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esf 2019 EUROPEAN STATISTICAL FORUM

10th European Statistical Forum

PRE-CONFERENCE **SEMINAR**

Analysis of safety data in clinical trials

Event rates, competing risks, varying follow-up times

Monday, **November 11th,** 2019

CONFERENCE

Statistical Methodology for the Assessment and Analysis of Risk and Safety Data in Clinical Development

Tuesday, **November 12th,** 2019

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Rome, Italy

Sheraton Parco De' Medici Rome Hotel

Via Salvatore Rebecchini, 145

Rome

Pre-Conference **Seminar**

· **Monday, November 11th, 2019**

Analysis of safety data in clinical trials

Event rates, competing risks, varying follow-up times

Introduction

Safety evaluation is a key aspect of any medical product development. The aim of this seminar is to give insights about structuring, analyzing and interpreting safety data recorded in clinical trials and observational studies, going through:

- review statistical methods for the analysis of adverse events;
- quantify the risk of false discoveries (false positive and false negative risk assessment);
- investigate and discuss conclusions drawn from the safety analysis and possible consequences.

Who is this course for?

The training is addressed to statisticians and clinical scientists analyzing and assessing drug safety data. Participants are supposed to have basic familiarity with adverse event recording in the pharmaceutical industry and some knowledge of statistical concepts and techniques.

Lecturer's Bio

Ekkehard Glimm is Senior Director in the Statistical Methodology group at Novartis Pharma AG; Basel, Switzerland, and a lecturer in Medical Statistics at the University of Magdeburg in Germany. He joined Novartis in 2005 wroking first on cancer trials, then moving to the statistical methodology group in 2006. He has 15 years of experience in planning and analysing clinical trials. Ekkehard has an MSc in Statistic from the University of Dortmnd and a PhD in Statistics from the University of Magdeburg. He has published around 30 papers on statistical methods and applications of statistics in medicine in perr-reviewed scientific journals.

Jan Beyersmann is professor of biostatistics and head of the Institute of Statistics at Ulm University, Germany.
Before moving to Ulm in 2013, he was with the Institute of Medical Biometry and Medical Informatics, University Medical Center Freiburg, Germany, from 2001 to 2012, where he also obtained in PhD in mathematics in 2005. His research interests are survival and event history analysis and statistical methodology for clinical trials. He is lead author of the 2012 Springer textbook Competing Risks and Multistate Models with R, jointly with Arthur Allignol and Martin Schumacher, and serves on the editorial boards of several biostatistical journals. Some of his views on the analysis of adverse events can be found in the open access paper On estimands and the analysis of adverse events in the presence of varying follow-up times within the benefit assessment of therapies, Unkel et al, Pharmaceutical Statistics. 2019;18:166–183.

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Programme

Part 1: adverse event types and signal detection | Lecturer: Ekkehard Glimm

Introduction

- MEDDRA hierarchy: system organ class to preferred terms
- Three types of adverse events: serious adverse events, adverse events of special interest, all other adverse event types
- Simple methods: event rates and incidence rates
- Quantifying risk or comparing with a standard of care?

Methodological basics

- Logistic regression and Poisson regression
- Dealing with overdispersion in Poisson regression
- Relations with time-to-event methods (see also part 2)
- Estimation, confidence intervals and testing for signals
- What to do when adverse events are rare

ADR screening

- Familywise error rate, false discovery proportion and false discovery rate
- False positive signals, false negative signals and risk assessment: How do we get the balance right?
- Simple methods for multiplicity adjustment
- Bayesian and frequentist hierarchical models

Example: Screening for adverse events in a large clinical phase III trial

- What is flagged?
- What might have been missed?
- Comparison of various methods for flagging events
- What do we do with the results?

