MEDIZINISCHE UNIVERSITÄT WIEN

Summer Symposium 2016

To New Shores in Drug Development
Implementing Statistical Innovation

Date: Monday, June, 27
Location: Jugendstilhörsaal der Medizinischen Universität Wien,
Bauteil 88 – Ebene 3, Spitalgasse 23, 1090 Wien
Map see http://cemsiis.meduniwien.ac.at/allgemeines/anschrift/
Start: 14:00 (s.t.)
End: 17:30
Organiser: Institut für Medinische Statistik, Zentrum für Medizinische Statistik, Informatik, und Intelligente Systeme, Medizinische Universität Wien
Wiener Biometrische Sektion (WBS) der Internationalen Biometrischen Gesellschaft Region Österreich – Schweiz (ROeS)

AGENDA

13:45 – 14:00 Registration and get-together

14:00-15:30 Session 1 - Chair: Franz König

- **Willi Mauer** (Novartis Pharma AG)
  A robust combination test for sample size adaptation in a two-stage cross-over trial for Average Bioequivalence
- **Peter Bauer** (Medizinische Universität Wien)
  Flexibility in confirmatory clinical trials – what is for free?
- **Election WBS**

15:30 – 16:00 *Break (Foyer)*

16:00-17:15 PUBLIC LECTURE - Chair: Martin Posch

- **Welcome by a representative of Medical University of Vienna**
- **Frank Bretz** (Novartis Pharma AG)
  Changing the Culture of Drug Development: The Need to Implement Innovative Scientific Solutions
- **Cui honorem, honorem**
  - Awards of IBS-ROeS honoray membership to Peter Bauer and Willi Maurer
  - Appointment of Adjunct Professorship to Frank Bretz

17:15 – *Get-Together - Reception Foyer*

Registration of attendance (free): per e-mail to medstat@meduniwien.ac.at until 22 June 2016.
Please feel free to distribute the announcement to other 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 with the subject "SUBSCRIBE WBS" to medstat@meduniwien.ac.at as well.

Abstracts Summer Symposium 2016
2016-06-27

A robust combination test for sample size adaptation in a two-stage cross-over trial for Average Bioequivalence
Willi Maurer, Byron Jones, Ying Chen (Novartis Pharma AG)

In a single-stage 2x2 cross-over trial for testing Average Bioequivalence (ABE) of a generic agent and a currently marketed drug the presently recommended test is the two one-sided test (TOST) procedure. Four methods for sample size re-estimation in a two-stage 2x2 cross-over trial for testing ABE with the TOST procedure were presented in Potvin et al. (2008). However, none of these methods formally controls the Type I error rate of falsely claiming ABE. In fact, the assessment of a possible inflation in the error rate has to be done in an ad hoc way using simulation.
We describe an alternative method of sample size re-estimation that is exact and guaranteed to control the Type I error rate. This method uses a new version of the weighted combination of p-values test in conjunction with standard group sequential techniques that is more robust to large deviations in initial assumptions regarding the variability of the pharmacokinetic endpoints. The sample size re-estimation step is based on significance levels and power requirements that are conditional on the first-stage results. This necessitates a discussion and exploitation of the peculiar properties of the power curve of the TOST testing procedure. We compare the operating characteristics of the new method with those of the Potvin et al. (2008).

References:
Potvin, D., et al. (2008).Sequential design approaches for bioequivalence studies with crossover designs. Pharmaceutical Statistics, 7, 245-262.
Kieser, M. and Rauch, G. (2014). Two-stage designs for cross-over bioequivalence trials. Statist. Med., 34, 2403–2416.

Flexibility in confirmatory clinical trials – what is for free?
Peter Bauer (Medical University of Vienna)

It is discussed which changes of a pre-planned design with a pre-fixed confirmatory statistical analysis can be performed during the running trial so that the original statistical test can still be applied without inflating the type I error rate. Changes exclusively based on information from outside trial, unplanned stopping for futility, blinded sample size reassessment and pre-fixed adaptation rules (generally with adapted critical boundaries) are candidates for such changes where still the original test statistics can be used safely.
The maximum type error rate inflation when applying the original test in case of unconstraint mid-trial design changes modification may become large. However, putting realistic limitations on sample sizes and allocation ratios the option of constraint flexibility may not compromise on the type I error rate at all. If more flexibility is intended the adaptive design methodology may be applied.

Changing the Culture of Drug Development: The Need to Implement Innovative Scientific Solutions
Frank Bretz

The revolutionary advances in basic biomedical science that occurred over the past decade have, so far, failed to translate into comparable improvements in clinical therapies and drugs. In fact, the number of new drug applications and approvals has shown a decline over the same period. Part of the reason is that changing the culture of a pharmaceutical company requires long-term commitment and stamina to implement innovative scientific solutions. We share our experiences of developing, implementing and fostering the use of an efficient statistical methodology (MCP-Mod) for dose finding studies. The development of the method started more than 10 years ago as an internal initiative to enable a consistent use of good dose finding practices across our projects. Adoption of the method within the company and beyond has been helped by the engagement of the Pharmaceutical Research and Manufacturers of America (PhRMA) cross-industry working group on ‘Adaptive Dose-Ranging Studies’ as well as the availability of an extensive software implementation at the Comprehensive R Archive Network (CRAN). We provide an overview of the challenges that we experienced throughout this period and describe the factors that ultimately led to a successful broader implementation of the MCP-Mod methodology in our company.