Mission impossible?

Specifying Target Estimands For Long-Term Risks and Benefits of Novel Treatments

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Acknowledging the contributions of several TG5 members, especially **Nicholas Bakewell, Suzanne Cadarette, Paola Rebora, Susan Halabi, Gail Mitchell**

About Topic Group 5 (TG5)

- Focus of TG5: Study design

(https://stratos-initiative.org/en/group_5)

- Aim: promote robust planning and design of observational studies
  - Highlight gaps in current guidance and design implementations
  - Propose novel guidance and tools

- Topic today: challenges with posing causal questions evaluating long-term outcomes after repeated exposure.

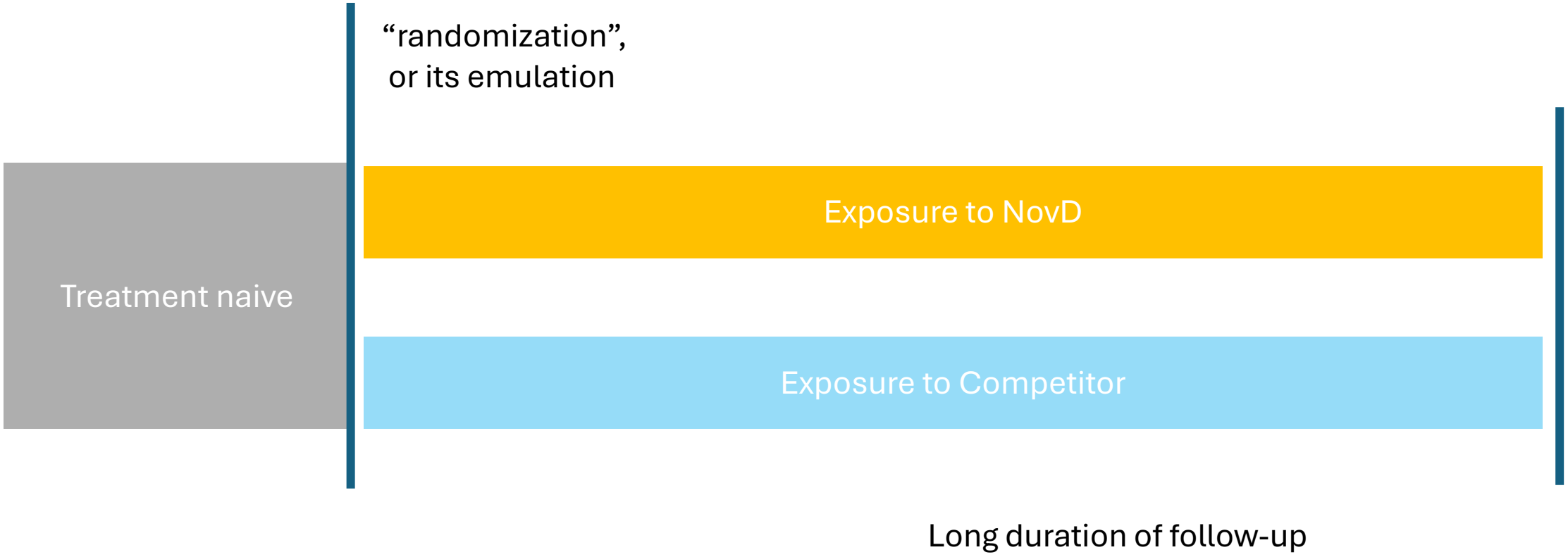
Relevance: long-term outcomes in chronic exposure

- Clinical care for chronic indications (e.g., diabetes, rheumatoid arthritis) include use of multiple/repeated exposure to treatments
- At time of approval of a new treatment in a chronic indication
  - Randomized clinical trials < 2 years exposure
  - Knowledge gap of long-term *comparative* treatment effect (benefits, risks)
  - Observational studies may fill this knowledge gap

