Welcome to the Basel Biometrics Society Seminar

April 12th 2023

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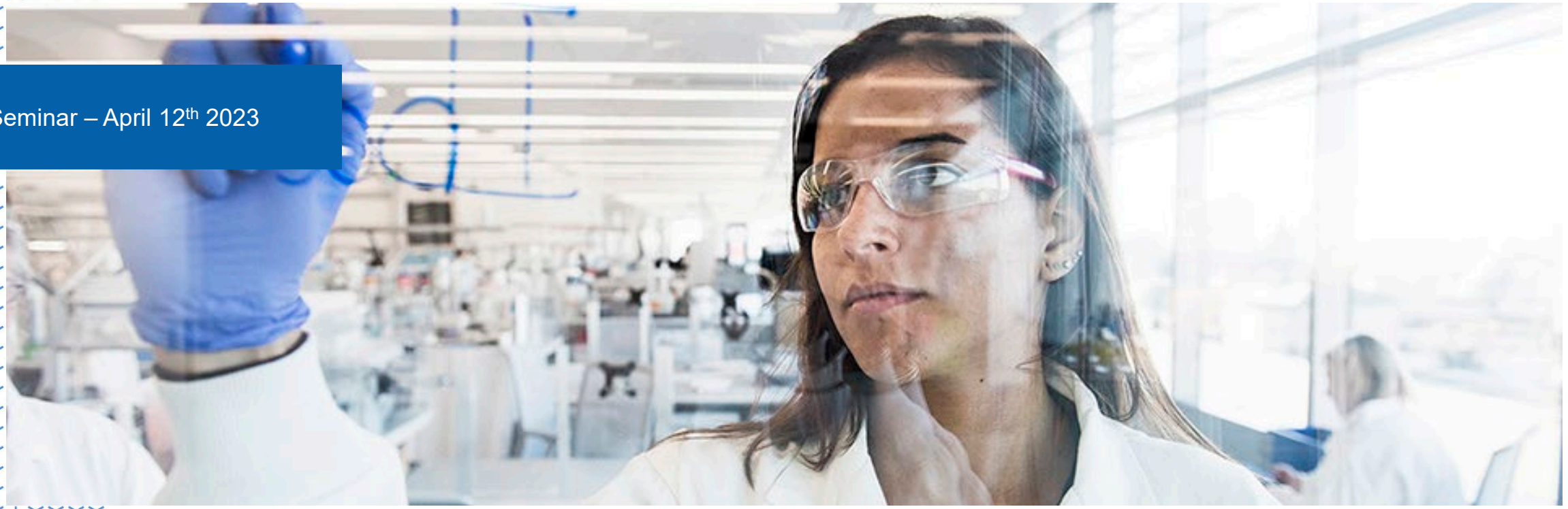
Basel Biometrics Section Seminar
Basel/hybrid, 12th April 2023

Agenda (times in CET)	
14:00 – 14:30	Rima Izem (Novartis)
14:30 – 15:15	Kaspar Rufibach (Roche)
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	Moderator: Tobias Muetze (Novartis)
16:55 – 17:00	Kaspar Rufibach (Roche, member of BBS board)
	Next webinars and closure

BBS Seminar – April 12th 2023



Safety Estimands First

the importance of putting the horse before the cart

Rima Izem, Valentine Jehl, Tobias Muetze
Basel
April 12, 2023

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Outline

1. Motivation and background: adverse events of special interest in pivotal studies
2. Discussion of two common analyses strategies: on-treatment and on-study
3. Strategies for eliciting safety estimands using the estimand framework and causal inference

Motivation and Background

Why safety matters to clinical trial statisticians?

