Basel Biometrics Society half-day seminar
March 20, 2018, 13:30-17:15

Competing Risks and Multi-State Models: Overview and Case Studies

Date: Tuesday, March 20, 2018, 13:30-17.15
Venue: Room "Kilimanjaro",
Swiss TPH, Socinstrasse 57, Basel

The BBS would like to offer a half-day seminar on competing risks and multi-state models. The seminar will provide an overview of these topics by academic speakers and several case studies from industry and academia. All talks will be accessible to general biostatisticians and highlight the relevance of these topics for clinical research and drug development.

Scientific committee:
Dietrich Knoerzer (Roche), Amanda Ross (Swiss TPH), Kaspar Rufibach (Roche), Marc Vandemeulebroecke (Novartis), Simon Wandel (Novartis), Marcel Wolbers (Roche)

The seminar is free of charge. For registration however please send an informal e-mail to Laurence Guillier (laurence.guillier@roche.com) or Barbora Martinec (barbora.martinec@roche.com).

Program:

13:30 – 14:15 **Competing risks with applications to oncology**
Claudia Schmoor, University Hospital Freiburg

14:15 – 15:00 **Analysis of co-time-to-event outcomes in randomized clinical trials**
Jan Beyersmann, University Ulm

15:00 – 15:30 Coffee break

15:30 – 15:55 **„Dual" competing risks prediction to support decision-making in cardiac resynchronization therapy**
Michael Koller, University Hospital Basel

15:55 – 16:20 **Survival prediction using multi-state models given limited expansion data for the active treatment and the presence of sufficiently large reference data**
Uli Beyer, Roche

16:20 – 16:45 **A discrete semi-Markov model for the effect of need-based treatments on the disease states**
Ekkehard Glimm, Novartis (joint work with L. Yau, Sandoz Pharma)

16:45 – 17:15 Panel discussion with the above speakers, final Q&A

We look forward to your participation!

Remark: Abstracts included below.

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Competing Risks and Multi-State Models - Abstracts

Competing risks with applications to oncology

Claudia Schmoor, University Hospital Freiburg

The majority of clinical trials in oncology and, perhaps, in medical research in general, are based on time-to-event endpoints. Most often so called composite time-to-event endpoints are analyzed. Popular examples are overall or progression-free survival, which is the time until progression or death without prior progression, whatever occurs first. As such endpoints are all-encompassing in the sense that every patient will experience it sometime (potentially after study closure), established standard survival techniques such as the log-rank test, the Kaplan-Meier estimator, and Cox' regression analysis for the all-events hazard are adequate.
Often, the focus is additionally on the specific event-type, i.e., the composite endpoint is decomposed into its single components resulting in a competing risks framework. For instance, progression-free survival is split into progression and death without prior progression. The major challenge is that, compared to the standard survival analysis setting, the one-to-one relation between the event-specific hazards and corresponding event probabilities gets lost. The latter probabilities have to be estimated by cumulative incidence functions, which depend on all event-specific hazards. Thus, naive Kaplan-Meier estimation, which censors competing events, leads to bias. Instead, the Aalen-Johansen estimator of the cumulative incidence function must be used. It generalizes the Kaplan-Meier estimator to multiple events and decomposes one minus the Kaplan-Meier estimator of the composite endpoint into the component-specific event probabilities. Treatment effects are assessed by event-specific hazard regression or subdistribution hazard regression.
The methods are illustrated in a randomized clinical trial comparing two regimens for graft-versus-host-disease (GvHD) prophylaxis in leukemia patients receiving hematopoietic cell transplantation, where various risks are present in the course of disease (acute GvHD, chronic GvHD, immunosuppressive therapy, relapse, relapse mortality, non-relapse mortality).
Finally, it is stressed that time-to-event methods are relevant not only for efficacy endpoints, but also for safety endpoints, which are still frequently analyzed by simple proportions without taking patients' time at risk for adverse events into account.

