Wiener Biometrische Sektion (WBS)
der Internationalen Biometrischen Gesellschaft
Region Österreich – Schweiz (ROeS)

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WBS Winter Seminar 2014

Innovative Statistical Approaches in Drug Development

Jointly organized with the EU FP7 project IDeAl

Datum: Dienstag, 2.Dezember

Ort: Jugendstilhörsaal der Medizinischen Universität Wien,
Bauteil 88 – Ebene 3, Spitalgasse 23, 1090 Wien
Plan siehe http://cemsiis.meduniwien.ac.at/allgemeines/anschrift/

Beginn: 13:30 Uhr (s.t.)

Ende: 18:00 Uhr

Vorsitz: Franz König & Martin Posch (CeMSIIS, Med. Univ. Wien), Stephan Lehr (Baxter Innovations GmbH)

AGENDA

13:00 – 13:30   Registration and get-together

13:30-15:30   Session 1, Chair: Franz König

- **Ralf-Dieter Hilgers** (Institut für Medizinische Statistik, RWTH Aachen)
  Some Aspects of Clinical Trials in Small Population Groups with Special Interest in Randomization
- **Stephen Senn** (Competence Center in Methodology and Statistics, CRP-Santé)
  Seven myths of randomization
- **Sergii Krasnozhon** (CeMSIIS, Med. Univ. Wien)
  Adaptive designs for confirmatory model based decisions using MCP-Mod

15:30 – 16:00   *Break (Foyer)*

16:00-18:00   Session 2, Chair: Martin Posch

- **William F. Rosenberger** (Department of Statistics, George Mason University)
  Bayesian Dose-Finding Procedure Based on Compound Information and Ethical Criteria
- **Holger Dette** (Lehrstuhl für Stochastik, Fakultät für Mathematik, Ruhr-Universität Bochum)
  Statistical inference for comparing dose-response curves
- **Gerald Hlavin** (CeMSIIS, Med. Univ. Wien)
  Adapted levels of Evidence for small populations. Evidence, Eminence & Extrapolation

18.30 –   Informal debriefing in Altes AKH

Registration of attendance (free): per e-mail to franz.koenig@meduniwien.ac.at until 1 December 2014.
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.

Innovative Statistical Approaches in Drug Development
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Some Aspects of Clinical Trials in Small Population Groups with Special Interest in Randomization
Ralf-Dieter Hilgers (Institut für Medizinische Statistik, RWTH Aachen)

Seven myths of randomization
Stephen Senn (Competence Center in Methodology and Statistics, CRP-Santé)

One frequently hears that the common analysis of randomised trial is valid to the extent that randomisation ensures the equal distribution of all-confounders. In fact, this is incorrect. If all confounders were balanced the common analysis of randomised clinical trials would be incorrect for the same reason that the analysis of a matched-pairs design as if it was a completely randomized design would be incorrect. In fact, the common analysis of clinical trials is valid not despite potential imbalance but precisely because such imbalance exists. What the critics of randomisation have overlooked is that inference is based upon a ratio and that confounders affect the denominator as well as the numerator and that the greater the uncontrolled effect of covariates, the greater the effect on both. Heterogenous trials with uncontrolled unseen confounders produce, other things being equal, wider confidence intervals and this is enough.

I discuss this and other myths of randomization and conclude that debate in this field would be much improved if those contributing to it make concrete suggestions tested against real practice as to possible alternatives to randomization rather than merely make vague suggestions as to what might be done better.

Adaptive designs for confirmatory model based decisions using MCP-Mod
Sergii Krasnozhon (CeMSIIS, Med. Univ. Wien)

