Biostatistical Analysis in Epidemiological Research

1st – 2nd October 2015

Faculty of Medicine, "Lucian Blaga" University of Sibiu

Invited speakers:

Willi Sauerbrei - "Research in the health sciences needs improvement – on statistical methods as one relevant component and progress through recent initiatives" and "Recognizing Differential Subgroups Treatment Effects: Problems and Solutions in Modelling Continuous Covariates"

Marius Măruşteri - "Common and Less Common Errors in Epidemiological Research"

Moderator Round Table "Reporting and Ethics in Epidemiological Research":

Leonard Mada

Organizing Committee:

Elisabeta Antonescu (Faculty of Medicine, "Lucian Blaga" University, Sibiu)
Liana Bera (Faculty of Medicine, "Lucian Blaga" University, Sibiu)
Gabriela Cioca (Faculty of Medicine, "Lucian Blaga" University, Sibiu)
Loredana Vonica Gligor (Faculty of Medicine, "Lucian Blaga" University, Sibiu)
Anca Ignat (Faculty of Computer Science, "Alexandru Ioan Cuza" University of Iasi)
Mădălina Răschip (Faculty of Computer Science, "Alexandru Ioan Cuza" University of Iasi)
Silviu Morar (Faculty of Medicine, "Lucian Blaga" University, Sibiu)
Elena Podoleanu ("Carol Davila" University of Medicine and Pharmacy, Bucharest)
Manuela Pumnea (Faculty of Medicine, "Lucian Blaga" University, Sibiu)
Corina Vernic ("Victor Babes" University of Medicine and Pharmacy, Timisoara)
Anca Vitcu (Faculty of Computer Science, "Alexandru Ioan Cuza" University of Iasi)

Event developed under the aegis of the International Society for Clinical Biostatistics (ISCB).

Biographic Details

Willi Sauerbrei, PhD

Prof. Dr. rer. nat. Willi Sauerbrei is a senior statistician and professor in medical biometry at the Institute for Medical Biometry and Statistics, University Medical Center Freiburg, Germany. He has worked for more than 30 years as an academic biostatistician. He has extensive experience of cancer research and a long-standing interest in modeling observational data. He is the initiator and chair of the STRATOS (STRengthening Analytical Thinking for Observational Studies) initiative. Methodological topics of interest include variable and function selection, model stability, treatment-covariate interactions, time-dependent effects in survival analysis, meta-analysis and reporting of research findings.

https://portal.uni-freiburg.de/imbi/team?showEmployee=wfs

Marius Mărușteri, PhD

Prof. Dr. Marius Mărușteri is the Head of Medical Informatics and Biostatistics Department at the University of Medicine and Pharmacy, Târgu Mureș (Romania).

His research interests include fields like Large Medical Database Management, Molecular Databases, Medical E-learning, Advanced Wearable Medical Devices, Clinical Trials Design and Analysis, Applied (Bio)Statistics, Advanced Scientometrics and Bibliometrics etc.

Dr. Mărușteri is the author of 6 books in the field of Medical Informatics, Biostatistics, Experimental Pharmacology and Research Methodology, and of more than 80 scientific papers published in extenso in national and international journals.

He is a statistical reviewer for 2 Thomson ISI indexed journals and is working also as a consultant in the field of clinical trials design and statistical analysis for various Romanian and International companies.

In the last years, he was awarded with 9 Awards and Medals for his educational and scientific activities, including a Silver Medal at The International Exhibition of Inventions, Lublijana, Slovenia - 2010, and The Romanian National Order for Educational Merit, in the rank of Officer - 2004.

Leonard Mada

Dr. Leonard Mada is the Head of Research Department at Syonic SRL (Timisoara, Romania) in charge with the development of icMED system. He previously collaborated with JW. Goethe University, Frankfurt on infection diseases, tropical medicine and microbiological related issues and Department of Medical Informatics of the University of Medicine and Pharmacy (Timisoara) on image and signal processing, database management and eHealth. Dr. Mada also acted as medical adviser in the Department of Prognosis and Development at the County Health Insurance House (Timisoara) and clinical database manager and programmer at Cmed SRL (Timisoara).

Outline and Schedule

Thursday, 1st October

9:00-9:30 Introduction – **Anca Vitcu**

9:30-11:00 Research in the health sciences needs improvement – on statistical methods as one relevant component and progress through recent initiatives – **Willi Sauerbrei**

Abstract: *For many years the quality of research in the health sciences has been criticized and it is obvious that 'waste in research' has to be reduced (Ioannidiset al 2014). Problems in design, analysis and reporting of studies are among some of the most important reasons for this very disappointing situation. Already more than 80 years ago deficiencies in statistical methods and their applications have been raised (Dunn 1929) and were constantly expressed over time (Altman et al 1994, Sauerbrei 2005). Statistical methodology has seen substantial development, but many of them are ignored in practice and insufficient statistical knowledge in the research community is strongly emphasized in an article entitled 'Why most published research findings are false' (Ioannidis 2005). It is obvious that fishing for significant p-values produces many false positive results (Kyzas et al 2005).*

During the last two decades several initiatives have been started that aim at improving the research process. Obviously, transparent and complete reporting is a pre-requisite to judge the usefulness of data and to interpret study results in the appropriate context. For many different types of studies reporting guidelines have been developed and the EQUATOR network acts as an "umbrella" for developers of such guidelines (Simera et al 2010, Altman et al 2012).