Part 2 : time-to-event analyses and competing risks for safety data | Lecturer: Jan Beyersmann

Introduction

- Varying follow-up times, censored data: Why event rates (incidence proportions) do not account for censoring (and underestimate) and why incidence rates do (but overestimate).
- The missing link: How competing risks connect event rates and incidence rates for uncensored data, and what to do when data are censored (hazards, not Kaplan-Meier).
- Why Kaplan-Meier is an overused method (and an estimated 50% of all Kaplan-Meier curves not too good) and how to extend Kaplan-Meier to competing risks. (The trick is to decompose one minus Kaplan-Meier)
- What's worse? Ignoring competing risks or the constant hazard assumption underlying (exposure adjusted) incidence rates?
- A case study from an anonymous RCT

Methodological basics

- Independent, non-informative or random censoring? Not the same, and the difference matters
- Really, what are competing risks? Can we trust the textbook literature ("Competing risks are present when risks compete") and is progression a competing risk or informative censoring?
- (Non-) Parametric estimation of hazards and cumulative event probabilties (and their relation to frequency categories)
- Regression modelling, two-group comparisons: Cox or Fine-Gray? Log-rank or Gray? Or maybe Kolmogorov-Smirnov-type?
- Computer practical using R (with pointers to SAS and other statistical software packages)

Further topics

- Reports from a recent simulation study
- Reports from a recent methodological meta-analysis
- Recurrent events: Incidence rates, Andersen-Gill, Lin-Wei-Yang-Ying or Ghosh-Lin?

Agenda

13:00 - 13:30		Participants registration
13:30		Course commences
15:15 - 15:30		Coffee Break
17:30 - 17:45		Q&A and conclusion

At the end of the training, you will be able to...

- analyze safety data from clinical trials;
- have a better understanding of the relevance and the limitations of quantification of drug safety risks;
- recognize some potential pitfalls.

Statistical Methodology for the Assessment and Analysis of Risk andSafety Data in Clinical Development

In the past years, companies have increased their focus on the oversight and prevention of potential risks impacting individual clinical studies or the overarching clinical program success by means of subject well-being and protection, data quality and site performance as well as accuracy and correctness of final study results.

This change in perspective has been encouraged by regulatory authorities with both FDA and EMA guidelines released in 2013 for risk-based quality management of clinical investigations and with the release, in 2016, of the integrated addendum to the ICH E6 guideline, specifically addressing the need for a quality management system using a risk-based approach.

Besides continued attention to patient safety and its analysis, two new modalities are emerging in this changing landscape:

- The shift in attention from traditional de-centralized monitoring to centralized monitoring of clinical development programs facilitated by the advances in use of electronic data capture
- The need to use a risk-based approach using probabilistic methods in focusing resources and in detecting signals.

Statisticians have then been called to develop and implement methodologies for the detection of signals not only impacting subject safety but also potential operational flaws in the clinical study conduct, therefore using not only clinical but also operational data.

The challenges offered by these requirements involve solutions ranging from traditional frequentist methods to more sophisticated Bayesian approaches by means of predictive models as well as meta-analytic approaches, leveraging information across studies and company. In parallel, the introduction of Data Science methodologies through Artificial Intelligence and Machine Learning are offering compelling approaches on how to complement biostatistical methods.

The 10th European Statistical Forum is therefore dedicated to statistical methodologies for safety data analysis, risk assessment and signal detection. This will include presentations focusing on:

- New ways to display, summarize and analyze patient safety
- Innovative statistical methods for the identification of potential risks
- Methods to effectively design and conduct a risk management and signal detection program
- Regulatory view on the implementation of above-mentioned approaches
- Data Science solutions to increase the effectiveness of the monitoring of clinical studies
- Case studies and practical approaches

The conference aims at promoting the exchange of expertise, bringing together statisticians, physicians, regulators, academia and other experts interested in the field of safety data analysis, signal detection and risk management.

