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Einladung zum Sample Size Seminar (Adventseminar)

des Zentrums für Medizinische Statistik, Informatik und Intelligente Systeme und der Wiener Biometrischen Sektion (WBS) der Internationalen Biometrischen Gesellschaft (IBS), Region Österreich – Schweiz (ROeS)

Datum & Zeit: Montag, 19. Dezember 2016, 9:00-12:30 Uhr

Ort: Seminarraum, Rektoratsgebäude (BT88), 3. Stock, Raum 513
Medizinische Universität Wien, Spitalgasse 23, 1090 Wien
Plan siehe http://cemsiis.meduniwien.ac.at/allgemeines/anschrift/

Agenda

09:00 – 10:30 Session 1 Chair: Martina Mittlböck

- Axel Benner (DKFZ Heidelberg): One for All - the Schoenfeld Formula
- Julia Krzykalla (DKFZ Heidelberg): Sample Size Calculation for High-Dimensional Molecular Data

10:30 – 11:00 Kaffeepause

11:00 – 12:30 Session 2 Chair: Harald Heinzl

- Gernot Wassmer (Medizinische Universität Wien): Sample Size Calculation for Group Sequential Designs with Small Samples
- Florian Klinglmüller (Medizinische Universität Wien): Randomization Tests for Adaptive Designs with Sample Size Reassessment
- Thomas Ondra (Medizinische Universität Wien): Optimized Adaptive Enrichment Designs for Clinical Trials with a Sensitive Subpopulation

Wir freuen uns über eine rege Teilnahme am Seminar.

One for All - the Schoenfeld Formula

Axel Benner

Division of Biostatistics, German Cancer Research Center, Heidelberg, Germany

First sample size calculations for time to event endpoints were published in the early seventies. George & Desu (1974) presented a simple formula for the required number of events to compare the length of time to event in two treatment groups assuming exponentially distributed event times. Their formula remains the core of many methods used today. However, most often it is referred to the later work of Schoenfeld (1981, 1983). Schoenfeld extended George & Desu's formula by computing the required sample size depending on the probability of an event during the study. But, more important, Schoenfeld could show that his formula is valid for the log rank test and extendable to proportional hazards regression including concomitant covariates. We will provide an overview and discussion of forty years of sample size calculation based on the formula of Schoenfeld and its predecessors. This includes sample size calculation under stratification, and proportional hazards models for a binary treatment covariate where correlated covariates are included in the model. Other examples consider power calculation for nested case-control or case-cohort sampling strategies.

References

George S, Desu M (1974). Planning the size and duration of a clinical trial studying the time to some critical event. Journal of Chronic Diseases 27:15-24.

Schoenfeld DA (1981). The asymptotic properties of nonparametric tests for comparing survival distributions. Biometrika 68:316-319.

Schoenfeld DA (1983). Sample-size formula for the proportional-hazards regression model. Biometrics 39:499-503.

Sample Size Calculation for High-Dimensional Molecular Data

Julia Krzykalla

Division of Biostatistics, German Cancer Research Center, Heidelberg, Germany

Thorough planning and designing of an experiment is crucial for its success. This is even more the case when dealing with high-dimensional molecular data. In the final analysis, the molecular variables can either play the role of the dependent variables (differential expression analysis) or that of the independent variables (identification of prognostic factors).

Due to the fact that the required sample size has to be assessed with respect to not only a single variable but a set of variables, the terms of power and test error have to be adapted to fit the characteristics of a multiple testing scenario.

A particular problem when dealing with such kind of data is that these variables are strongly correlated and distribution assumptions are often questionable. Therefore, it might not be appropriate to use a multiple testing adjustment applied to some simple closed formula. As an alternative, tools try to capture the complexity of the data by a set of parameters which exceeds those of one particular distribution. For example, for RNASeq data, the library size acts as a normalizing factor on the mean of the negative binomial distribution. The required sample size is then determined by means of simulations. Another idea would be to use a real data and manipulate it such that the parameters of interest are known with certainty, a so-called Plasmode data set.

An overview over these methods for sample size calculation of varying complexity will be given and their advantages and pitfalls will be discussed.

Sample Size Calculation for Group Sequential Designs with Small Samples

Gernot Wassmer

Section for Medical Statistics, CeMSIIS, Medical University of Vienna, Austria

Group sequential trials were introduced by testing the hypothesis about a normal mean, the variance to be known, and by assuming the independent and normally distributed increments structure. Based on this "prototype case", the decision regions are derived and sample size calculations (maximum and average sample size) can be performed. For other designs, e.g., the t test situation, testing a binary endpoint or the survival case, these computations can be used to provide approximately valid testing procedures. In this talk, the basic computations are described and the way of how to perform a sample size calculation in more general cases is provided. The approximate validity of the test procedures is assessed by simulation or direct computation and it is shown were a suitable adjustment should be used.

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Literature

Wassmer, G. and Brannath, W. (2016). Group Sequential and Confirmatory Adaptive Designs in Clinical Trials. Springer Series in Pharmaceutical Statistics.

Randomization Tests for Adaptive Designs with Sample Size Reassessment

Florian Klinglmüller

Section for Medical Statistics, CeMSIIS, Medical University of Vienna, Austria

Adaptive designs use information emerging from an ongoing clinical trial to perform mid-trial design modifications. Most of the available test procedures for adaptive designs rely on restrictive assumptions about the distribution of outcome measures and test statistics. We propose a frame-work of randomization tests for confirmatory adaptive designs that provides control of the Type I error rate under minimal distributional assumptions. One limitation of the proposed approach is that sample sizes may not be reduced. To address this, we suggest efficient rules for adaptive sample size extension, that on average require fewer samples to achieve the same power as corresponding fixed sample designs. We show that the proposed tests are robust in terms of power for a wide variety of outcome distributions and outperform existing parametric and nonparametric tests for adaptive trials, especially when sample sizes are small.

Optimized Adaptive Enrichment Designs for Clinical Trials with a Sensitive Subpopulation

Thomas Ondra[1], Sebastian Jobjörnsson[2], Carl-Fredrik Burman[3,4], Franz König[1] and Martin Posch[1]

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An important objective in the development of targeted therapies is to identify subgroups of patients where the treatment under investigation has a positive benefit risk balance. We are considering clinical trials investigating a treatment in a subpopulation (*S*), defined by a binary biomarker, as well as the full population (*F*), consisting of biomarker positive patients (*S*) and biomarker negative patients (*S'*). Based on a decision theoretic approach, assigning gains and losses to a particular trial design we compare optimized single stage and adaptive two stage designs. We model the gains of a particular trial design from both the sponsor's (reflecting commercial interests) as well as a societal view (reflecting public health interests). For single stage designs we optimize the number of patients from *S* and *S'* to be included in the trial. The optimization of adaptive two stage designs relies on a dynamic programming approach as well as extensive numerical calculations. In particular we optimize the number of patients to be included from *S* and *S'* in the first stage and present optimized decision rules, assigning an optimized second stage trial design to a given interim observation. The optimizations are performed for both the sponsor's and the public health utility.

This project has received funding from the European Union's 7th Framework Programme for research, technological development and demonstration under the IDEAL Grant Agreement no 602552, and the InSPiRe Grant Agreement no 602144.