Estimands to the rescue?

Role of estimands in randomized controlled studies

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Outline

1. Motivation
2. ICH E9 (R1) addendum
3. What happened since the development of ICH E9 (R1)?
4. Conclusions

Motivation

What challenges are we facing in drug development?

Research questions in randomized clinical trials are sometimes not defined precisely

→ **Misaligned** trial objectives, designs and statistical analyses

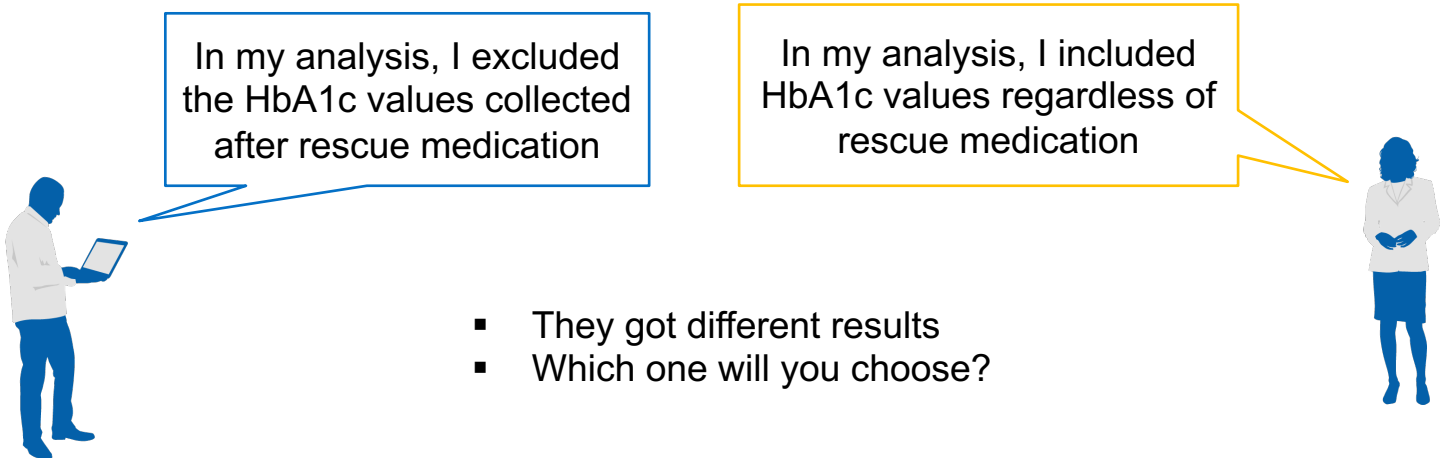
This lack of precision and transparency has led to

→ **Stakeholder misalignment**

→ **Regulatory challenges**

Estimands: Motivating example*

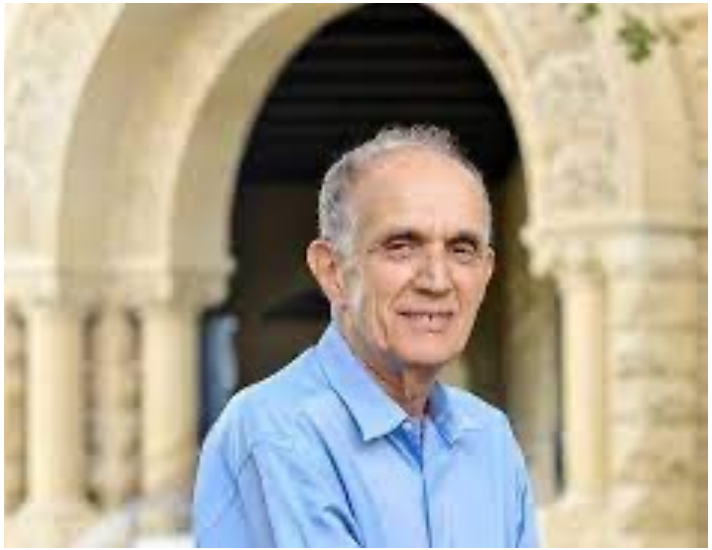
- Imagine that there is a clinical trial to compare treatment vs. control in patients with diabetes and the endpoint of interest is change from baseline in HbA1c at week 24
- A certain proportion of patients in both arms took rescue medication before week 24



- They got different results
- Which one will you choose?