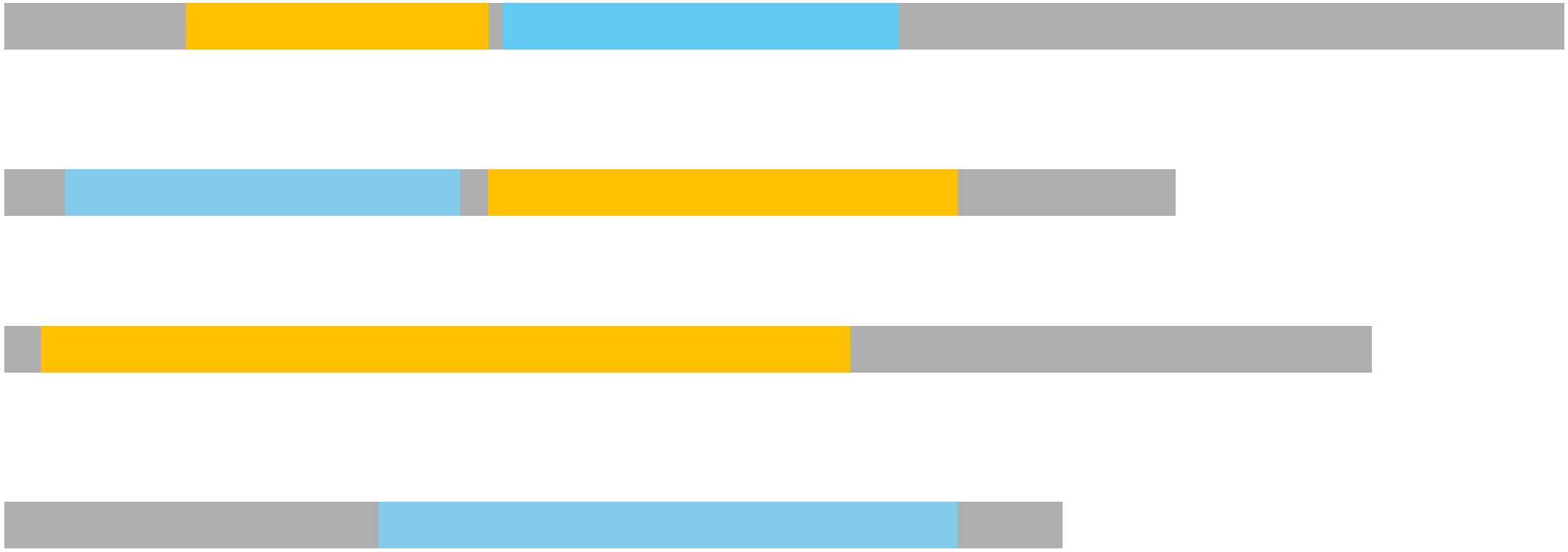
Challenges in asking (comparative) questions on (long-term) outcomes

- Evolving treatment landscape in time and geographies as clinical guidelines change and new treatments are approved
- Dynamic treatment landscape in real-world utilization (switching, dose escalation, gaps in therapy, concurrent treatment)
- Flexibility needed in planning studies to handle above challenges go against pre-specification principles recommended in most guidelines