Scientific Board

Jens-Otto Andreas

Head Statistical Sciences & Innovation - Bone & New Diseases
at UCB Biosciences GmbH

Lisa Comarella

Director Biostatistics
at CROS NT

Giacomo Mordenti

Director, Statistics & Data Management
at Livanova

Marc Vandemeulebroecke

Global Group Head
at Novartis Biostatistics

Who should attend?

The conference is addressed to statisticians, pharmacometricians, physicians, regulators, academia and other experts interested in the field belonging to:

- Universities/Hospitals
- Academic Research
- Pharmaceutical, and Biotechnology companies
- CROs

Statistical Methodology for the Assessment and Analysis of Risk and Safety Data in Clinical Development

08:00 - 08:30 **Registration and welcome coffee**

08:30 - 08:40 **Welcome from the Scientific Board**

08:40 - 09:20 **Bridging the divide between efficacy and safety for time-to-event endpoint**

Andrew Thomson - *Statistician* at European Medicines Agency

09:20 - 10:00 **Statistical methods for the evaluation of toxicity and outcome in clinical studies**

Maria Grazia Valsecchi - *Professor of Medical Statistics* at University of Milano-Bicocca

10:00 - 10:40 **Rationale and some results from the "Survival analysis for AdVerse events with VarYing follow-up times" (SAVVY) project**

Tim Friede - *Professor of Biostatistics* at University Medical Center Göttingen

10:40 - 11:10 **Coffee break**

11:10 - 11:50 **Bayesian Models for Safety Signal Detection in Ongoing Blinded Studies**

Cindy McShea - *Safety Standards Lead, Statistical Sciences and Innovation* at UCB Biosciences, Raleigh, NC USA

Daniel Meddings - *Statistical Methodology Expert, Center of Excellence Statistical Innovation* at UCB Pharma, Slough, UC

11:50 - 12:30 **A Bayesian model for meta analyses of safety studies where the outcome is interval censored in some studies**

Manuel Wiesenfarth - *Biostatistician* at Cogitars

12:30 - 13:30 **Networking lunch**

13:30 - 14:10 **Final Rule' and blinded detection of an increased risk: sounds easy but isn't**

Matthias Trampisch - *Safety Statistician* at Boehringer Ingelheim

14:10 - 14:50 **A Mixed Models Approach to Confidence Interval Estimation for Clustered Safety Data Under an Extrapolation Setting**

Daniel Bonzo - *VP, Global Biometry* at LFB

14:50 - 15:20 **Coffee break**

15:20 - 15:50 **SafetyGraphics R Library – An Open-Source and Clinical Workflow for Assessing Hepatoxicity in Clinical Trials**

Zachary Skrivanek - *Research Advisor, Visual Analytics* at Eli Lilly and Company

15:50 - 16:30 **Longitudinal burden of therapy assessment in oncology clinical trials: applying the Burden of Therapy analysis to the EORTC-26101 trial**

Corneel Coens - *Lead statistician* at European Organisation for Research and Treatment of Cancer (EORTC)

16:30 **Conclusions**

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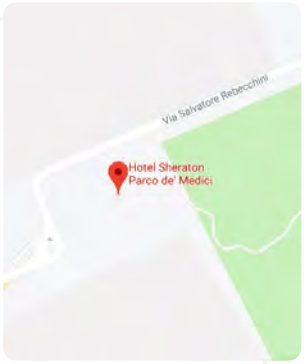
HOW TO REACH THE CONFERENCE VENUE

