larger than the cost per repeated measure, however, more than three measures are required to obtain highly efficient treatment effect estimators. If the covariance structure is unknown, the optimal design based on a first-order autoregressive structure with measurement error is preferable in terms of robustness against misspecification of the covariance structure. Given a design with three repeated measures and a second-order polynomial treatment effect, equidistant time-points are either optimal (D_s-) or highly efficient (c-optimality criterion). The results are illustrated by a practical example.