* This example is a simplified version of the example in the ICH E9(R1) training materials available on the ICH website

Why haven’t research questions been defined sufficiently precisely?



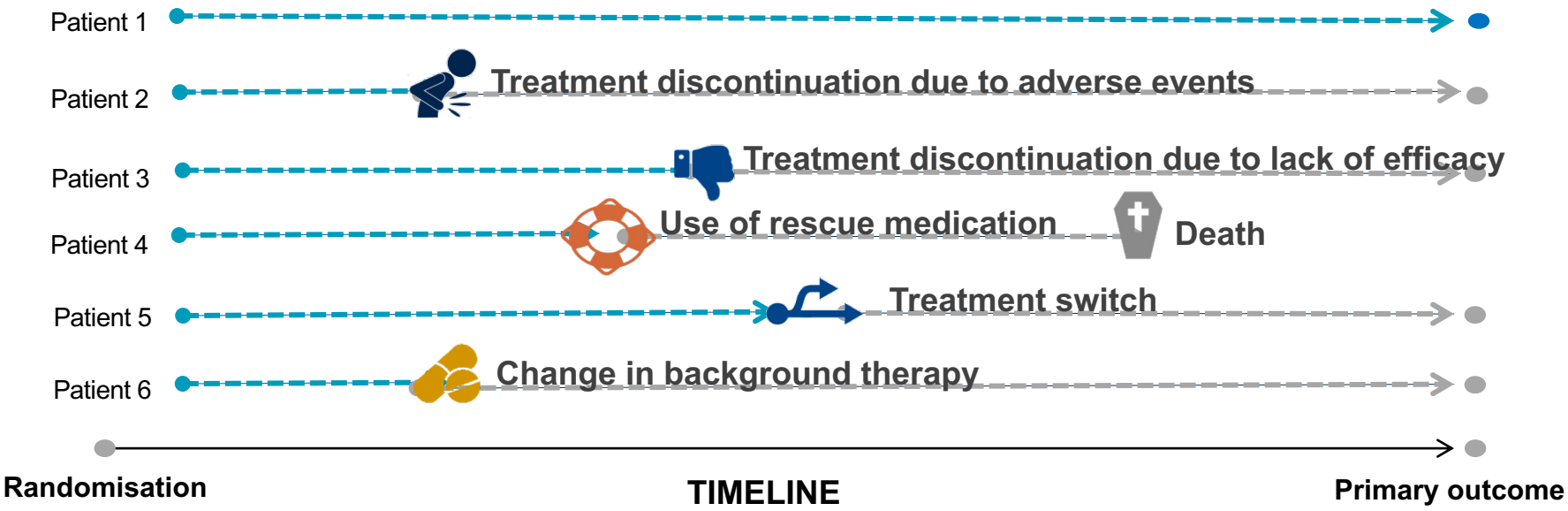
Efron is the second winner of International prize in Statistics Foundation

“There could not be worse experimental animals on earth than human beings;

- they complain,
- they go on vacations,
- **they take things they are not supposed to take**,
- they lead incredibly **complicated lives**, and, sometimes,
- they **do not take their medicine**.”