Venue

Sheraton Parco De' Medici Rome Hotel

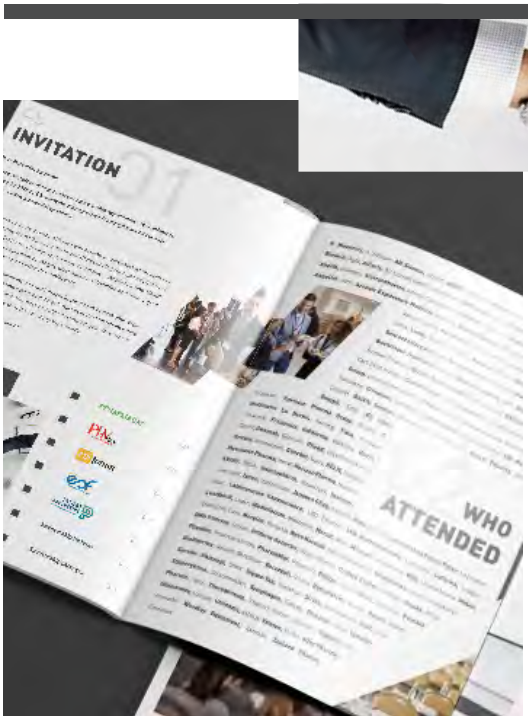
Via Salvatore Rebecchini, 145

Rome, Italy



The Sheraton Parco de' Medici Rome Hotel is located to the south west of Rome and near the New Roman Trade Fair, Fiumicino and Ciampino International Airports.

- **13 km** from Fiumicino International Airport
- **18 km** from Ciampino International Airport
- **18 km** from city centre



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For further information

Please visit the conference website or contact the organisational offices:

Ilaria Butta Phone: +39 (0)35.4123594 | ilaria.butta@lsacademy.com

REGISTRATION FORM CHOOSE YOUR TICKET TYPE

Pre-Conference **Seminar**

- Monday, November 11th, 2019

Conference

- Tuesday, November 12th, 2019

- REGISTRATION FEE FOR THE

SEMINAR + CONFERENCE

- ☐ **€ 1.090,00* Super Early Bird fee** until August 9th, 2019
- ☐ **€ 1.170,00* Early Bird fee** (until October 11th, 2019)
- ☐ **€ 1.345,00* Ordinary fee** (after October 11th, 2019)
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- ☐ **€ 630,00*** Academy, Public Administration, Freelance

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The fee includes: seat at the seminar, informative literature for the 1/2 day, coffee break, organisational office assistance, certificate of attendance. Seat at the conference, copy of presentations of Speakers who allow the distribution, informative literature for the day, networking lunch, coffee break, organisational office assistance, certificate of attendance.

- REGISTRATION FEE FOR THE

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- ☐ **€ 660,00* Early Bird fee** (until October 11th, 2019)
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Two ways to register

- **Online**

  please register here

  https://esf-2019.lsacademyevents.it/orders/new

  In this case, you can choose to pay

  by credit card or by bank transfer

- By **email o fax**

  please fill the registration form below for each attendee

  and send it by **email : ilaria.butta@lsacademy.com**

  or by **fax : +39(0)35.4501262**

  In this case, you can pay by bank transfer.

PAYMENT BY **BANK TRANSFER**

The full amount must be paid on registration to EasyB S.r.l by bank transfer. If you pay by bank transfer, please attach proof of payment to the registration form.

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For any additional information, please contact:

Ilaria Butta | ilaria.butta@LSacademy.com **Phone:** +39 (0)35.4123594

Surname _____ Name _____

Company _____ Job title _____

Address _____

City _____ Post code _____

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Special Dietary Requests _____

I wish that my data (name, surname, job position and company) are inserted in the list of attendees distributed the day of the event ☐ Yes ☐ No

Invoicing details

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Cancellation Please note that refunds (70% refund of the registration fee) will only be given if cancellation is received at least one week before the event date. Cancellations will only be valid if made in writing. Transfer of registrations (or name changes) are allowed and should be made in writing within 7 days prior to the event. EasyB reserves the right to postpone or cancel an event, to change the location of an event or to alter the advertised speakers for an event. EasyB is not responsible for any loss or damage as a result of substitution, alteration, postponement or cancellation of an event due to causes beyond its control including without limitation, acts of God, natural disasters, sabotage, accident, trade of industrial disputes, terrorism, or hostilities.

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