Wiener Biometrische Sektion (WBS)
der Internationalen Biometrischen Gesellschaft
Region Österreich – Schweiz (ROeS)
http://www.meduniwien.ac.at/wbs/
WBS Herbstseminar 2015

ADVANCES IN TRIAL DESIGN

Datum&Zeit: Mittwoch 7. Oktober 2015, 9-13 Uhr
Ort: Seminarraum (Ebene 3, Raum 88.03.513) des Zentrums für Medizinische Statistik, Informatik und Intelligente Systeme (CeMSIIS) der Medizinischen Universität Wien, Bauteil 88 – Ebene 3, Spitalgasse 23, 1090 Wien
Plan siehe http://cemsiis.meduniwien.ac.at/allgemeines/anschrift/

AGENDA

Session 1		Chair: Franz König
9.00-9.10	Franz König	Welcome and Introduction
9.10-9.55	Toshimitsu Hamsaki	Sizing clinical trials when comparing two interventions with bivariate time-to-event data
9.55-10.25	Kentara Sakamaki	Study duration extension using blinded survival data
10.25-10.40	Discussion	
10.40-11.00	Break	
Session 2		Chair: Martin Posch
11.00-11.20	Gerd Rosenkranz	Remarks on designs enriching for placebo non-responders
11.20-11.40	Matthias Brückner	Group-Sequential Permutation Tests for Survival Data
11.40-12.00	Faidra Stavropoulou	Optimization of the euglycemic clamp in mice
12.00-12.20	Susanne Urach	Group sequential designs for Clinical Trials with multiple treatment arms
12.20-12.40	Franz König, Martin Posch	Discussion and Wrap-up
13.00 –	Informal lunch, Come together	

Registration of attendance (free): per e-mail to franz.koenig@meduniwien.ac.at until 5 Oct 2015.
Please feel free to distribute the announcement to colleagues. The WBS runs a mailing list for announcing talks in the field of biostatistics. For subscription to the mailing list, send an e-mail to franz.koenig@meduniwien.ac.at as well.

Abstracts

Sizing clinical trials when comparing two interventions with bivariate time-to-event data

Toshimitsu Hamsaki
National Cerebral and Cardiovascular Center, Japan

The use of two time-to-event outcomes as primary endpoints is common in clinical trials evaluating interventions in medical areas such as infectious disease, oncology, or cardiovascular disease. For example in anti-cancer drug trials, the most commonly used primary endpoint is overall survival (OS) defined as the time from randomization until death from any cause. OS often requires a considerable follow-up period which leads to a long and expensive study. Therefore, many clinical trials now also include progression-free survival (PFS) (defined as the time from randomization until the first of tumor progression or death from any cause) as a short-term primary endpoint. We have previously developed a logrank test-based method using the normal approximation, for sizing clinical trials with two primary time-to-event outcomes under three bivariate exponential distributions when both events are non-fatal and each event-time is not censored by other event. We extend these results to accommodate three additional situations: (1) when one is fatal, (2) when one is fatal and the other is a composite including the fatal event, (3) when both are fatal. We also assume that the association between the two time-to-event dependent could be change with time and consider the two situations of the asymmetric late (tail) dependence and the early (tail) dependence. We derive correlation structure between the test statistics for each situation. With application to sample size determination, we consider the two inferential goals of clinical trials with multiple endpoints: (1) “multiple co-primary endpoints” (i.e., the trial is designed to evaluate if the intervention is superior to the control on all endpoints), and (2) "multiple primary endpoints" (i.e., the trial is designed to evaluate if the intervention is superior to the control on at least one endpoint). We evaluate how the sample size behaves with design parameters including censoring scheme and time-dependent association.

Study duration extension using blinded survival data

Kentara Sakamaki
Yokohama City University, Japan

Sample size and study duration for clinical trials with survival data are calculated based on the expected number of events. In some trials, the actual number of events at the end of planned study duration is lower than the expected number of events. This may be because the actual survival probabilities are higher than the expected survival probabilities, or because the experimental treatment is more effective than expected. Clinical trials may be continued if the former is true. However, we can finish clinical trials if the latter is true. When the enrollment is finished, we would like to determine the extension of follow-up period using blinded survival data because any interim analysis is not planned. In this talk, we propose Bayesian method for study duration adjustment and compare with existing method based on simulation study.