(Efron, 1998)

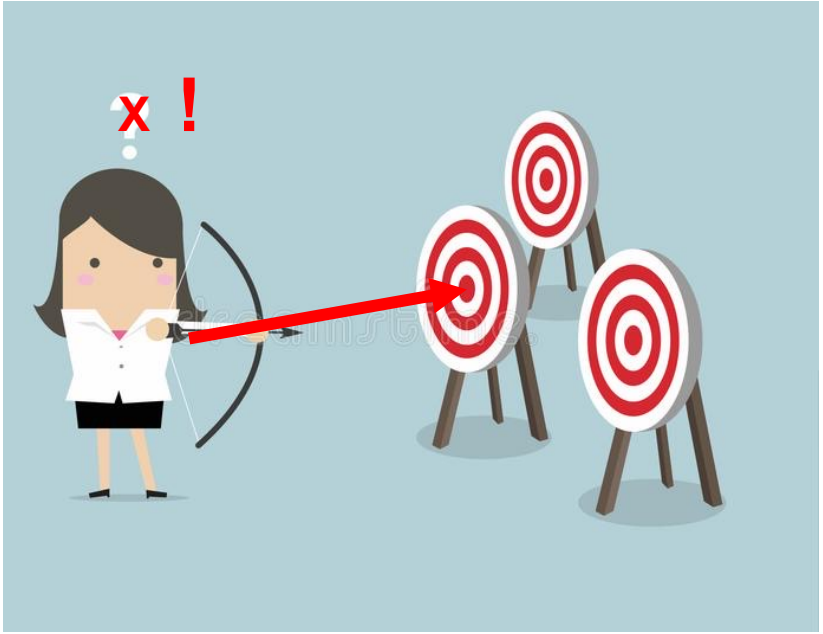
Complications ≈ Intercurrent events



Intercurrent event: An event that occurs after randomization/treatment initiation and either precludes observation of the variable or affects its interpretation.

ESTIMAND framework was developed to address these challenges

- Framework developed in the context of a **regulatory guideline**
- **Precise description of the treatment effect** reflecting the clinical question posed by the trial objective
- **Structured approach** to answer research questions accounting for intercurrent events



ICH E9 (R1) addendum

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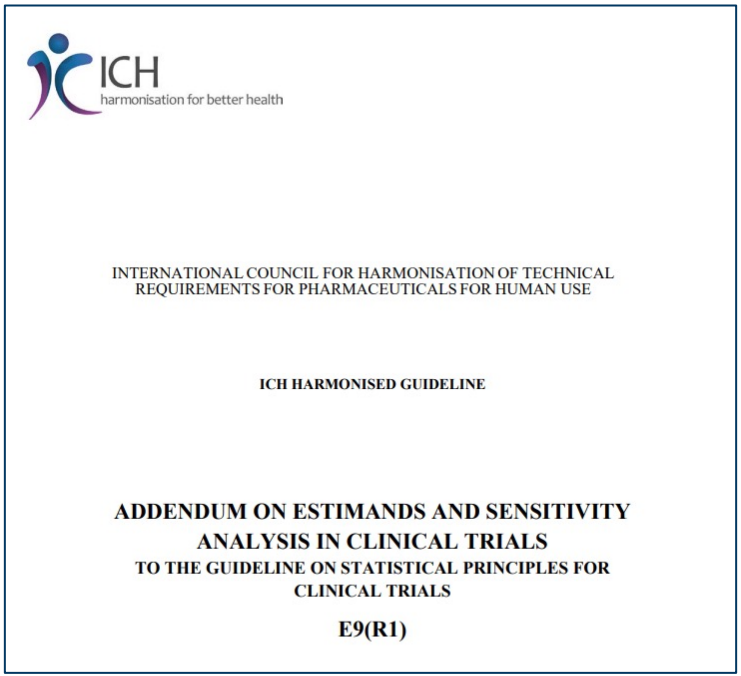