Analysis of co-time-to-event outcomes in randomized clinical trials

Jan Beyersmann, University Ulm

This talk will start with some survival or event history fundamentals, namely that the analysis of time-to-event data is based on hazards and that there is an overemphasis on survival functions and the Kaplan-Meier method. In general, there are as many hazards as there are event types. E.g., in a joint model for overall survival and progression-free survival there are hazards for alive → death (w/o progression diagnosis), alive → progression and progression → death transitions. The general counting process/martingale machinery allows for a rather straightforward analysis of these hazards, but translating results into outcome probabilities requires more than Kaplan-Meier, and competing risks methodology does not suffice either. We will consider two RCT examples. In a study on stem cell transplanted leukemia patients, we will aim at demonstrating superiority w.r.t the outcome probability "alive w/o immunosuppressive therapy". In a treatment trial for severe infectious diseases, we will aim at demonstrating non-inferiority w.r.t the outcome probability "cured and alive" on the entire follow-up period. Both of these outcome probabilities are non-monotone, and the first outcome

is complicated by immunosuppressive therapy being switched on and off a random number of times. To this end, we will suggest two novel resampling techniques on the hazard scale which will be translated onto probabilities using the lesser known theory of product integration. Comparison of treatment groups will be based on time-simultaneous confidence bands. Unlike the standard bootstrap which draws with replacement from the data, we will not require an i.i.d. data structure; this makes our approach particularly attractive for event driven studies which are analyzed after a given number of events have been observed. We will also outline how one of our resampling approaches can be used for planning, e.g., of sample size calculation based on published data only.

„Dual" competing risks prediction to support decision-making in cardiac resynchronization therapy

Michael Koller, University Hospital Basel

Cardiac resynchronization therapy (CRT) is an effective therapy in patients with chronic heart failure (CHF). The CRT device sends electrical signals to the heart to synchronize the contraction of the left ventricle to improve the cardiac output. Certain patients who suffer from CHF, however, are at increased risk of life-threatening cardiac arrhythmia. CRT devices can therefore in addition incorporate a cardioverter-defibrillator component (CRT-D). In practice, cardiologists are faced with the challenging decision when to prioritize the more costly and complex CRT-D device over a simpler pacer-only CRT-P device. Decision analytic support requires prediction of cardiac arrhythmia events in an often elderly and frail population of patients who are a priori at an increased risk to die prior to utilizing the device for arrhythmia termination ("prior death"). We provide a more detailed insight into the predictive modelling of clinically relevant competing events and how these models can be translated into a tool for clinical decision-making.

Survival prediction using multi-state models given limited expansion data for the active treatment and the presence of sufficiently large reference data

Uli Beyer, Roche, Basel

Early development programs in oncology are usually gated based on intermediate endpoints like response (ORR) or disease control rate (DCR) in small cohorts (e.g. N=40). The correlation between these endpoints and survival has traditionally been explored via meta-analyses on the study level but this approach often performs poorly. For cancer immune therapies the relationship between these endpoints has changed and there are not enough data to explore such relationships based on meta-analyses. Sometimes, no difference in response rates and only minor differences for PFS are observed whereas the OS hazard ratio shows a clinically relevant difference. Usually, sufficient survival data for the comparator arm are available, whereas for the new compound we mainly observe time of response and time of progression and a few cases of deaths before progression, but only limited post progression survival data at time of internal decision making. The presentation shows based on simulation, how in the early setting with sufficiently large reference data multistate models can predict the long-term survival for the new agent by taking all intermediate transitions and transition-times into account, even if for the novel treatment only very limited post-progression data are observed.

A discrete semi-Markov model for the effect of need-based treatments on the disease states

Ekkehard Glimm, Novartis Pharma, Basel, Switzerland; L. Yau, Sandoz Pharma, Munich, Germany

We use a semi-Markov model to describe the history of treatment episodes in patients who are treated for a chronic condition pro re nata (i.e. as needed). The patients receive medication only when needed, for example when symptoms occur. In the specific case we discuss here, the patients' condition (=states) can only be assessed at regular visits and the states may be "treatment needed", "treatment not needed", "treatment not possible due to inflammation" and the like. The semi-Markov model is setup to answer a variety of questions, like for example the total medication load in a time interval, but also the duration of episodes and the frequency of switches between the states based on a patient's history. We will illustrate how the model is setup, how we estimate its parameters and how to derive the mentioned quantities of interest.