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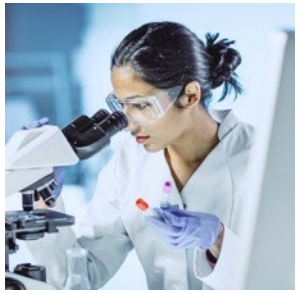
Target trial and Estimand in Post-market Safety Studies





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Acknowledging input of several industry colleagues

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Take home messages

- Specifying the target causal estimand is critical in post-authorization safety study (PASS). They clarify
    1. **Purpose & estimand:** the knowledge gap and the causal discovery objectives
    2. **Planning & interpretation:** align (data source, design, and analyses) with the estimand
- Practical considerations when using these frameworks
    A. Knowledge gaps/estimands of interest evolve: consider sequential multi-stakeholder evaluation of the gaps and the estimands
    B. Relevant information accrues post-market: consider its impact on the estimation (e.g., master target trial, methods for integrated evidence)
    C. Premature pre-specification is detrimental: allow time for reducing the knowledge gap (e.g., exposure patterns, and confounding) prior to pre-specifying estimand and estimation methods

(Hypothetical) case study: NovD

•**NovD:** Biologic drug *first* approved to treat patients with **a chronic** indication by repeated exposure

•PASS request:

- Compare the risk of **malignancy** of NovD to other therapies for this indication in a (new) prospective epidemiological study with long-term follow-up (> 8 years follow-up, 4 years of recruitment)
- Submit protocol and analyses plan for review in *a few* months.

*NovD is a fictitious name, for illustration purposes only

NovD case study: milestones and timelines

Protocol and SAP development

A *few* SAP amendments

Selection of external partners

First patient recruited

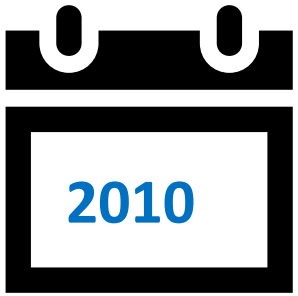
A *few* annual reports

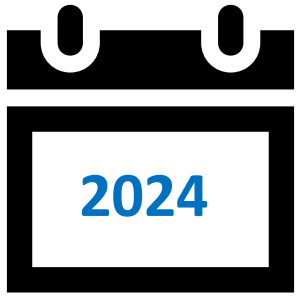
***Last* patient recruited**

...

Final analyses and reporting

Marketing authorization of NovD



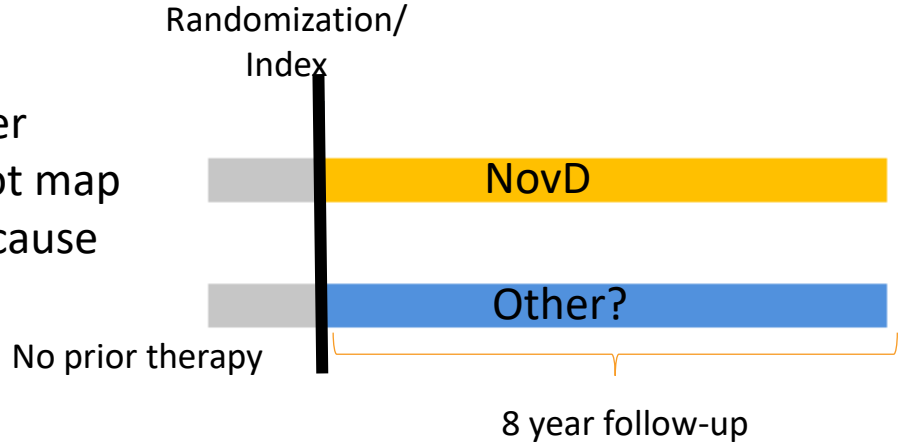


* Start and end dates for illustration purposes only

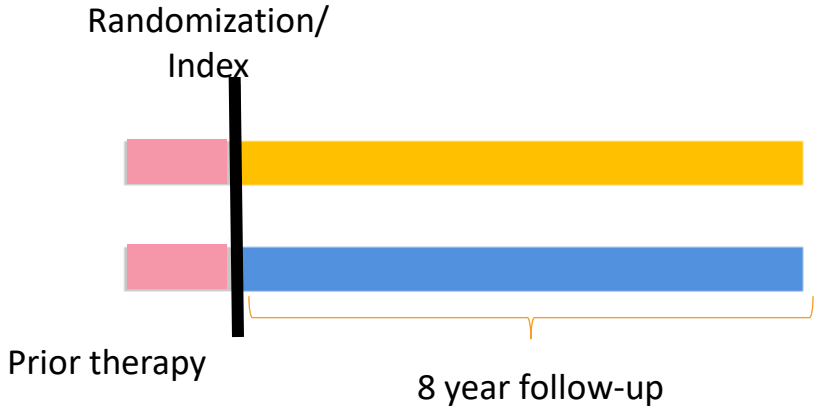
Specifying the target causal estimand(s) clarifies the main comparison(s) of interest

Note: ever vs. never comparisons do not map to a target trial because ill-defined time-0

Target Trial 1: naive users?

