Quantitative Safety & Epidemiology (QSE)

Long term safety – how to hit a moving target

V Jehl, P Lopez Romero, R Izem
BES
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Disclaimer

I’m a full time Novartis employee.

The views and opinions expressed in this presentation represents my own views and interpretations and does not represent Novartis.

Safety: different paths, same available frameworks

Even though different questions are addressed, the available frameworks whether target trial or estimand also apply to Safety...

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Agenda

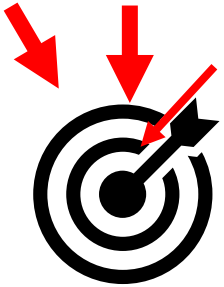
1. Background
   - Setting for case study
   - FDA request
2. Emulating the target trial
   - Application
3. Take home messages

Take home messages

- The different target trial /estimand existing **quantitative frameworks** are also **helpful** in **safety**

- When working on a post-marketing approval request (PMR):
  - **Drug utilisation study is key**

- When switching is present
  - «**Trade-off**» between clear target clinical question and drug use needs to be found
  - **Mitigations** include providing several estimates, knowing they address different questions



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Background

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Setting for case study

Indication

- **Chronic** indication for which life long treatment is required

Therapeutic landscape

- Drugs are already available for the indication including non-biologics and biologics
  - Their number increased over time (**>10 different drugs**)

Post-approval i.e., after initial drug approval

- At time of drug approval, the safety events categorized as identified vs. potential risks
  - **Potential risks**:
    - Include **theoretical risks** based on mechanism of action of the drug
      - Often limited information available at time of approval
        - Can include latent events

Post approval marketing request

FDA post marketing authorization request (PMR)

A **postmarketing prospective, long-term, observational study** to assess the **long-term safety** of *Drug NovD* compared to other therapies used in the treatment of adults with moderate to severe *Indication* who are candidates for systemic therapy in a real-world clinical setting.

The study's **primary outcome is malignancies**.

Describe and justify the **choice of appropriate comparator population(s).**

Design the study around a **testable hypothesis** to assess, with sufficient sample size and power, a **clinically meaningful increase in malignancy risk above the comparator background rate**.

Specify concise case definition and validation algorithms for the primary outcome.

Enroll patients over an initial **4-year period** and **follow for a minimum of 8 years from the time of enrollment**.

Is the clinical question of interest clearly defined?

Little survey...
For you what is long term safety?

Is the clinical question of interest clearly defined?

What is long term safety?

A) Drug exposure **8 years** and safety assessed after **8 years**?

B) Drug exposure **5 years** and safety assessed after **8 years**?

C) Drug exposure **1 year** and safety assessed after **8 years**?

D) Drug exposure **2 months** and safety assessed after **8 years**?

E) Drug exposure **2 months** and safety assessed after **2 years**?

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Emulating the target trial

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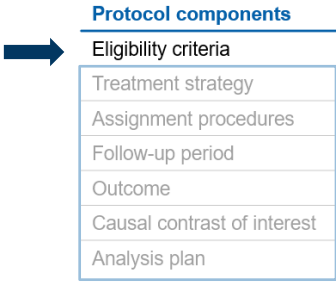
Target trial emulation: protocol components

Table 1 in Hernan and Robins 2016,
Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available

Protocol components	Estimand attribute «equivalent»$$
Eligibility criteria	Population
Treatment strategy	Treatment
Assignment procedures	*Randomization*
Follow-up period	
Outcome	Variable/endpoint
Causal contrast of interest	Population level summary
Analysis plan	
	Intercurrent event + handling

Ref: Am J Epidemiol. 2016; 183(8):758-764



Target trial emulation: protocol components – Eligibility criteria

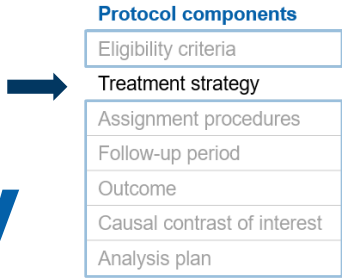
- Adult (≥18 years at enrollment)
- Patients with moderate to severe *Indication*
- Eligible for systemic therapy in real-world setting for *Indication*
- No prior history of malignancy

- Any need to restrict prior medication *(TBD later)*?

PMR:

A postmarketing prospective, long-term, observational study to assess the long-term safety of *Drug NovD* compared to other therapies used in the **treatment of adults with moderate to severe *Indication*** who are **candidates for systemic therapy in a real-world clinical setting**.