Adaptive seamless designs for confirmatory clinical trials have attracted a lot of attention because they offer the possibility to combine different phases of drug development into a single trial. This is of paramount interest in small populations, e.g., when developing drugs for rare diseases. Though the sample size is limited still an appropriate dose has to be found and sufficient evidence for its efficacy to be demonstrated.
We propose adaptive clinical trial designs with multiple doses and use modelling approaches to (i) establish a positive dose-response profile, (ii) increase the power of declaring effective dose statistically significant, and (iii) support dose selection at an adaptive interim analysis. We extend MCP-Mod methodology to adaptive two-stage designs by using the closed-testing principle and applying an adaptive combination test to each intersection hypothesis. Combining the data from both stages in adaptive confirmatory designs allow for flexible interim decisions based on all (interim) data available of the ongoing trial while always ensuring strict type I error control. In particular, the MCP-Mod approach can be used to obtain model-based dose effect estimates at interim to guide early futility stopping and/or re-design the second stage (e.g. choice of doses, sample size, allocation ratio) and analysis (e.g., dropping of inadequate response models). By the means of clinical trial simulations we show the operating characteristics (e.g., power for PoC or individual dose-control comparison, bias of effect estimates) for specific adaptations rules.

Bayesian Dose-Finding Procedure Based on Compound Information and Ethical Criteria

William F. Rosenberger (Department of Statistics, George Mason University)

In dose-finding studies with toxicity-efficacy responses, penalty functions and Bayesian procedures are used to find a single optimal dose with ethical toxicity-efficacy trade-offs. It has been widely seen that such designs can select the wrong dose when the working prior is wrong, largely due to a "stickiness" property of miring at a single dose. As one possible remedy, we present a family of compound optimal designs that involve both efficiency of estimation for updating prior parameters and the ethical criteria that minimize highly toxic or ineffective doses. It is shown that most Bayesian sequential designs for dose finding in the literature can be thought of as a special case of this family of designs. We conduct simulations using Markov chain Monte Carlo (MCMC) algorithms to examine the convergence of Bayesian dose finding designs and investigate their operating characteristics. A stopping rule is considered to protect the patients. We use a hypothetical trial redesign to illustrate how graphics and simulation can aid the trial designer in selecting priors and the tuning parameter of the compound optimization in practice.

William Rosenberger is University Professor and Chairman, Department of Statistics, George Mason University (GMU). He received his PhD in Mathematical Statistics from George Washington University in 1992 and was the 2nd recipient of the David Byar Award in 1995. He is a Fellow of the ASA (2005), IMS (2011), was named the Outstanding Research Faculty in the Volgenau School of Engineering, GMU (2012), and was promoted to the highest honorary rank of University Professor at GMU this year. Prof. Rosenberger has authored over 80 refereed papers and two books. He is currently working on the second edition of the first book, Randomization in Clinical Trials: Theory and Practice, as a Fulbright Scholar at RWTH University, Aachen, Germany.

His areas of research interest include randomization, optimal and adaptive designs, sequential analysis, and clinical trials.

Statistical inference for comparing dose-response curves

Holger Dette (Lehrstuhl für Stochastik, Fakultät für Mathematik, Ruhr-Universität Bochum)

This talk discusses methods for establishing the similarity between two dose-response curves. A bootstrap approach is proposed, which substantialy improves current methodology. Moreover, in the second part of the talk, we demonstrate that the use of optimal design provides a substantial
improvement in the power of such tests.

Adapted levels of Evidence for small populations. Evidence, Eminence & Extrapolation

Gerald Hlavin (CeMSIIS, Med. Univ. Wien)

A full independent drug development programme to demonstrate efficacy may not be ethical and/or feasible in small populations such as paediatrics populations or orphan indications. Different levels of extrapolation from a larger population to smaller target populations are widely used for supporting decisions in this situation. There are guidance documents in drug regulation, where a weakening of the statistical rigour for trials in the target population is mentioned to be an option for dealing with this problem. To this end we propose clinical trials designs, which make use of prior knowledge on efficacy for inference.

We formulate a framework based on prior beliefs in order to investigate when the significance level for the test of the primary endpoint in confirmatory trials can be relaxed (and thus the sample size can be reduced) in the target population while controlling a certain posterior belief in effectiveness after rejection of the null hypothesis in the corresponding confirmatory statistical test.

We show that point-priors may be used in the argumentation since under certain constraints they have favourable limiting properties among other types of priors.

The crucial quantity to be elicited is the prior belief in the possibility of extrapolation from a larger population to the target population. We try to illustrate an existing decision tree for extrapolation to paediatric populations within our framework.