Basel Biometrics Section Seminar
Basel / hybrid, 12th April 2023

Quantification of risk: ask the right questions or time to apply the estimand framework to safety!

Date: 12th April 2023, 14:00-17:00

In-person: Novartis campus, Fabrikstr. 6, Auditorium U2 (map at the bottom).
Registered attendees will receive their badge at maingate

Virtual: Dial-in details will be communicated to registered virtual participants

Safety evaluations are critical in informing the benefit-risk profile of a new therapy for decision making by ethicists, investigators, regulators, payers, patients, and clinicians. This seminar will give an overview of current thinking and share recent development in safety evaluation and reporting in clinical trials.

Unlike efficacy evaluations that are primarily investigated in pivotal trials, safety evaluations start early in the development lifecycle, with the pre-clinical safety profile informing whether the product is safe enough for clinical assessment, and can continue for decades beyond marketing authorization. While clinical trials are primarily designed to answer efficacy questions, they also inform many safety aspects of a new product. Thus, collecting adverse event (AE) information and estimating the risk for an AE (quantified as the probability of the AE occurring) in clinical trials, is an essential part of the characterization of the drug's safety profile. These analyses inform approval decisions and weighting the risk against the benefit, the communication of risk to patients and clinicians, and the planning of any post-market evaluation of the risk, in clinical trials or epidemiological studies.

Safety questions are not always explicitly stated and simple analyses of complex designs may not align with those (unstated) questions. Tools such as the estimand framework can help explicitly state and refine the safety questions, and ensure the safety assessments align with those questions. For instance, many clinical studies observe patients beyond the typical fixed follow-up (e.g., event-driven studies, allowing treatment switching). Thus, a one-size-fits all approach of quantifying risk by proportion of AE across subjects or person-time may not be meaningful. These simple but typically biased summary statistics can not only erroneously inflate some risks, they can also erroneously miss some risks. In this seminar, we will discuss the following questions:

1. What scientific/clinical questions of interest are related to "risk quantification"?
    a. What are the differences between objectives for "unexpected" or "unknown" AE vs. objectives for expected drug-related AEs?
    b. What is the role of establishing causality of therapy to AE in the objective?
    c. What is the relevance of treatment policy as a strategy in typical intercurrent events?

2. How can study design, data collection, and estimation be aligned with the aforementioned scientific objectives and estimands derived from it?

The event will feature discussions from statisticians in industry and regulators.

The organizing committee of this event are Rima Izem (Novartis) and Kaspar Rufibach (Roche). Slides and recordings of the talks will be made available after the event on the BBS webpage, both pending speaker approval. The webinar is free of charge.

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We plan to continue this discussion: An invited session is organized at ISCB in Milan and further BBS seminars may follow.

Agenda:

14:00 – 14:30 **Rima Izem (Novartis)**
Welcome, scene setting and “Let us put the scientific objective first!”

14:30 – 15:15 **Kaspar Rufibach (Roche)**: Stop the abuse: A plea for a more principled approach to the analysis of time-to-event endpoints with varying follow-up times and/or competing risks, with a focus on analysis of AEs.

15:15 – 15:45 Coffee break

15:45 – 16:00 Discussant 1: Andrew Thomson (EMA, virtual)

16:00 – 16:15 Discussant 2: Shanti Gomatam (FDA, virtual)

16:15 – 16:55 Q&A

16:55 – 17:00 **Kaspar Rufibach (Roche, member of BBS board)**
Next webinars and closure

We look forward to your participation!