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SCIENCE MEDICINES HEALTH

Use of Estimands in Target Trial Emulation

ENCePP plenary meeting, 1st December 2023

Juan Jose Abellan, EMA, Data Analytics and Methods Taskforce
With thanks to Chantal Quinten and Marcia Rueckbeil

Target Trial Emulation

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- Questions around **comparative effectiveness or safety** should ideally be addressed with a randomised clinical trial (RCT)
- Causal inference from observational databases can be viewed as an attempt to emulate an RCT: the target trial
- Evidence from RCTs is considered stronger over non-interventional studies (NIS)
  - Confounding, bias, time zero,…
- Hernán and Robins (2014) outlined the Target Trial Emulation framework for comparative studies (using large RWD sources) that makes the target trial explicit
- A promising tool to better bridge between RCTs and NIS

Target Trial Emulation

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- Suggested key elements of the target trial to be specified:
  - Eligibility criteria → **P**opulation
  - Treatment strategies → **I**ntervention / **C**ontrol
  - Assignment procedures
  - Follow-up period
  - Outcome → **O**utcome
  - Causal contrasts of interest
  - Analysis plan
- The TTE **has been used in real settings** to support regulatory decision making

RWD Studies using TTE*

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Effectiveness in a large-scale setting

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting

Noa Dagan, M.D., Noam Barda, M.D., Eldad Kepten, Ph.D., Oren Miron, M.A., Shay Perchik, M.A., Mark A. Katz, M.D., Miguel A. Hernán, M.D., Marc Lipsitch, D.Phil., Ben Reis, Ph.D., and Ran D. Balicer, M.D.

STUDY DESIGN

We designed this observational study to emulate a target trial of the causal effect of the BNT162b2 vaccine on Covid-19 outcomes.[4] Eligibility criteria

Annals of Internal Medicine ORIGINAL RESEARCH

COVID-19 Vaccination Effectiveness Against Infection or Death in a National U.S. Health Care System

A Target Trial Emulation Study

George N. Ioannou, BMBCh, MS; Emily R. Locke, MPH; Ann M. O'Hare, M... Denise M. Hynes, MPH, PhD, RN; and Kristin Berry, PhD

Vaccination Effectiveness: Target Trial Emulation

We designed this observational study to emulate a target trial of COVID-19 vaccination versus placebo (10).

Head-to-head comparisons

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Comparative Effectiveness of BNT162b2 and mRNA-1273 Vaccines in U.S. Veterans

Barbra A. Dickerman, Ph.D., Hanna Gerlovin, Ph.D., Arin L. Madenci, M.D., Ph.D., Katherine E. Kurgansky, M.P.H., Brian R. Ferolito, M.Sc., Michael J. Figueroa Muñiz, B.Sc., David R. Gagnon, M.D., Ph.D., M.P.H., J. Michael Gaziano, M.D., M.P.H., Kelly Cho, Ph.D., Juan P. Casas, M.D., Ph.D., and Miguel A. Hernán, M.D., Dr.P.H.

SPECIFICATION OF THE TARGET TRIALS

We designed this observational analysis to emulate a target trial (i.e., a hypothetical pragmatic trial that would have answered the causal question of interest) of BNT162b2 as compared with mRNA-1273 for the prevention of Covid-19 outcomes in the VA health care system. The key com-

Safety in a large-scale setting

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Safety of the BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting

Noam Barda, M.D., Noa Dagan, M.D., Yatir Ben-Shlomo, B.Sc., Eldad Kepten, Ph.D., Jacob Waxman, M.D., Reut Ohana, M.Sc., Miguel A. Hernán, M.D., Marc Lipsitch, D.Phil., Isaac Kohane, M.D., Doron Netzer, M.D., Ben Y. Reis, Ph.D., and Ran D. Balicer, M.D.

STUDY SETTING

We analyzed observational data from Clalit Health Services (CHS) in order to emulate a target trial of the effects of the BNT162b2 vaccine on a broad range of potential adverse events in a population without SARS-CoV-2 infection. CHS is the larg-

Effectiveness in special populations

nature medicine BRIEF COMMUNICATION https://doi.org/10.1038/s41591-021-01490-8

Check for updates

Effectiveness of the BNT162b2 mRNA COVID-19 vaccine in pregnancy

Noa Dagan[1,2,3,4,14], Noam Barda[1,2,3,4,14], Tal Biron-Shental[5,6], Maya Makov-Assif[1], Calanit Key[7], Isaac S. Kohane[3,4], Miguel A. Hernán[8,9], Marc Lipsitch[10], Sonia Hernandez-Diaz[8], Ben Y. Reis[4,11,12] and Ran D. Balicer[1,4,13]

Effectiveness of boosters in large-scale setting

Effectiveness of a third dose of the BNT162b2 mRNA COVID-19 vaccine for preventing severe outcomes in Israel: an observational study

Noam Barda*, Noa Dagan*, Cyrille Cohen, Miguel A Hernán, Marc Lipsitch, Isc...

