Please take note of the agenda for the upcoming

BBS Seminar on

Safety monitoring during the life cycle of a drug

Date and time:
November 29, 2016
15.00-17.00

Venue:
Actelion Pharmaceuticals
Hegenheimermattweg 95
Robert Cawthorn Auditorium (Building H95)
4123 Allschw

Registration:
- Free of charge
- But please send an email to Caroline Schwechlen to have badges prepared. (email: caroline.schwechlen@ext.actelion.com)>
- Badges shall be picked up at the reception of building H95, latest 15 min prior to start of the meeting.

Agenda

15:00 - 15:10	**Conny Berlin, Novartis** Welcome & Introduction
15:10 – 15:35	**Yusuf Tanrikulu (Roche)** Signal Detection - Quantitative analysis of safety data
15:35 – 16:00	**Pritibha Singh (Novartis)** ADR screening in Clinical Trials
16:00 – 16:25	**Gianmario Candore (EMA)** Routine signal detection at EMA
16:25 – 16:50	**Soheila Aghlmandi (University Bern)** Choice of prior distribution in rare-events meta-analysis
16:50 – 17:00	**Marisa Bacchi (Actelion)** Discussion

Abstracts

Yusuf Tanrikulu (Roche), Principal PV Process Leader, Roche, yusuf.tanrikulu@roche.com

Signal Detection - Quantitative analysis of safety data

Signal detection is the first step of signal management which is a process mandated by legislation for any pharmaceutical company developing a medicinal product for human use or holding a marketing authorization for a given compound in any of the worldwide markets. Signal detection is of utmost importance for the safe use of drugs by patients, because it provides means for early identification of associations between compounds and adverse events. The growing number of available safety sources and the lack of exposure data in the post-marketing scenario led to the development of quantitative analysis methods. Most popular are frequentist or Bayesian approaches which have the common goal to highlight disproportionate reporting to support scientific decision-making by medical personnel. This talk provides an overview of data sources and the challenges with medical review of such, presentation of industry-wide employed quantitative methodologies and recent developments at Roche to identify increased reporting in time periods.

Pritibha Singh (Novartis)

ADR screening in Clinical Trials

Safety monitoring spans the entire lifecycle of a drug and covers a large spectrum of data: adverse events (AEs), laboratory data, electrocardiograms and vital signs. At the pre-submission phase, adverse drug reaction (ADR) screening is one of the components of safety monitoring during the lifecycle of a drug. This talk focuses specifically on using AEs in the ADR screening during the pre-submission phase. With the use of a case study of a submission dossier containing one very large pivotal phase 3 study, one of the methods of screening, the Double False Discovery Rate (DFDR), will be illustrated.

Gianmario Candore (EMA), Data Scientist, EMA, gianmario.candore@ema.europa.eu

Routine signal detection at EMA

Many sources of data are used to detect adverse drug reactions (ADRs) but one kind of data collection in particular, the collection of individual case safety reports (ICSR) concerning suspected ADRs in people exposed to medicines, is specifically performed for this purpose. The data processing system for ICSRs used by the EU regulatory network is called EudraVigilance (EV) and includes a management system for reporting and evaluating suspected ADRs of medicinal products marketed in the European Economic Area. The first version was launched in December 2001.

When EV was first set up, direct access to the data was limited to regulatory authorities. At the current time plans are under way to extend routine access to Marketing Authorisation Holders and the Uppsala Monitoring Centre. Moreover, access is granted in various forms to research groups and the public. Hence, there is increased interest in how the processes of signal detection are performed in EV.

The purpose of this talk is to describe the potential uses of EV in screening for ADRs and to clarify the changes implemented and the rationale behind them based on evidence from recent research activities, including the IMI PROTECT project. The talk will summarise the main concepts developed in the new guidance on ‘Screening for adverse reactions in EudraVigilance’.

Soheila Aghlmandi (University Bern)

Choice of prior distributions in rare-events meta-analysis

Soheila Aghlmandi[1], Marcel zwahlen[1]

[1] Institute of Social and Preventive Medicine, University of Bern, Switzerland

Word counts (358)

Objectives: To study in rare events meta-analysis (MA) the sensitivity of results to the choice of prior distributions for the model parameters for the risk of control group for fixed effect (FE) and the risk of control group and between study variation of random effects (REs) methods.