Much more difficult is the development of guidance for the statistical analysis of observational studies. The STRATOS (STRengthening Analytical Thinking for Observational Studies) has recently been founded (Sauerbrei et al 2014). Currently there are nine topic groups (TG),all working on specific tasks such as study design, missing data, measurement error and misclassification or causal inference. TGshave started to review the literature and to work towards state-of-the-art documents. Emphasize of this talk will be on issues from TG2: Selection of variables and functional forms in multivariable analysis. Many published papers clearly illustrate that analyses have not been conducted by experienced statisticians but rather by analysts with low statistical knowledge. It is important that these have access to documents which clearly explain strengths and weaknesses of approaches

In the context of prognostic marker research I will discuss issues of good reporting and will show that improvement is needed and easily possible when authors, reviewers and editors follow reporting guidelines. The emphasis will be on model building with continuous variables. I will illustrate weaknesses of categorization, present model-building with fractional polynomials as a relatively simple and suitable approach for many cases, consider spline based approaches as a potential alternative and discuss the important role of model complexity to derive a suitable multivariable model for explanation.

Many others projects with influence on methodological quality of single studies and meta-analyses have been started. I will briefly discuss the main ideas behind study registration, all trials campaign, data sharing and reproducible research.

11:00-11:15 **Q & A**

11:15-11:30 *Coffee/Tea Break*

11:30-13:00 Round table moderated by **Leonard Mada** (topics: links between medical informatics/eHealth, biostatistics and computing science; ethical and legal aspects during the collection, archiving and processing of health data; methods for securing records and information exchange; networks related issues) - study case Romania (+ and - at practical level, things which can be done and investigate how can be implemented)

13:00-14:00 *Lunch* (La Turn, Piața Mare)

14:00-15:15 Common and less common errors in epidemiological research (study cases) – **Marius Mărușteri**

15:15-15:30 **Q&A**

15:30-15:45 Coffee/Tea Break

15:45-17:15 Common and less common errors in epidemiological research (study cases) – **Marius Mărușteri**

17:15-17:30 **Q&A**

19:00 Dinner (Hermania Restaurant)

Friday, 2nd October

9:30-10:15 Recognizing Differential Subgroups Treatment Effects: Problems and Solutions in Modelling Continuous Covariates – **Willi Sauerbrei**

Abstract **(Willi Sauerbrei & Patrick Royston)***:* When assessing the influence of prognostic covariates in regression models, continuous factors are often either categorized or linearity is assumed. However, both approaches can have major disadvantages and modelling non-linear functions may improve the fit. The multivariable fractional polynomial (MFP) approach simultaneously determines a suitable functional form and deletes weak or non-influential variables (Royston & Sauerbrei, 2008; Sauerbrei et al, 2007a).

In clinical trials there is considerable interest in investigating whether a treatment effect is similar in all patients or whether a subgroup of patients profits more from a treatment than the remainder. For a continuous covariate Z, the usual approach to analysis is to categorize Z into groups according to cutpoint(s) and either to estimate the treatment effect in subgroups or/and to test for an interaction between the categorized (usually binary) transformation of Z and treatment, with or without adjustment for other factors. As for prognostic covariates, the cutpoint approach raises several critical issues.

The MFP approach has been extended to MFPI to investigate for interactions of continuous covariates with treatment, or more generally with a categorical variable, (Royston & Sauerbrei, 2004). A 'treatment effect function' is estimated and an interaction is tested by using a likelihood ratio test. Four variants of MFPI, allowing varying flexibility in functional form for Z, were suggested. In a similar way spline based approaches can be used as an alternative to linearity. MFPI and spline approaches use the full information from the data and have the additional advantage that cutpoints are avoided.

In a large simulation study we investigated significance level and power of the MFPI approaches, compared with versions based on categorization and on cubic regression splines. We believe that the results provide sufficient evidence to recommend MFPI as a suitable approach to investigate for interactions of treatment with a continuous covariate (Royston & Sauerbrei 2013;2014).

Using an example we will briefly introduce an alternative that has sometimes been appliedin breast cancer research, the STEPP approach (subpopulation treatment effect pattern plot;Bonetti&Gelber, 2000). Issues of using STEPP will be illustrated by a comparison to result from MFPI (Sauerbrei et al, 2007b).

By using a new approach to average functions across trials (Sauerbrei and Royston 2011) and combine it with the results from MFPI analyses in several RCTs, we will propose a new meta-analysis strategy to investigate for differential subgroup treatment effects of continuous covariates. It will be illustrated using data from three randomized trials in acute lung injury. Compared to the popular cutpoint-based meta-analysis approaches it provides more detailed insight into whether treatment effects are influenced by a continuous variable (Kasenda et al, 2014).

10:15-10:30 **Q & A**

10:30-11:00 Coffee/Tea Break

11:00-12:30 Further discussions on reporting and ethics. Conclusions.

13:00 Lunch (Location Village Museum: http://www.muzeulastra.ro/)

Participation fee:
100 RON (Researchers and academic staff); 50 RON (Master and Doctoral students)

The fee payment is allowed until **25th September 2015**, in the following account:

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