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Safety is critical to benefit-risk

Safety Concerns Turn FDA Panel Thumbs Down for Novel CKD-Anemia Drug

— Advisory committee rejected oral anemia drug for dialysis and non-dialysis patient populations

by Kristen Monaco, Staff Writer, MedPage Today July 16, 2021

Safety differentiation: emerging competitive edge in drug development

Marianne Uteng[1], Laszlo Urban[2], Dominique Brees[1], Patrick Y. Muller[3], Gerd A. Kullak-Ublick[4,5], Page Bouchard[2], Gervais Tougas[4] and Salah-Dine Chibout[1]

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References: (Left) Monaco K. (2021), (Right) Uteng et al (2019)

Focus today: quantifying safety adverse events of special interest in pivotal trials

In scope

- Adverse events (AE) of special interest*
- Signal refinement goals informing benefit-risk
- Clinical questions relating to incidence of AE
- Clinical trials as the main source of reporting
- Quantitative evaluations

* As defined by CIOMS (2005)

Adverse events of special interest analyses, simple?

General recommendation

AESI Assessment	Drug Name Dosage X N=XXX n (%)	Drug Name Dosage Y N=XXX n (%)	Active Control N=XXX n (%)	Placebo N=XXX n (%)	Risk Difference (%) (95% CI)[2]
AE Grouping Related to AESI	n (%)	n (%)	n (%)	n (%)	X (Y, Z)

Case study illustrating one safety discussion in an Advisory committee

Non-dialysis-dependent population

	Number of Events/ PY/ Rate Roxadustat (N = 2386)	Placebo (N = 1884)	HR [95% CI]
MACE (On-Study)	480/ 4510/ 10.6	350/ 3406/ 10.3	1.10 [0.96, 1.27]
MACE (OT+7)	277/ 3843/ 7.2	131/ 2332/ 5.6	1.38 [1.11, 1.70]

What clinical question is each analysis answering?

What other questions may be relevant?

Source: (Top) from FDA presentation slide 129 at the Duke Margolis Workshop for Advancing Pre-Market Safety (2022)

Source: (Bottom) from Slide 64 (FDA Adcom 2021)

Discussion of on-study and on-treatment analyses

Illustration with a case study

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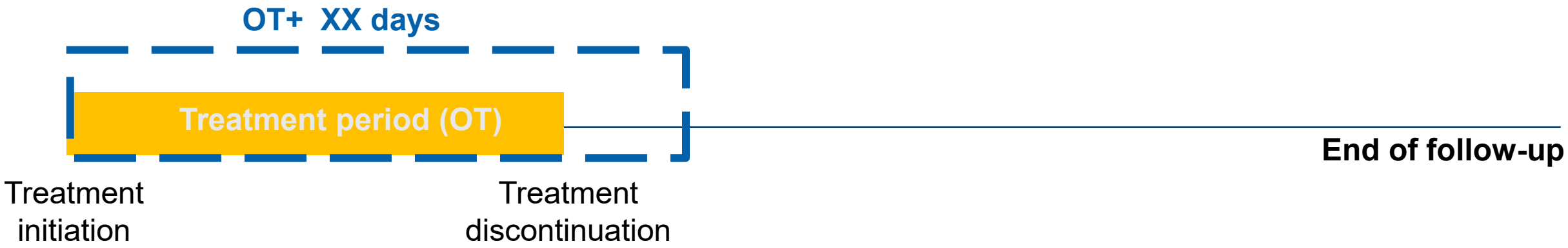
Case study: Roxadustat and MACE

- The proposed US indication of Roxadustat was treatment of anemia due to chronic kidney disease in adult patients not on dialysis (NDD) and on dialysis (DD)
- In NDD, MACE was a safety outcome of special interest (≈ 5/100 PY)
  - Predefined as a composite of stroke, myocardial infarction, and all cause mortality
  - Evaluated in **3 double-blind placebo-controlled** studies and one open-label active controlled study, and reported throughout the study duration
  - In each study, outcome evaluation time was the same for all participants (max of 208 weeks for two studies, and 104 weeks for two studies)

 Reference (FDA Adcom 2021)

