FINAL ANNOUNCEMENT

BBS Spring Seminar

➔ Thursday, April 28, 2016 from 9:00-17:00
Roche ITC learning center located at
Aeschenvorstadt 56, Basel

This Seminar is free with food and drinks included, but please register by sending an email in advance to fred.sorenson@xcenda.com

Agenda

8:30 – 9:00 **Registration**

09:00 – 9:10 **Welcome**
Uli Burger, BBS President

9:10-9:40 **First Session: Event prediction**
Session chair: Fabrice Bancken

Kaspar Rufibach (Roche, Basel)
Event projection for a time-to-event endpoint: quantify the uncertainty and how to manage expectations of broader teams

Beat Neuenschwander *(Novartis, Basel)*
Predicting milestone events for time-to-event trials

Melissa Penny (Swiss TPH, Basel)
Model-based public health impact and cost-effectiveness estimates informing the WHO recommendation on malaria vaccine RTS,S

10:40 – 11:10 **Coffee break**

11:10 – 12:40 **Second Session: Handling of treatment switching and crossover**
Session chair: Amanda Ross

Iain Bennett (Roche, Basel)
Designing in Treatment Switching (case study review and recommendations)

Viktoriya Stalbovskaya (Novartis, Basel)
Practical aspects of handling treatment switching in randomized clinical trials

Panel discussion on both sessions

12:40 – 13:30 **Lunch**

13:30 – 15:00 **Third Session: Development of Immunotherapies**
Session chair: Fred Sorenson

Daniel Sabanes (Roche, Basel)
Cancer immunotherapies: Which efficacy endpoints and statistical analyses to use?

Andy Stone (AstraZeneca, Manchester)
Non-proportional hazards – so what?

Karine Lheritier (Novartis)
Complex study design in patients with Hereditary Periodic Fevers, an orphan autoimmune disease

15:00 – 15:30 **Coffee break**

15:30 – 17:00 **Fourth Session: Statistics for Combination therapies**
Session chair: Dominik Heinzmann, Uli Burger

David Dejardin (Roche, Basel)
Bayesian dual endpoint decision making in combination studies

Alessandro Matano (Novartis, Basel)
Bayesian approach for Combination Phase I Trials in Oncology

Panel discussion

17:00 **End of the meeting**
Uli Burger, BBS President

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Abstracts

9:10-9:40 **First Session: Event prediction**
Session chair: Fabrice Bancken

Event projection for a time-to-event endpoint: quantify the uncertainty and how to manage expectations of broader teams
Kaspar Rufibach, Roche, Basel, kaspar.rufibach.roche.com

In a clinical trial with a time-to-event primary endpoint, it is generally of interest to estimate timepoints when a pre-specified number of events will be reached, e.g., timepoints for planned interim or the final analysis. We summarize a simple frequentist framework how to do such event predictions based on either an assumed or estimated survival function. The approach proposed by Fang and Su (2011), that estimates the survival function by Kaplan-Meier up to a formally detected changepoint and uses an Exponential tail fit beyond that changepoint, will be used to do the predictions. We apply the methodology to a real clinical trial in oncology and provide a confidence interval around predicted timepoints via bootstrapping of survival data. We share our experience in how expectations from broader teams on such type of predictions can be managed.

Fang, L. and Su, Z. (2011). A hybrid approach to predicting events in clinical trials with time-to-event outcomes. Contemp Clin Trials 32 755-759.

Predicting milestone events for time-to-event trials
Beat Neuenschwander, Novartis, Basel, beat.neuenschwander@roche.com

For resource planning and other operational aspects of a clinical trial, it is important to accurately predict the time of interim or final analysis. We consider these milestone events for time-to-event trials, which require predictions for the event, dropout, and enrollment process. The proposed approach extends previous work. It is Bayesian, builds on piece-wise exponential models, which imply analytic predictive distributions, and has an extra mixture component allowing to assess deviations such as changes in study conduct. A recent trial illustrates various aspects of how to implement the proposed approach.