Background: Randomized controlled trials (RCTs) analyzing serious adverse events often include zero events in one or both treatment and control arms. It is unclear whether trials with zero events in both arms provide any information on risk ratio (RR) or odds ratio (OR), both in frequentist and Bayesian statistical inference**.** To calculate RR or OR and their 95% confidence interval (CI) in such situations, solutions have been proposed that use continuity correction (CC) or delete the trials with zero in both arms. Also, statistical methods that use the information of trials with no events have been proposed.

Methods: We used fully probabilistic approach, Bayesian framework for the MA of sparse data. The outcome of interest was binary and OR was the target effect measure. We conducted a simulation study to assess variability of the coverage of the 95% posterior interval for the OR depending on different choices of prior for the model parameters under the specific assumptions for FE and REs methods. In the simulations we varied assumptions on the true OR, the standard deviation of random effects, the risk in the control group, the total number of patients in treatment and control group, and the ratio of patients between these two groups.

Results: When we used different prior distributions for meta-analytical approaches, we found that our Bayesian methods (for both FE and REs) returned similar interval statements for log(OR). For FE, the conjugate Beta distributions calculation method did not provide good coverage or a precise mean estimate. But weakly informative (normal(0,10) & normal(0.100)) and hierarchical priors provided coverage similar to the MH without CC. For REs half-normal(mean = 0.5) and exp(2) as prior distributions for τ performed very similarly in all aspects while U(0, 2) performed poorly. For both FE and REs, the results of the Bayesian methods were almost identical when studies with no events were included or excluded.

Speaker bio sketches

Yusuf Tanrikulu (Roche)

Yusuf gained his PhD in bioinformatics at the University of Frankfurt in Germany in 2009, and subsequently joined Roche at Nutley, NJ, to support the big data analysis and chemoinformatics group with the statistical identification of active compounds signaling in high-throughput screening data. After an assignment at Merz Pharmaceuticals, his career path led him to Merck Serono where he was responsible for signal management including setup of detection activities and statistical methodology. Currently, he is a member of the processes group at Roche in Basel steering upcoming challenges in safety. In addition to having rigorous knowledge of international regulations, Yusuf is well versed in the end-to-end medical surveillance of drugs starting from signal detection up to changes to product labels including implementation of electronic signal detection reports and signal tracking systems, development of procedural documents, global PV training and participation in audits and inspections.

Pritibha Singh (Novartis)

Pritibha Singh joined Novartis Drug Safety & Epidemiology (Switzerland) as a Senior Quantitative Safety Scientist in the Quantitative Safety & Epidemiology group in April 2016. Over the last 10 years Pritibha gained cross-industry (research, biosimilar and pharmaceutical) experience in statistics at Sandoz (Germany), UCB (Germany), Contractor AstraZeneca (UK), Eli Lilly (Australia) and the University of Auckland (New Zealand). During this time Pritibha has worked in numerous therapeutic areas: Cardiovascular, Diabetes, Neuroscience, Respirator, Oncology, Immunology, and Hematology and she gained experience in discovery, development and late phase. Prior to her statistics career Pritibha worked in the FMCG industry and experienced a brief stint in banking.

Pritibha received a MSc in Medical Statistics, a Post Grad. Dip. in Statistics and a BSc in Psychology from the University of Auckland, Auckland, New Zealand. She also holds a Master of Business Administration from the University of St Gallen, St Gallen, Switzerland, and an Executive Diploma in Business (Program for Leadership Development) awarded jointly by the University of St Gallen and ESADE Business School, Barcelona, Spain.

Gianmario Candore (EMA)

Gianmario Candore gained his MSc in Political economy and subsequently in Statistics at the London School of Economics. He also attended different courses in Epidemiology at the London School of Hygiene and Tropical Medicine and McGill University. He joined the European Medicines Agency in 2009 and became responsible of the production and development of the tool used to support signal detection activities; the development of the algorithm to identify potential duplicate ICSRs in EV and he is also providing expert contribution to scientific research activities and data analysis activities across the whole Agency.

Soheila Aghlmandi (University Bern)

Soheila has obtained a master in applied mathematics in 2012 at the University of Aveiro in Portugal and then she moved to Switzerland and started her PhD at the Institute of Social and Preventive Medicine. Currently, she works as a biostatistician at the clinical trial unit of the University of Bern.