Target trial emulation: protocol components – Treatment strategy



- Exposure arm: Drug NovD
- Comparator arm:
  - Other systemic therapies for treatment of moderate to severe *Indication*

PMR:

A postmarketing prospective, long-term, observational study to assess the **long-term safety** of *Drug NovD* **compared to other therapies used in the treatment of adults with moderate to severe *Indication*** who are **candidates for systemic therapy** in a real-world clinical setting.

Describe and justify the **choice of appropriate comparator population(s).**

Target trial emulation: protocol components – Treatment strategy (2)

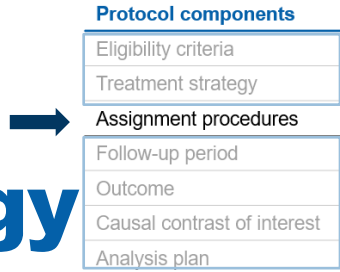
Protocol components
- Eligibility criteria
- → Treatment strategy
- Assignment procedures
- Follow-up period
- Outcome
- Causal contrast of interest
- Analysis plan

- Many other systemic therapies available for moderate to severe *Indication*
- Link between treatment strategy <-> eligibility criteria

Trial 1: No prior biologic therapy	Trial 2: Prior biologic therapy
Treatment strategies: 1) NovD 2) Biologic therapy 3) Non-biologic therapy	Treatment strategies: 1) NovD 2) Biologic therapy

=► Not one single target trial but rather two

Target trial emulation: protocol components – Assignment strategy



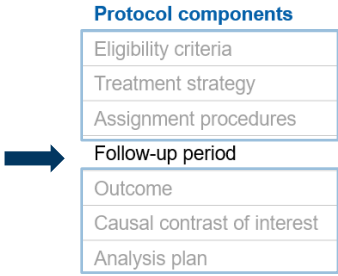
- In target trial, treatment would be assigned randomly to each treatment strategy

Trial 1: No prior Biologic therapy	Trial 2: Prior Biologic therapy
3 arm treatment strategy: 1) NovD 2) Biologic therapy 3) Non- Biologic therapy	2 arm treatment strategy: 1) NovD 2) Biologic therapy

PMR:

No details included

Target trial emulation: protocol components – Follow-up period

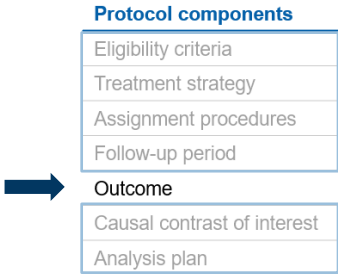


- Follow-up expected to be a **minimum of 8 years** from enrollment
  - Patient level translating into follow-up time is the minimum of time until event of interest, study discontinuation, death, lost to follow-up

PMR:

Enroll patients over an initial **4-year period** and **follow for a minimum of 8 years from the time of enrollment**.

Target trial emulation: protocol components – Outcome



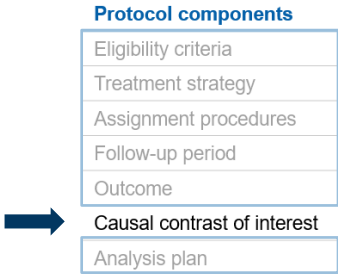
- Primary outcome: malignancy
  - With supporting source documentation to confirm diagnosis i.e. only validated events are considered

PMR:

The study's **primary outcome is malignancies**.

Specify concise case definition and validation algorithms for the primary outcome.

Target trial emulation: protocol components – Causal contrast of interest



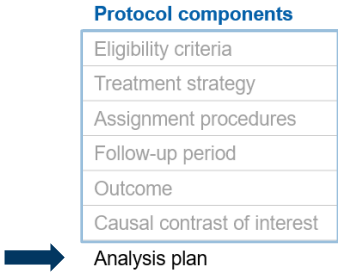
- Intention-to-treat effect
  - [using *Hernan& Robin's 2016* notation ↔ $$Treatment policy$$]

PMR:

Design the study around a **testable hypothesis** to assess, with sufficient sample size and power, a **clinically meaningful increase in malignancy risk above the comparator background rate**

Ref: Hernan and Robins, *Am J Epidemiol. 2016; 183(8):758-764*

Target trial emulation: protocol components – Analysis plan



- Intention-to-treat (ITT) effect via comparison of the 8-year malignancy risk among individual assigned to the treatment strategies
  - [ITT using *Hernan& Robin's 2016* notation ↔ $$Treatment policy$$]
  - Comparison **irrespective** of whether the treatment strategy is followed
    - $$Intercurrent events of treatment=discontinuation
      Handling via treatment policy strategy$$

PMR:

Design the study around a **testable hypothesis** to assess, with sufficient sample size and power, a **clinically meaningful increase in malignancy risk above the comparator background rate**