ICH
harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

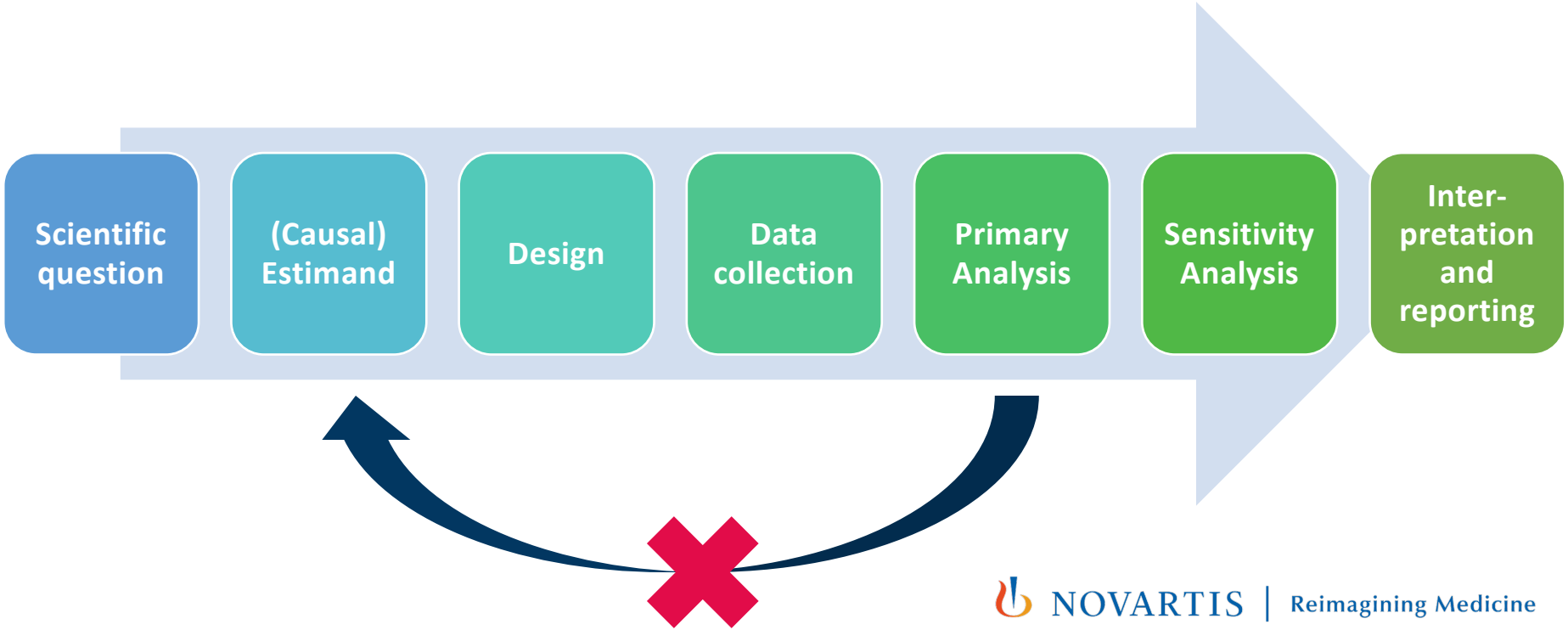
ICH HARMONISED GUIDELINE

ADDENDUM ON ESTIMANDS AND SENSITIVITY ANALYSIS IN CLINICAL TRIALS
TO THE GUIDELINE ON STATISTICAL PRINCIPLES FOR CLINICAL TRIALS

E9(R1)

- Adopted by ICH in the end of 2019
- FDA, EMA and others have adopted the guideline in the meantime
- Provides a framework to translate clinical questions of interest into suitable *estimands*
- "...summarizes at a population-level **what the outcomes would be** in the **same patients** under **different treatment conditions** being compared."
- Word of caution: 'causal' is not mentioned / uses partly different terminology to mainstream causal inference literature

ICH E9 (R1) provides a helpful framework



Description of an estimand: 5 attributes

Treatment

The test treatment of interest, and the control treatment to which comparison will be made

