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Frailty Models in Cluster-Randomized Clinical Trials

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Background

Frequently, the design of a study involves clusters of individuals who have in common some factor that might influence the outcome of interest (for example, the outcomes of patients treated at the same clinic might be more similar to each other than to the outcomes of patients treated at a different clinic). This design requires consideration of the relevant components of variability arising both within and among the clusters. One simplifying assumption for the analysis in such a design is that each cluster contributes its own "random effect" to the outcome and that the distribution of these "random effects" follows some known distribution, usually a normal distribution.

A more complex situation extends this "random effects" logic to the design of a study in which the outcome of interest is time-to-event. Time-to-event data are common in clinical studies and are generally analyzed through survival models, such as the Cox proportional hazards model. However, when analyzing clusters of individuals, the models are termed "frailty" models to incorporate some unobserved differential survival probabilities among clusters. Commonly, a "shared frailty model" is assumed, whereby the random effect is a positive random variable that has a multiplicative effect on the individual hazard. The distribution of this random effect is frequently modeled as a Gamma distribution. Power calculations for such a study are a level of magnitude more complex than those for random effects linear or logistic regression models.

Power calculations in the design of a clinical study often rely on simplifying assumptions in order to make the solution tractable. To ensure adequate power, these assumptions tend to be deliberately conservative and typically cover a range of possible scenarios. When the outcome is dichotomous, the calculation frequently assumes a standard logistic regression model and includes the treatment as a covariate, possibly adjusting for other covariates. Statistical power under this scenario is relatively straightforward with the use of simulation. However, when the outcome is extended to capture time-to-event rather than a

dichotomous event, the estimation of power becomes more complex, especially when groups of subjects have some common affiliation.

Next Steps

A question worth investigating is the extent to which the use of the logistic model can be considered conservative for calculating statistical power for a time-to-event model. It is generally the case that a statistical test for treatment effect on a continuous outcome will be more powerful than the corresponding test applied to the binary outcome that is constructed by dichotomizing the continuous outcome. It may be that power calculations based on a logistic regression model would be conservative relative to the actual calculations based on a time-to- event variable. The question then arises of whether simplifying power calculations for a frailty model to those of a random-effects logistic regression model represents a conservative approach.

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