Target trial emulation: Further item

Protocol components
Eligibility criteria
Treatment strategy
Assignment procedures
Follow-up period
Outcome
Causal contrast of interest
Analysis plan
Further

- **Time 0** replacing randomization time in observational study
  - Key to align this time between eligibility checks, treatment assignment and start of follow-up
    - Target trial 1 (Biologic naive): time 0 is start of Biologic therapy
    - Target trial 2 (Not «Biologic naive»): less clear
      - time 0 is start of a new Biologic therapy ?
        - i.e., A therapy the patient was to exposed to in the past

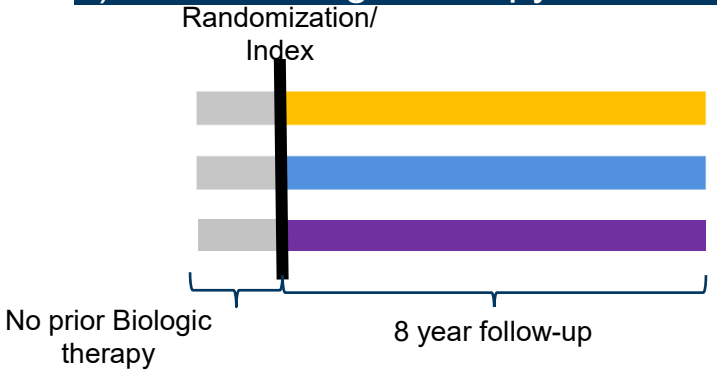
- **Correcting for confounder at baseline**
  - No randomization can lead to confounder at index
  - Propensity score are used to correct for possible confounder at index
    - Patients are weighted so that the characteristics at index are balanced between treatment strategies at index
      - Main focus: characteristics affecting both treatment strategy and outcome

From PMR to two Target trials

Trial 1: No prior Biologic therapy

Treatment strategies:

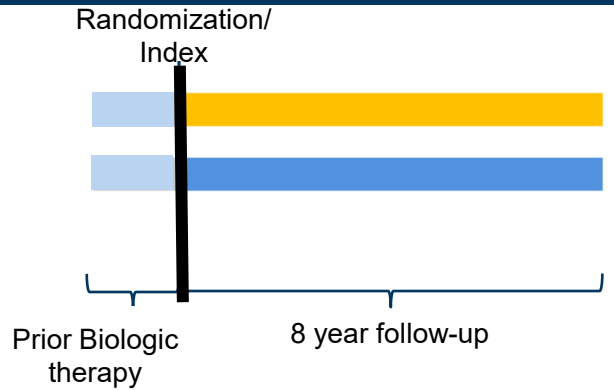
1) NovD
2) Biologic therapy
3) Non- Biologic therapy



Trial 2: Prior Biologic therapy

Treatment strategies:

1) NovD
2) Biologic therapy



Alas!

Alas! Real world use can often not be fully anticipated

In real-world, patients changed therapies «a lot».

Even though we target the ITT estimate, we now wonder...

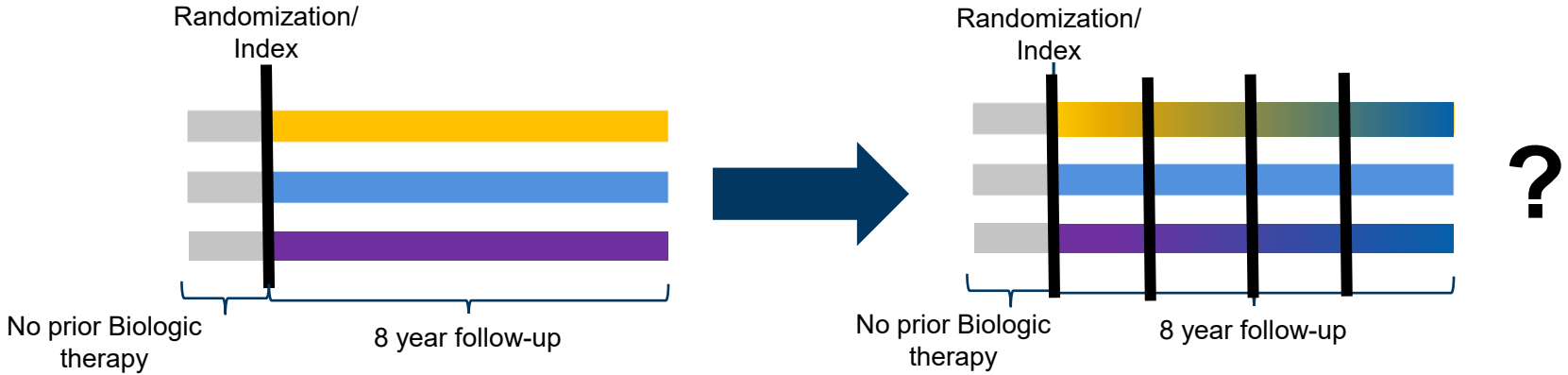
Looking at NovD use:

a) 40% of patients discontinue within 12 first months

b) 25% of patients discontinue within 12 to 24 first months

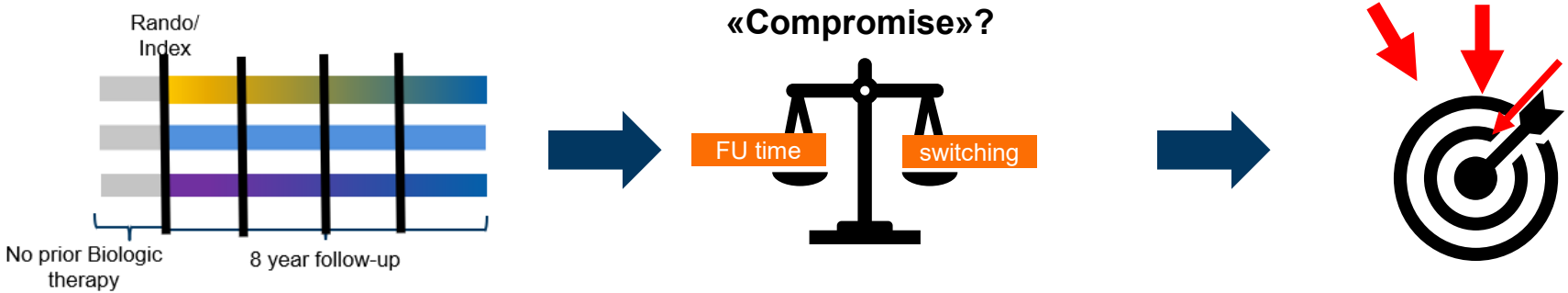
➢ **Is the clinical question (looking at 8-year FU) still relevant?**

Is the 8-year ITT question still clinically relevant?



- Is this switching and 8-year ITT **“compatible”?**
- Do we need to **change the question of interest** so that what we conclude would be more interpretable?

A series of «new» clear questions… rather than only the 8-year ITT question?



Continue with "ITT"- type question

- **Reduce FU time**
- **Consider also 4 or 5 years?**

Affect Target trial element: **FU changed**

Change to "per-protocol"*/Adherence-type question/ $$Hypothetical strategy$$]

- **Consider 2, 3, 4-year adherent?**

Affect Target trial element: **Causal contrast+ Analysis**

*Hernan and Robins, *Am J Epidemiol. 2016; 183(8):758-764*

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Our learnings

1. The **existing frameworks were usefull**
   - Emulating the target trial(s)
     - Two separate target trials are needed
     - Time 0 is an issue when biologic non-naive is considered
   - $$Estimand$$
     - Helped us thinking and reasoning on the intercurrent event/discontinuation

2. Understanding the **real-world drug use** was key, when treatment **switching** is predominant
   - The **clinical question of interest** becomes **less clear**
   - Is the **long term (8-year) safety question** at all **relevant/identifiable** in this context?

A **trade-off** need to be found between Switching and FU time

May be better adressed using a «**series» of well defined questions** rather than one less relevant one

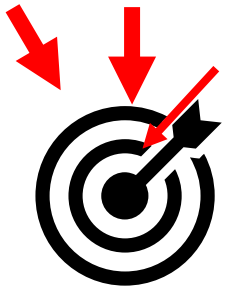
3. Re-negotiation with HA may be needed

Take home messages

- The different target trial /estimand existing **quantitative frameworks** are also **helpful** in **safety**

- When working on a post-marketing approval request (PMR):
  - **Drug utilisation study is key**

- When switching is present
  - «**Trade-off**» between clear target clinical question and drug use needs to be found
  - **Mitigations** include providing several estimates, knowing they address different questions



Take home messages

Main references

Hernan and Robins; Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available; Am J Epidemiol. 2016; 183(8):758-764

Hernan; The Hazards of Hazard Ratios; *Epidemiology* 21(1):p 13-15, January 2010.; *DOI:* 10.1097/EDE.0b013e3181c1ea43

Danaei et al; Observational data for comparative effectiveness research: An emulation of randomised trials of statins and primary prevention of coronary hearth disease; Statistics Methods in Medical Research 2011; 22 (1) 70-97

Thank you

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