Model-based public health impact and cost-effectiveness estimates informing the WHO recommendation on malaria vaccine RTS,S/AS01
Melissa Penny, Swiss TPH, Basel, Melissa.penny@unibas.ch

The RTS,S/AS01 malaria vaccine candidate demonstrated modest efficacy against *Plasmodium falciparum* malaria in a multi-study Phase III trial. In addition to the trial results, both the EMA pre-licensure decision and the WHO policy recommendation required model-based predictions of impact on clinical and severe disease, and importantly estimates of impact on malaria mortality for settings outside the trial. To address this, we undertook a harmonised comparison of the predicted public health impact and cost-effectiveness of the vaccine using four independent models of malaria parasite transmission.
Individual level and aggregated trial data were used to parameterize vaccine efficacy in the models. Estimates of cases, deaths and disability adjusted life years (DALYs) averted were calculated over a 15-year time horizon for parasite prevalences ($Pf\text{PR}_{2\text{-}10}$) from 3% to 65% and for 6 anonymized countries in malaria-endemic sub-Saharan Africa. Two vaccine schedules in children were considered.

11:10 – 12:40 **Second Session: Handling of treatment switching and crossover**
Session chair: Amanda Ross

Designing in Treatment Switching (case study review and recommendations)
Iain Bennett, Roche, Basel, iain.bennett@roche.com

This presentation will review some published examples of trials where treatment switching has occurred. A framework is used to group the different trial design decisions made that lead to the treatment switching and the impact on the overall survival results. Finally some general recommendations are made on what could be considered when designing a trial where switching is anticipated.

Practical aspects of handling treatment switching in randomized clinical trials
Viktoriya Stalbovskaya, Novartis, Basel, viktoriya.stalbovskaya@novartis.com

The focus of the presentation will be on practical aspects of handling one directional treatment switch in randomized clinical trials. An algorithmic implementation will be described for two model-based methods, marginal structural model and rank preserving structural time failure model. Real life examples of analysis, presentation along with some practical recommendations will be provided as well.

Panel discussion on both sessions

12:40 – 13:30 **Lunch**

13:30 – 15:00 **Third Session: Development of Immunotherapies**
Session chair: Fred Sorenson

Cancer immunotherapies: Which efficacy endpoints and statistical analyses to use?
Daniel Sabanes, Roche, Basel, sabanesd@roche.com

Cancer immunotherapies (CITs) are revolutionizing Oncology, as evidenced by recent CIT drug approvals in melanoma and lung cancer, currently followed by a second wave of other tumor indications granted breakthrough designation by FDA and a large number of combination CIT trials ongoing. CITs modulate the immune system of the patients in order to enable it to kill the cancer cells. Their mode of action (MoA) is fundamentally different from the established cytotoxic or targeted therapies, which directly kill or target the cancer cells, respectively. The new paradigm of "treating the patients, not the cancer" has presented a number of challenges in drug development. Firstly, the indirect MoA can lead to patients having progressive disease according to the established RECIST tumor response criteria soon after treatment start, although later they can be observed to live longer and/or presenting stabilized tumor lesions. This challenge is particularly difficult in early phase clinical trials, and new tumor response criteria and short-term endpoints have been proposed to address it. Secondly, the delayed treatment effect in the individual patient may lead to a delayed decrease in the death hazard in the treatment population and thus a delayed separation of the experimental CIT and (non-CIT) comparator survival curves in late phase clinical trials. Hence, the classical survival analyses may not be appropriate as the proportional hazard assumption is violated, leading to a decrease in power with further risk from interim analyses for futility. Finally, a relevant proportion of patients can be cured and lives longer than the usual follow-up times. The assumption of exponential survival curves hence does not apply and a relevant cure rate can increase the study duration. Set in this context, this talk will discuss some alternative endpoints such as milestone overall survival and statistical analyses including the weighted log-rank test and the non-proportional hazards cure rate model.

Non-proportional hazards – so what?