On-treatment vs. on-study periods

Popular concepts in safety analyses



- On-treatment period, also called **at-risk ascertainment period**, typically includes the treatment period and some additional follow-up to account for exposure (e.g., XX= 5 times the half-life of the drug, pre-set 7 days or pre-set 28 days)

- On study period starts at treatment initiation and ends at end of follow-up for each patient (e.g., until administrative censoring or pre-set max follow-up)

On-treatment vs. on-study

Case study results

NDD	Number of Events/ PY/ Rate Roxadustat (N = 2386)	Placebo (N = 1884)	HR [95% CI]
MACE (On-Study)	480/ 4510/ 10.6	350/ 3406/ 10.3	1.10 [0.96, 1.27]
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Mean exposure duration
Roxadustat: (84.8 weeks)
Placebo (64.3 weeks)

"... Although the exclusion of 1 in the OT+7 analysis merits concern, the differential exposure between roxadustat and placebo complicates the interpretation of the OT+7 analysis in isolation, as this may not represent a fair randomized comparison." (FDA Adcom 2021)

"Discontinuation for ESA rescue therapy was ~4 times higher in patients who received placebo (13.4%) than in roxadustat-treated patients (3.2%)." (FDA Adcom 2021)

On-treatment vs. on-study analyses

Review of recommendations in safety

- On-study is more “fair”, or on-treatment is harder to interpret
  - Similar arguments favoring intent-to-treat to per-protocol analyses in a randomized study (e.g., Yang F, Wittes J, Pitt B (2019) and DeMets DL, Cook T (2019))

- The importance is to pre-specify and prioritize
  - (e.g., Crowe et al (2009), Ball et al (2020), Henrickson et al (2021))
- Note: in the case study, on-study analysis was primary and OT+7 was a sensitivity analysis

What is the role of randomization in “fairness” of the comparison of on-study versus on-treatment?
What is the impact of rescue therapy on the interpretation of the on-study analysis?
Are those the only analytical strategies?

Strategies for eliciting (novel) estimands in safety

...or why the estimand framework, causality, and time are relevant

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Estimand thinking process

The Question Drives the Design and Analyses

- What made the safety outcome of special interest? What are the biological mechanism at play?
- How are the study design elements (e.g., recruitment/eligibility, outcome assessment, frequency, end of follow-up) suited to address the safety question of special interest?
- How does the analysis plan align with the question(s), what are the assumptions? (e.g., primary and sensitivity analyses aim to target the same estimand)

Estimand thinking process
Attributes, and eliciting intercurrent events

Population	Treatment	Variable	Intercurrent event (ICE)	Summary Measure
NDD	Roxadustat vs. placebo	Time to first MACE (*up to 108 weeks*)	??	*Hazard ratio*

- ***An intercurrent event (ICE):*** *Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest. (ICH-E9 addendum, 2019)*

- In the case study, two ICE that played an important role were: **treatment discontinuation** and **use of rescue therapy/ESA**

Estimand thinking process
Eliciting ICE helps refine questions

- What are the **potential ICEs**? How will the estimand account for **each ICE**?

AND

- Multiple potential strategies for handling **each ICE**, including
  - Treatment policy - what happened regardless of whether the ICE occurred or not?
  - While on-treatment – What happened only before the ICE occurred?
  - Hypothetical strategy (e.g., Hernan et al (2013))- What would have happened if the ICE had not occurred?
  - Composite strategy – If the ICE is a precursor or within the severity spectrum of the outcome, shall the variable change to include the ICE?
  - Principal stratum strategy – What would have happened in the subset of patients who would have had the ICE regardless of treatment?