Variable

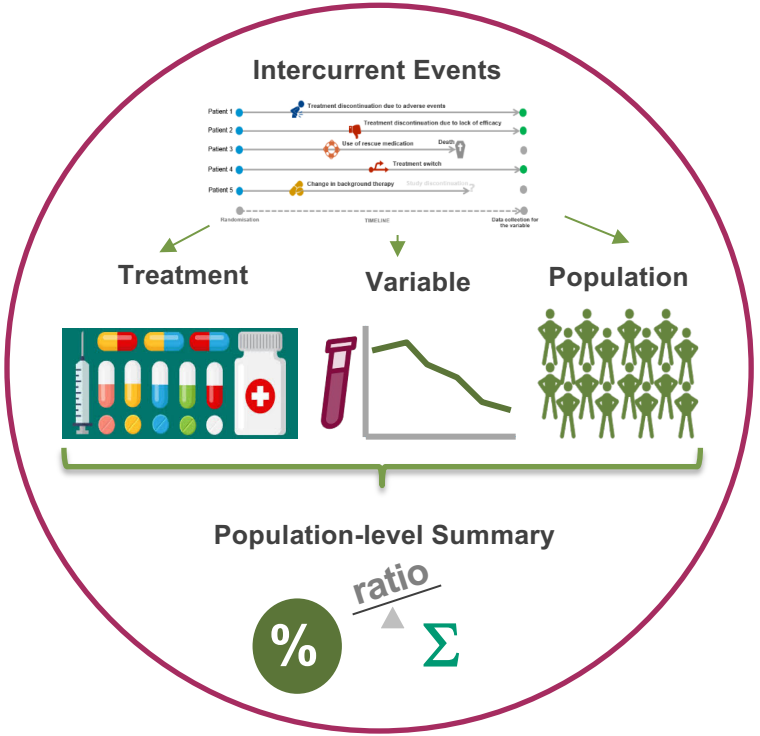
Measure(s) required to address the scientific question

Population

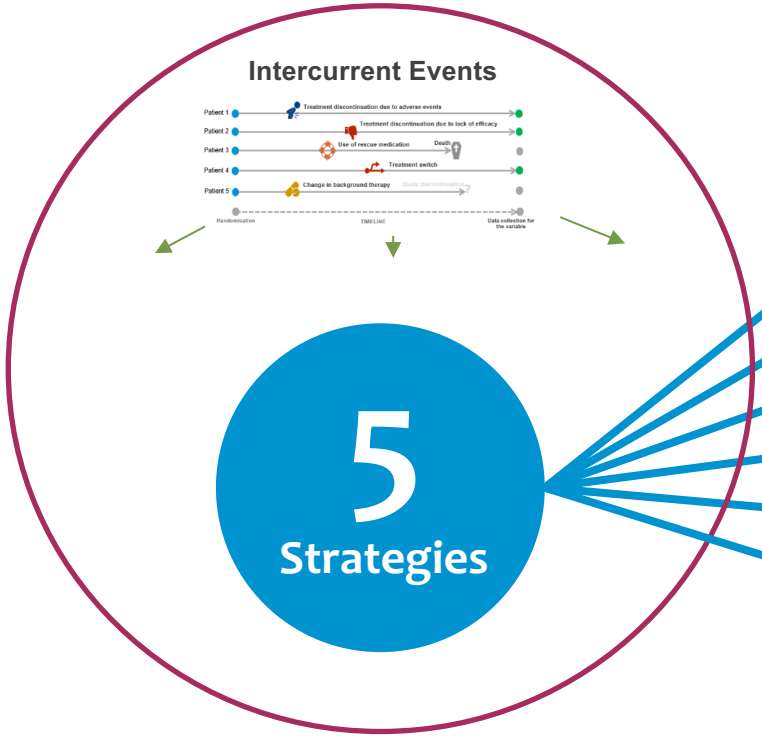
The patients targeted by the scientific question

Population-level summary

Population summary of the comparison e.g. difference between means, ratio of proportions, etc.



How are intercurrent events reflected in the scientific question of interest?



Treatment policy

Composite

Hypothetical

Most common strategies

Principal stratum

While on treatment

...