Andy Stone, AstraZeneca, Manchester, andrew.stone@astrazeneca.com

It has been predicted that survival curves for immontherapies will feature a delayed separation and hence exhibit non-proportional hazards (NPH). This presentation will discuss the following

- to what extent NPH causes challenges in interpretation
- additional measures that may help in the assessment of overall benefit
- extra considerations in the design of trials especially with regard to maturity and the design of futility analyses
- whether alternative analyses should be employed that weight patients differently and hence place more importance on increasing survival of the best prognosis patients

Complex study design in patients with Hereditary Periodic Fevers, an orphan autoimmune disease

Karine Lheritier, Novartis, Basel, karine.lheritier@novartis.com

We will present a case study in a challenging design for a cluster of orphan autoimmune diseases.
Hereditary periodic fever (HPF) syndromes are rare and distinct heritable disorders characterized by short and recurrent attacks of fever and severe localized inflammation that occur periodically or irregularly. The 3 rare diseases Familial Mediterranean fever (FMF), Hyperimmunoglobulinemia D with periodic fever syndrome (HIDS) and TNF-receptor–associated periodic syndrome (TRAPS) are a group of clinically distinct auto-inflammatory conditions, which, together withcryopyrin-associated periodic syndromes (CAPS), have been classified under this single term of HPF syndromes.
Canakinumab is an anti-interleukin-1β monoclonal antibody being developed for the treatment of IL-1β - driven inflammatory diseases and has already been shown to be effective in treating CAPS patients. Preliminary studies have shownefficacy and safety of Canakinumab in colchicine resistant FMF, MKD and TRAPS. However, there are currently no approved treatments for cr-FMF, HIDS and TRAPS.
Our challenge was to design a single study on patients suffering from these 3 rare conditions. This required inclusion of a randomised, double-blind, placebo-control and a randomized withdrawal element, a long-term follow-up part, in addition to clinical constraints such as up-titration of the dose, change in the dose frequency, co-primary efficacy endpoints with different timepoints. Requests from different health authorities such as the Paediatric Committee at the European to include patients >28 days in this clinical trial were also built into the design.

15:30 – 17:00 Fourth Session: Statistics for Combination therapies

Session chair: Dominik Heinzmann, Uli Burger

Bayesian dual endpoint decision making in combination studies

David Dejardin, Roche, Basel, david.dejardin@roche.com

Early phase trials studying the efficacy of combination of drugs have specific challenges. For example, in most of the Poc studies, one looks for evidence of efficacy in presence of an active combination partner. In this situation, a benefit in overall response rate (ORR) is already obtained from combination partner and the added experimental drug effect needs to be differentiated form this “baseline” effect . Another example is in combinations with immunotherapies, where an increase in ORR due to the immunotherapy is not expected, but improvements are seen on different endpoints. These situations illustrate the need for a more granular evaluation of efficacy of combinations in early stage trials.

A flexible framework to make the decision of continuing or stopping the development of the combination is the Bayesian framework where the decision is based on posterior probability of being above a target. We present here an extension of this framework where the decision criteria based on 2 endpoints (eg. ORR/disease control rate or ORR or ORR/ duration of disease control). This dual endpoint criteria allows more flexibility in the evaluation of the efficacy of the combination. We also discuss the different ways to build / define the target and illustrate the methodology on a few examples.

Bayesian approach for Combination Phase I Trials in Oncology

Alessandro Matano, Novartis, Basel, alessandro.matano@novartis.com

Phase I trials are still perceived as simple by many. While this is controversial in the single-agent setting, it is certainly mistaken for combinations of two or more compounds. In Oncology, there are many challenges: while keeping patient safety within acceptable limits, the trials should be small, adaptive, and enable a quick declaration of the maximum tolerable dose (MTD) and/or recommended phase II dose (RP2D). This presentation will attempt to “square the circle" by presenting a Bayesian approach which has been implemented for a large number of combination phase I trials. In particular, an overview of phase I design structure will be given, followed by a rationale based on general clinical and statistical considerations, a summary of methodological components, an application and some references to model extensions.