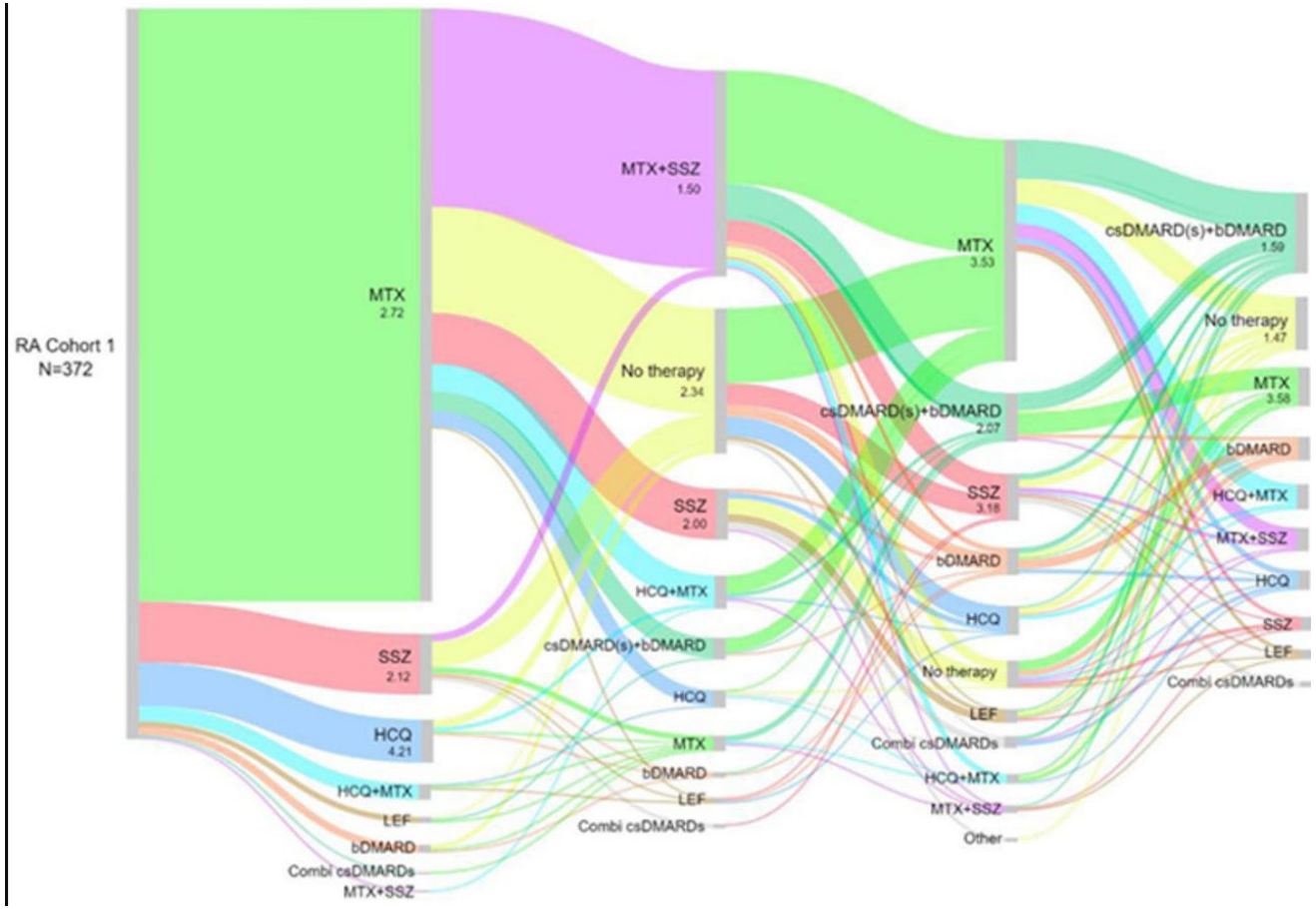
Expectation (idealized target trial)



