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An Approach for Estimation in Hierarchical Clustered Data Applicable to Rare Diseases

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Abstract : Practical considerations lead to the use of unit of analysis within subjects, e.g., bleeding episodes or treatment-related adverse events, in rare disease settings. This is coupled with data augmentation techniques such as extrapolation to enlarge the subject base. In general, one can think about extrapolation of data as extending information and conclusions from one estimand to another estimand. This approach induces hierarchichal clustered data with varying cluster sizes. Extrapolation of clinical trial data is being accepted increasingly by regulatory agencies as a means of generating data in diverse situations during drug development process. Under certain circumstances, data can be extrapolated to a different population, a different but related indication, and different but similar product. We consider here the problem of estimation (point and interval) using a mixed-models approach under an extrapolation. It is proposed that estimators (point and interval) be constructed using weighting schemes for the clusters, e.g., equally weighted and with weights proportional to cluster size. Simulated data generated under varying scenarios are then used to evaluate the performance of this approach. In conclusion, the evaluation result showed that the approach is a useful means for improving statistical inference in rare disease settings and thus aids not only signal detection but risk-benefit evaluation as well.

Keywords : clustered data, estimand, extrapolation, mixed model
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