Remarks on designs enriching for placebo non-responders

Gerd Rosenkranz
Novartis Pharma AG, Basel, Switzerland

High response under placebo constitutes a concern in clinical studies, particularly in psychiatry. Discontinuation of placebo responders identified during a placebo run-in is often recommended to avoid failures of clinical trials in the presence of high placebo effects. Evidence for the benefit of this approach is ambiguous. We investigate under which conditions a placebo lead-in can be beneficial in the context of continuous data assuming that the data in the placebo run-in and the treatment stage follow a bivariate normal distribution. Placebo responders are defined as patients with an effect larger than a pre-defined threshold during placebo lead-in. As a result, data are less variable under either placebo or test treatment after placebo non-responders have been removed. Whether the effect of test over placebo increases or decreases after enrichment for placebo non-responders depends on the parameters of the distribution, in particular the covariance structure, and the threshold in the definition of placebo responders. The findings explain to some extent the ambiguity in the assessments of the usefulness of placebo lead-in periods in clinical trials, however, besides the clear statement on variability reduction, it is not straightforward to judge upfront whether placebo lead-in is useful.

Group-Sequential Permutation Tests for Survival Data

Matthias Brückner
Medical University of Vienna, Austria
University of Bremen, Germany

For small sample sizes the type-I-error of the asymptotic log-rank test and related linear rank tests may be inflated. In such cases permutation tests can be used instead. Mehta et al. [1] have developed a network algorithm for exact group-sequential permutation tests for general linear rank tests, which works also for censored data. However, standard permutation tests are only valid when the underlying censoring distributions are equal in both groups. To overcome this problem, approximate permutation tests using (multiple) imputation have been developed by Heinze et al. [2] and Wang et al. [3] for fixed sample size trials, which remain valid even when the censoring distributions differ between the treatment groups. We adapt these imputation-permutation tests to the group-sequential setting and compare the methods in a simulation study for group-sequential trials with up to two interim analyses.

References

[1] C. R. Mehta, N. Patel, P. Senchaudhuri, A. Tsiatis, Exact Permutational Tests for Group Sequential Clinical Trials, Biometrics, 50, 1042-1053, 1994.
[2] G. Heinze, M. Gnant, M. Schemper, Exact Log-Rank Test for Unequal Follow-Up, Biometrics, 59, 1151-1157, 2003.
[3] R.Wang, S. W. Lagakos, R. J. Gray, Testing and interval estimation for two-sample survival comparisons with small sample sizes and unequal censoring, Biostatistics, 11:4, 676-692, 2010.

Optimization of the euglycemic clamp in mice

Faidra Stavropoulou
Medical University of Vienna, Austria

We are dealing with the optimization of the euglycemic hyperinsulinemic clamp test in mice, the gold standard test in diabetes research for the quantification of insulin resistance. The problem falls in the area of real-time optimal control under parametric uncertainty. In a Bayesian framework, we combine a model predictive control type approach based on the exact solution of the control optimization problem with a sequential Monte Carlo step for the parameter estimation. The method relies on the representation of the parameters and of the unknown state of the system by their polynomial chaos expansions. The latter are approximations of arbitrary random variables in polynomials of random variables with given distribution.

Group sequential designs for Clinical Trials with multiple treatment arms

Susanne Urach and Martin Posch
Medical University of Vienna, Austria

For the comparison of several experimental treatments, doses or dosis regimens to a control, recently several multi-armed group sequential clinical trial designs have been proposed. They allow one to stop randomization to individual arms early if the corresponding null hypothesis can be rejected in an interim analysis. To minimize the required number of patients, we consider a variant of such designs where the overall trial stops as soon as for any of the arms the null hypothesis of no treatment effect can be rejected. While standard multi-armed group sequential designs control the type I error rate if such a stopping rule is used, they are typically strictly conservative. This can be explained by the fact that treatment arms for which no rejection can be achieved at the interim analysis could be further tested in the final analysis if the trial was continued. For the comparison of two experimental treatments we derive improved stopping boundaries that exhaust the type I error rate for stopping rules where the trial is stopped as soon as a null hypothesis can be rejected. We search for optimized boundaries that minimize the expected sample size while maximizing the probability to show efficacy in both arms. We compare the operating characteristics of these optimized designs to standard multi-armed group sequential designs. Furthermore, several extensions as trials with futility boundaries and group sequential t-tests for small sample sizes are discussed.