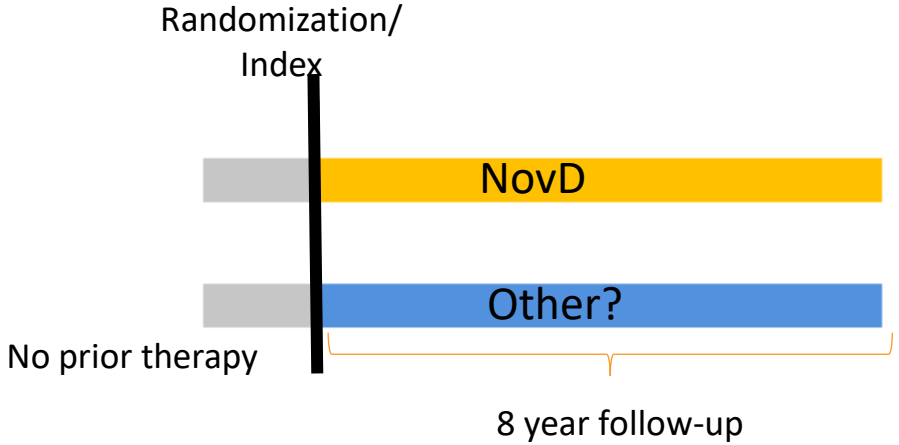


Target Trial 2: experienced users?



Specifying the target causal estimand(s) clarifies the main comparison(s) of interest (contd)

Target Trial 1: naive users?



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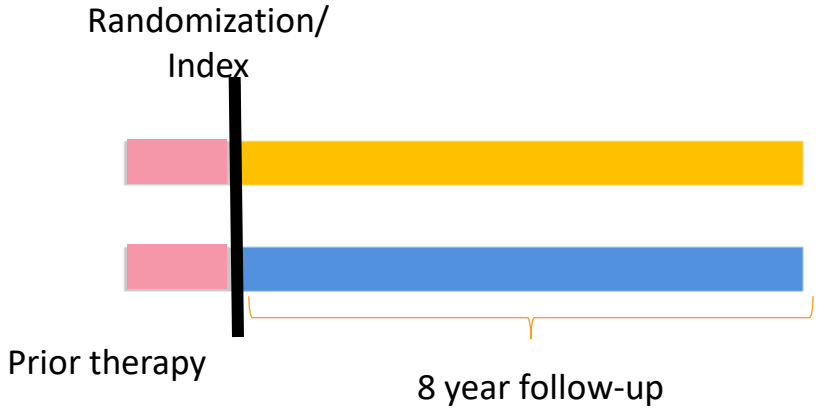
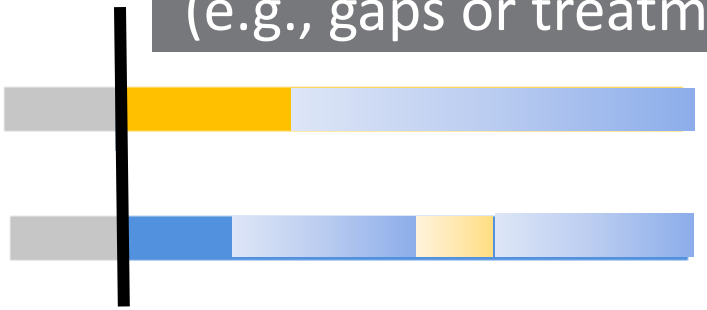


Handling intercurrent event(s)? (e.g., gaps or treatment switching)

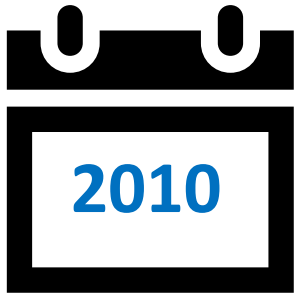


Benefit of specifying target causal estimand on planning and interpretation

- Specifying the target causal estimand simplifies multiple planning and evidence interpretation decisions, such as
    - Identifying data sources needed based on relevance and reliability
    - Designing a study emulating the target trial
    - Assessing power and feasibility of a specific design
    - Identifying potential sources of bias
    - Pre-specifying design and analytical methods to eliminate, minimize, and mitigate sources of bias

Practical considerations

Marketing authorization of NovD

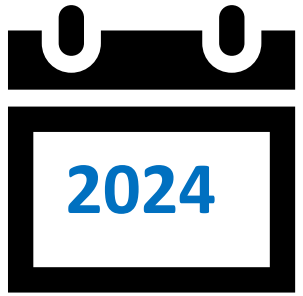


Accrual of information about NovD from other clinical studies

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

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

Final PASS report

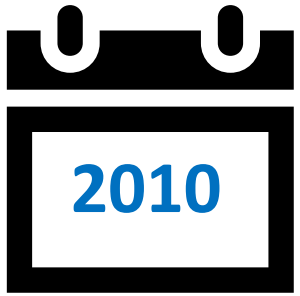


Knowledge gaps/Estimands of interest evolve

High knowledge gap motivated PASS

Knowledge gap status?

Marketing authorization of NovD



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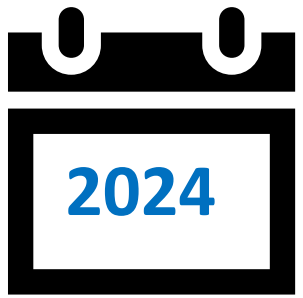

Relevant information accrues post-market

Set target estimand

Design PASS
Plan to integrate other relevant information?

Marketing authorization of NovD

Final PASS report

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

Premature pre-specification is detrimental

Too early:
Larger knowledge gap,
Many assumptions

Just right?
Smaller knowledge gap,
Fewer assumptions

Too late:
Potential investigator bias

Marketing authorization of NovD

Final PASS report

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

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Thank you