Reality

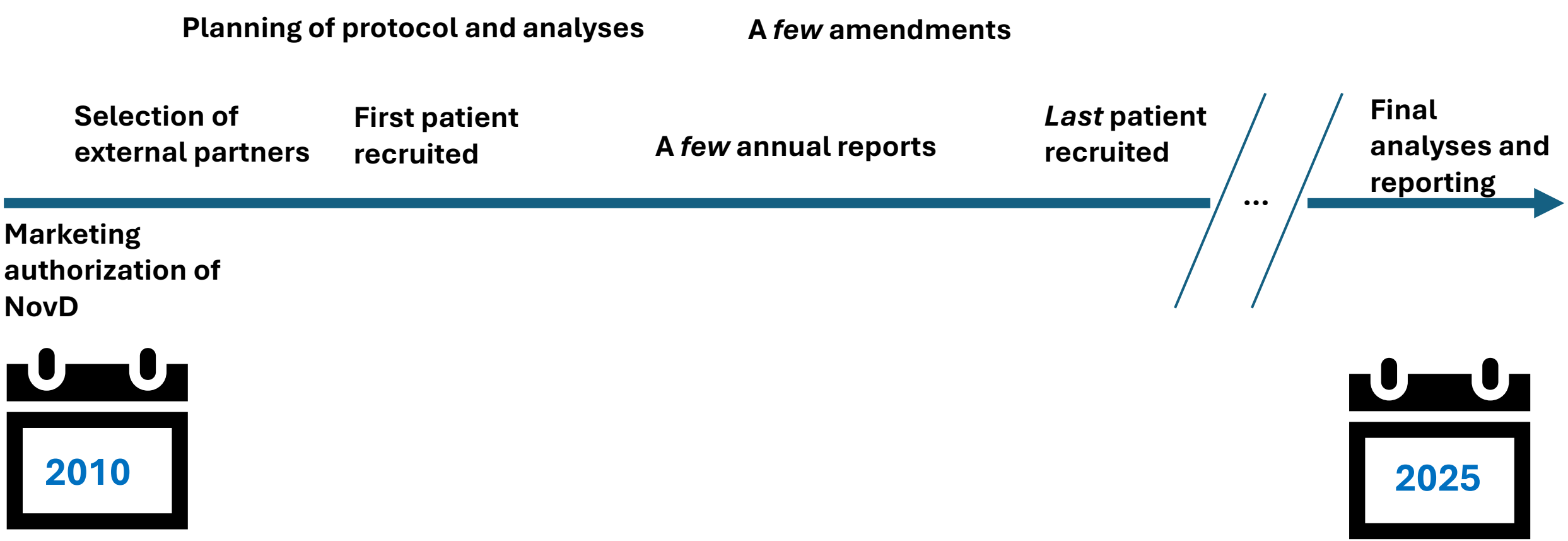


Reality (continued): dynamic treatment landscape e.g., Real-world use in rheumatoid arthritis



Source: (Figure 1) Sankey diagram of the treatment pathway of the first 3 switches of RA (Coppes et al 2025)

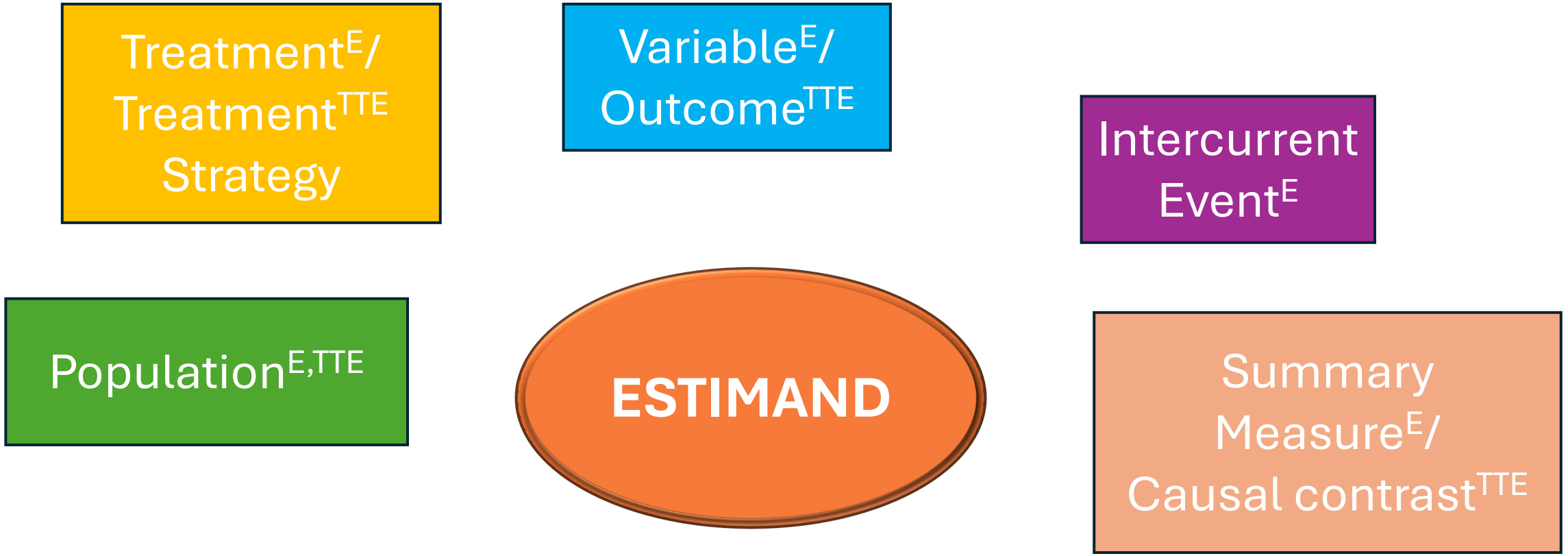
Reality (continued): milestones and timelines for planning studies (hypothetical NovD)



