PROJECT

Interaction tests in clinical trials

proposed jointly by

International Drug Development Institute (IDDI)

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BACKGROUND

In randomized clinical trials of new drugs, there is increasing interest in testing interactions between the effect of treatment and the presence of potential "predictive" factors. A factor can be any patient or disease characteristic, a biomarker or a gene profile measured at baseline. Often a factor is thought to be predictive, but a definitive trial is required to confirm that the effect of treatment is indeed modulated by the presence of the factor. For the sake of simplicity, the factor can be dichotomized, i.e. considered absent or present. There are very few references on sample sizes required to confirm that a factor is indeed predictive. Even if one restricted focus on survival outcomes, a fully general sample size calculation software would be difficult to develop because it would depend on many parameters, including the duration and rate of accrual, the duration of follow-up, the rate of attrition, the distribution of the factor, the baseline hazard for the two factor levels, and the treatment effects in the two factor levels. Simulations could be quite helpful to calculate the sample size required for any combination of these parameters, and to assess the sensitivity of the sample size to a change in these parameters.

PROJECT DESCRIPTION

This project will consist of

1. reviewing the literature on predictive factors and interaction tests;
2. participating to the development, testing and validation of a simulation package for the determination of sample sizes required to detect interactions;
3. using the simulation package to design trials aimed at detecting both main effects and interactions;
4. writing up a summary paper to describe the approach and the main findings.

PRE-REQUISITES

No particular theoretical background is needed for the project, unless the student wishes to contrast some theoretical results with those obtained through simulation. Proficiency in SAS and/or Excel and/or Visual Basic would be an asset.

LOCATION & SUPERVISION

The project can be carried out anywhere, providing the students can plan regular visits to the offices of IDDI in Ottignies Louvain-la-Neuve. The project will be carried out in collaboration with IDDI and Cytel Inc. It will be supervised by Marc Buyse and Linda Danielson at IDDI, and by Prof Suresh Ankolekar, who will lead the development of the simulation package for Cytel Inc.

REFERENCES

1. Peterson B, George SL: Sample size requirements and length of study for testing interaction in a 2 x k factorial design when time-to-failure is the outcome. Controlled Clinical Trials 14:511–22, 1993.
2. Betensky RA, Louis DN, Cairncross JG. Influence of unrecognized molecular heterogeneity on randomized clinical trials. J Clin Oncol. 20:2495-9, 2002.

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