Estimand thinking process
Revisiting on-study vs. on-treatment

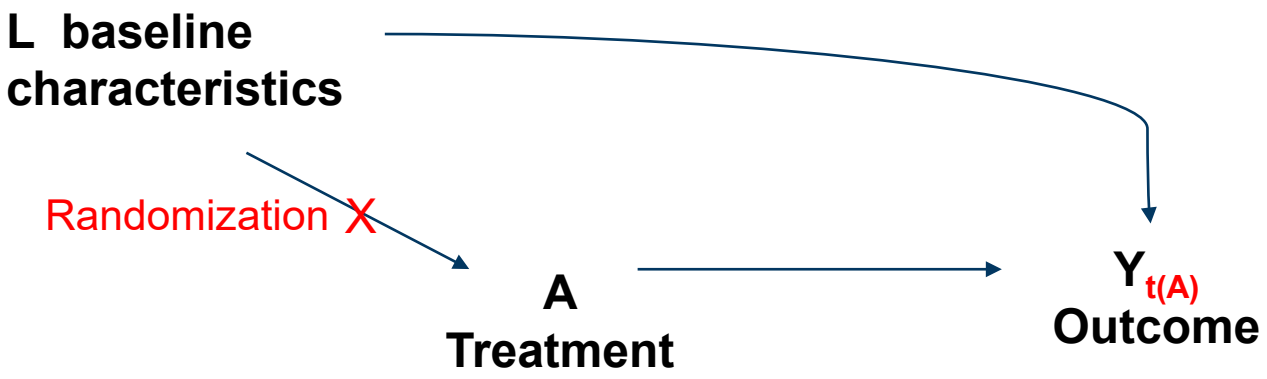
- On-treatment analyses target the while-on treatment strategy estimand for **only the treatment discontinuation ICE**

- On-study analyses target the treatment policy strategy estimand **for all ICE**
  - Assumes the design collects data for the duration of the study

Two different questions/estimands => two different answers/interpretations

Thus, using one as a sensitivity analysis to the other goes against recommendations of the ICH-E9 addendum

Beyond ICE, time
Revisiting on-treatment



On-treatment or while on treatment strategy compares

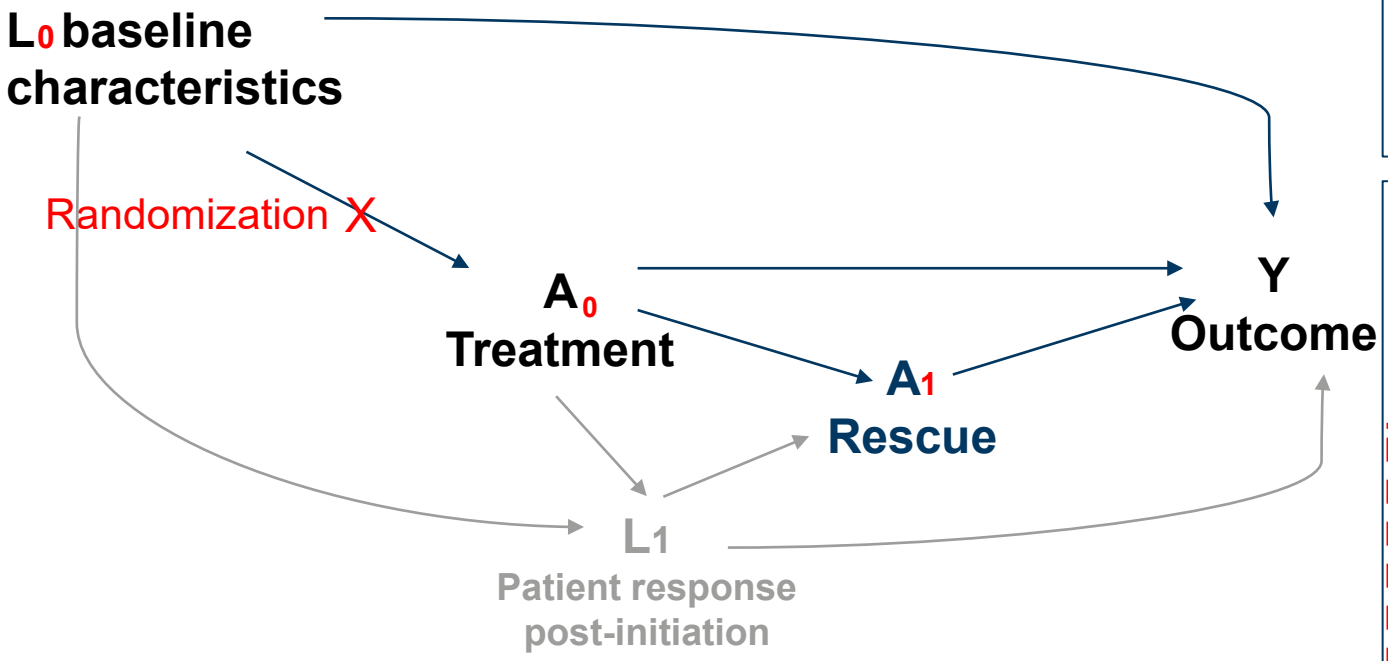
$Y(A=\text{test at time}<t_1)$, where $t_1 = t(\text{test})$
versus
$Y(A=\text{placebo at time}<t_0)$, where $t_o = t(\text{placebo})$