* Start and end dates for illustration purposes only

Estimands, existing and novel considerations

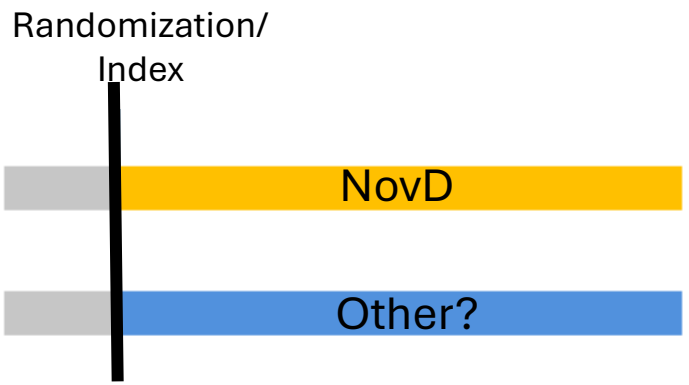
Estimands, Existing Frameworks (refresher)



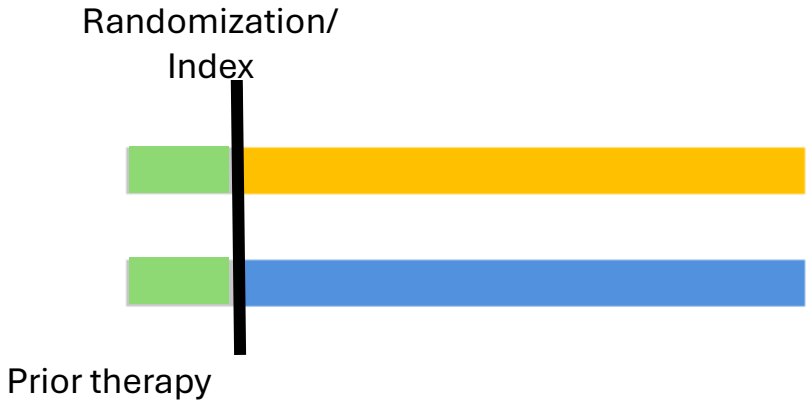
E: Estimand Framework (ICH-E9 (R1))
TTE: Target Trial Emulation (Hernan & Robins 2016)

Specifying the target causal estimand(s) can identify the comparator(s) and index date