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Strategies to address intercurrent events

Intercurrent event: 'Intake of additional medication'

Treatment policy: Treatment effect regardless of the intercurrent event

'Drug, plus additional medication as needed' vs. 'Placebo, plus additional medication as needed'

Composite: Occurrence of intercurrent event included in the endpoint definition

'Intake of additional medication is considered a treatment failure'

Hypothetical: Treatment effect if the intercurrent event did not occur

'Effect of Drug vs Placebo if additional medication had not been made available'

Principal stratum: Treatment effect in a population without the intercurrent event

'Effect of Drug vs Placebo in patients who do not take additional medication regardless of the assigned treatment arm'

While on treatment: Treatment effect before the occurrence of the intercurrent

'Effect of Drug vs Placebo before additional medication is taken'

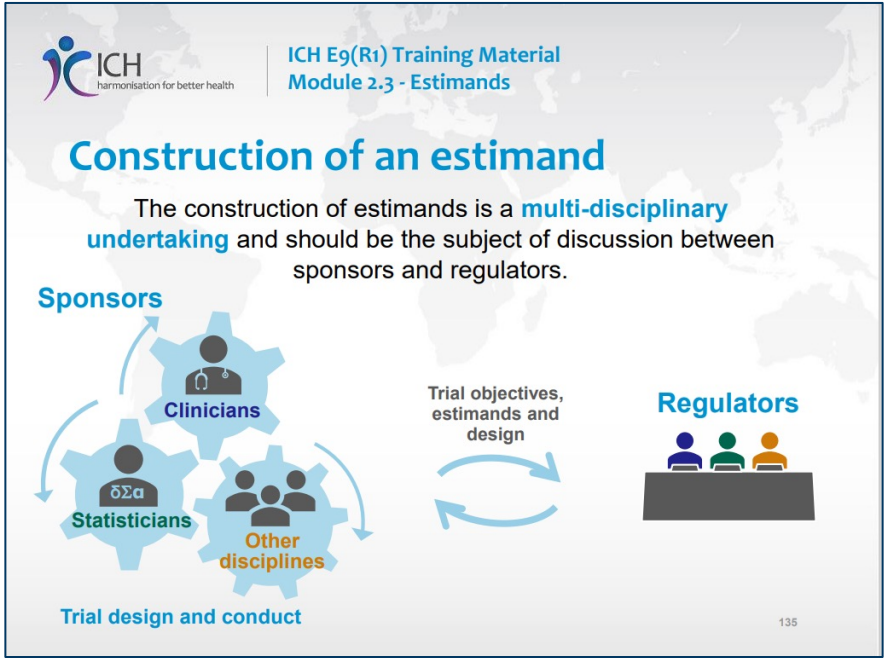
What happened since the development of the ICH E9 (R1)?

"... As COVID-19 will likely be endemic ..., we recommend handling any intercurrent events that may be related to operational complications caused by COVID-19 with treatment policy strategy."

"We do not agree with using hypothetical strategy for handling use of [XYZ]. All the observed periods prior to the trial cut-off date should be included in the efficacy analyses regardless of use of [XYZ]."

"CHMP invites the Applicant to better motivate the proposed estimand which is likely to overestimate the effect that would be observed if [XYZ] were to be applied on a large scale in a realistic setting where such medications are applied. "

More transparent cross-stakeholder discussions are taking place



Implementation at Novartis

Awareness	Education	Implementation
'what has changed?'	**'a new way of thinking'**	**'how do I..?'**
• Why do I need to know about the estimand framework? • What is the reason for change? • What is the benefit and value to the business?	• Increase depth of knowledge about the rationale for change and the benefits of the estimand framework • Introduction to the thinking process – train cross-functional teams by asking them to work through case studies • Templates with key questions to gear the discussion amongst clinical, regulatory and statistics at the design stage	• Providing clinical teams guidance on the practical aspects through informal forums to discuss their estimand of choice with cross-functional experts • How to document a chosen estimand in Briefing Books / Study Protocols / SAPs / CSRs / Submission Dossiers • Engage with regulatory agencies on rationale for chosen estimands • Uptake of causal inference methods