Times on treatment t_0, t_1 are not randomly assigned at baseline and can be caused by many mechanisms post-randomization

While on-treatment strategy/on-treatment estimator is flawed
...but... are the ideas of accounting for time & cumulative exposure critical for the estimand?

Beyond ICE, causality

Revisiting on-study analyses



On-study/treatment policy strategy, no ICE:

Y(A=test trt) vs. Y(A=placebo)

On-study/treatment policy strategy, with ICE (A_1=rescue)

$Y(A_0$=test trt & A_1=rescue)

$Y(A_0$=test trt & A_1=no rescue)

vs.

"fair" randomized & meaningful?

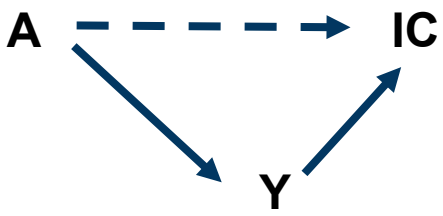
$Y(A_0$=placebo & A_1=rescue)

$Y(A_0$=placebo & A_1=no rescue)

Additional discussion and illustrations in Hernan et al (2013), and Hernan and Sharfstein (2018)

Eliciting causal structure

e.g., A= Treatment of anemia or placebo



Definition of ICE implies an association of ICE with Y

- When can the ICE occur relative to the outcome Y? can it only precede or also follow the AE?
- Is the ICE (or its cause) a mediator in the causal pathway of A to Y?
- Is the ICE (or its consequence) a competing event?
- Shall we target a direct effect of A on Y or a total effect (across all causal pathways)?
- If total effect, with/without elimination of (other) censoring and competing events?

 More discussion in: Young, JG et al (2020)

Estimands, causality, and time

- Causality (suspicion) mechanism of **test-drug** plays a role in identifying safety outcomes of special interest and duration of on-treatment period
  - We can exploit this knowledge further to identify the counterfactual of interest, and ask targeted questions about dose/cumulative exposure
- Explicitly accounting for time in the estimand is crucial
  - Helps with assumptions on background incidence, eliciting ICE and their impact on plausibility of the counterfactual
  - Helps tailor the duration of follow-up and choice of the appropriate summary measure contrast

Question to SAVVY WG: what causal estimand does the Aalen Johansen estimator target? When is it meaningful? How do you account for time and causality?

In summary

- Elucidating the relevant safety questions is a difficult task that is nonetheless worthwhile to meaningful reporting of benefits and risks of a medical product

- Two commonly used safety analyses: on-treatment and on-study focus on estimation, target different estimands, and make many implicit assumptions

- The estimand framework, causal thinking, and timing are broadly relevant to safety to elicit the right questions,
  - It can better align design and analyses to the questions, make assumptions and handling of different intercurrent events explicit
  - It can expand the universe of relevant analyses

Acknoweldgments

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Thank you

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