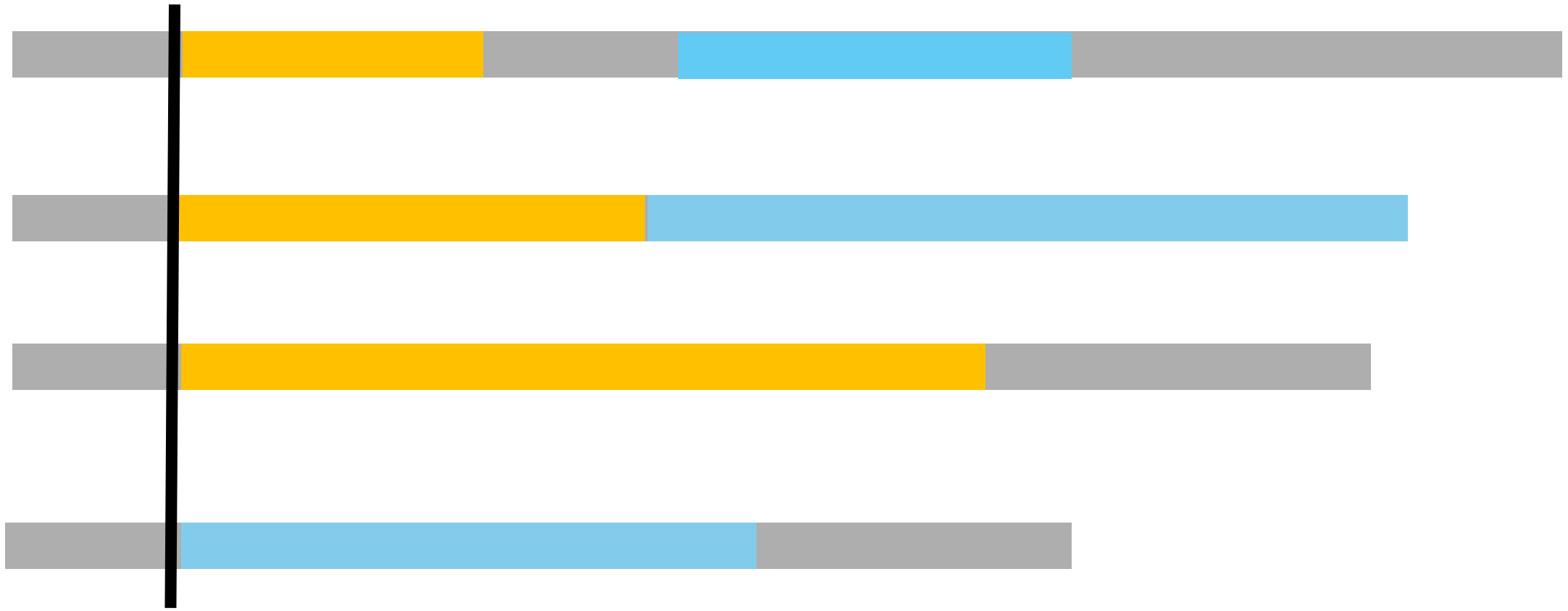
Target Trial 1: naive users



Target Trial 2: experienced users



Existing handling strategies fall short in long latency/long- follow-up



Alternative estimands?

- Background descriptive estimands: to clarify what time-frame are relevant for exposure and outcomes
  - How does the outcome change over the natural history of each patient since diagnosis? (across all treatments)
  - What is the treatment landscape, how does it change over natural history and over calendar time/geography?
- Estimands considering a continuum of exposure:
  - Does the outcome change as a function of cumulative dose (to a product or to a drug class)?
  - What is the impact of time since diagnosis prior to exposure on outcome?
  - Considering patients exposed to a mix of therapies for X years, what was the impact of including NovD in the mix versus not having NovD in the mix on outcomes?

Pre-specification at the right time

Too early:
Larger knowledge gap,
Many assumptions

Just right?
Smaller knowledge gap,
Fewer assumptions

Too late:
Potential investigator bias

Marketing authorization of NovD

Final analyses and reporting

Accrual of information about NovD from other clinical studies

Accrual of information about real-world utilization (e.g., drug utilization)

Changes in clinical practice and/or the competitive landscape of NovD

References

Hernan, M. A. & Robins, J. M., 2016. Using big data to emulate a target trial when a randomized trial is not available. *American journal of epidemiology,* 183(8), pp. 758-764.

ICH, 2019. *ICH E9(R1) Addendum: Statistical principles of clinical trials*. [Online] Available at: https://www.ich.org/page/efficacy-guidelines#9-2

T. Coppes, et al (2021), POS0620 Treatment pathways of rheumatoid arthritis patients leading to biologic therapy visualized in a Sankey diagram. Annals of the Rheumatic Diseases, 80(1), 2021, pp 547-548

Acknowledgments

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Thank you

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Back-up