Some of our internal activities

Trainings

- Cross-functional estimand trainings
- Statistical analyses targeting estimands
- Introduction to causal inference

Communities

- Promotion of Estimand Thinking (POET team)
- Estimand Journal Club
- ‘Causal Inference in Practice’ interest group

Selection of publications and methodological work

Combining the target trial and estimand frameworks to define the causal estimand: an application using real-world data to contextualize a single-arm trial

Authors: Lisa V Hampson[1], Jufen Chu[2], Aiesha Zia[1], Jie Zhang[2], Wei-Chun Hsu[3], Craig Parzynski[3], Yanni Hao[2], Evgeny Degtyarev[1]

Estimands in clinical trials – broadening the perspective

Mouna Akacha,[a*†] Frank Bretz[a] and Stephen Ruberg[b]

Generating the right evidence at the right time: Principles of a new class of flexible augmented clinical trial designs

C Dunger-Baldauf[a,1], R Hemmings[b,1], F Bretz[a,c], B Jones[d], A Schiel[e], C Holmes[f]

Connecting Instrumental Variable methods for causal inference to the Estimand Framework

Jack Bowden, Björn Bornkamp, Ekkehard Glimm, Frank Bretz

Principal stratum strategy: Potential role in drug development

Björn Bornkamp[1] | Kaspar Rufibach[2] | Jianchang Lin[3] | Yi Liu[4] | Devan V. Mehrotra[5] | Satrajit Roychoudhury[6] | Heinz Schmidli[1] | Yue Shentu[7] | Marcel Wolbers[2]

Estimands for Recurrent Event Endpoints in the Presence of a Terminal Event

Heinz Schmidli[a], James H. Roger[b], and Mouna Akacha[c]

[a]Statistical Methodology, Novartis, Basel, Switzerland; [b]Medical Statistics Department, London School of Hygiene & Tropical Medicine, London, UK; [c]Statistical Methodology, Novartis, Basel, Switzerland, on behalf of the Recurrent Event Qualification Opinion Consortium*

Bayesian inference for a principal stratum estimand to assess the treatment effect in a subgroup characterized by postrandomization event occurrence

Baldur P. Magnusson, Heinz Schmidli, Nicolas Rouyrre, Daniel O. Scharfstein

Bayesian inference for a principal stratum estimand on recurrent events truncated by death

Tianmeng Lyu[1] | Björn Bornkamp[2] | Guenther Mueller-Velten[2] | Heinz Schmidli[2]

Sensitivity analyses for the principal ignorability assumption using multiple imputation

Craig Wang[1] | Yufen Zhang[2] | Fabrizia Mealli[3,4] | Björn Bornkamp[1]

More broadly…

- Estimand framework was very helpful in assessing the impact of the Covid-19 pandemic on clinical trials
- Several working groups exists to discuss relevant estimands for specific settings, e.g. oncology, neuroscience, safety,...
- Some regulatory, therapeutic area guidelines are picking up estimand concepts
- Increasing number of case studies use causal inference methodology (prospectively and retrospectively)
- Numerous publications, conference sessions, workshops and short courses with cross-stakeholder involvement

Conclusions

Conclusions

- Estimand framework plays an important role in drug development and RCTs
- Besides aiding clarity and providing structure, it creates opportunities to push traditional boundaries
- Increasing interest in causal inference for RCTs
  - FDA guidance on covariate adjustment
  - More case studies where causal inference methodology was used to gain insights into trial data
- What is missing?
  - Recommendations on which estimands are relevant for which setting
  - Clearer alignment between the different schools of thought, e.g. ICH E9 (R1) vs. target trial framework vs. causal roadmap vs. ...
  - More discussion on the role of identification assumptions vs. statistical assumptions
  - More discussion on the role of designs
  - Easy-to-use tools for implementation of estimation approaches which are not traditionally used in drug development
  - ...

Long journey and we are just at the beginning...

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Thank you

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