Study design and participants

This study was designed to emulate a target trial[14] of the effects of a third dose of the BNT162b2 vaccine in a population of individuals who had already received two doses of the vaccine at least 5 months before recruitment. The study design is similar to our previous

* Xabier Garcia de Albeniz presentation at ENCePP Plenary Meeting 2022

FDA RCT DUPLICATE

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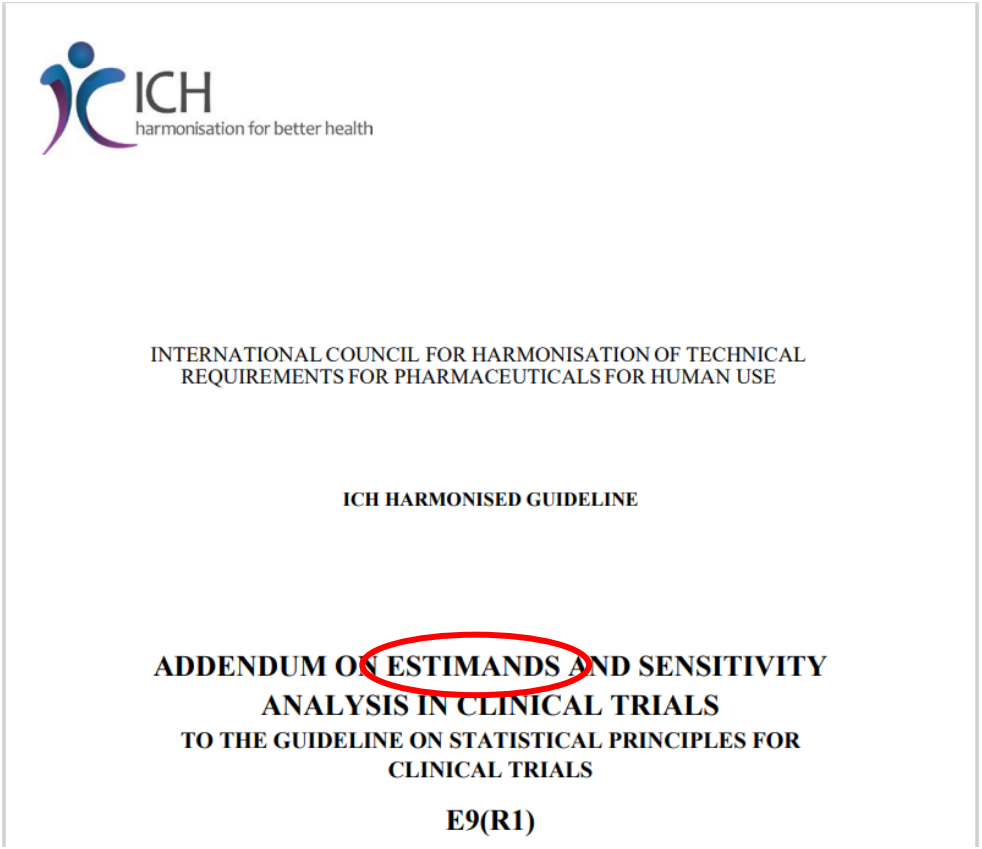
- Can RCTs results be replicated using NIS based on RWD?
- NIS emulating design of 30 completed + 2 ongoing RCTs
- Using data from 3 US claims databases from *SENTINEL* system (Optum Clinformatics, MarketScan, and Medicare): 'fit for purpose'
- PICO(T) framework was used to define the research question of interest
  - PICO(T) (Richardson et al, 1995) is well established in RWE
  - The closer the NIS can emulate the PICO(T) elements of the RCT, the closer the results

Framework to define the research question in an RCT?



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)

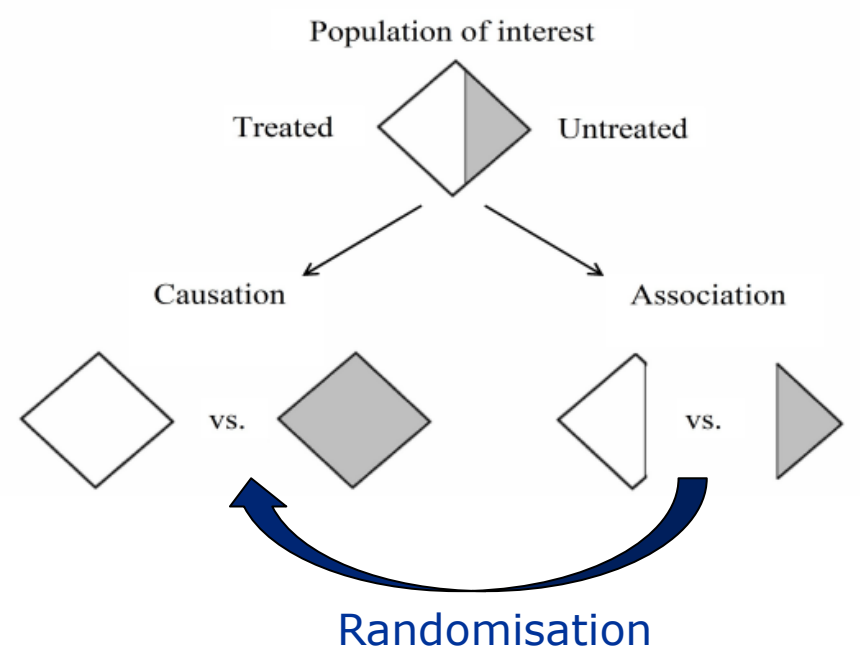
*"An estimand is a **precise description of the treatment effect** reflecting the clinical question posed by a given clinical trial objective."*

ICH E9(R1) is driven by causal inference principles

Definition of treatment effect in guideline:

A.3. ESTIMANDS
[…] treatment effects: how the outcome of treatment compares to what would have happened to the same subjects under alternative treatment (i.e. had they not received the treatment, or had they received a different treatment).

Fig 1.1 from Hernán and Robins (2020)



ICH E9(R1) addressed other gaps and lack of clarity in RCTs

- Lack of logical connectivity between trial objectives, design, conduct, analysis and interpretation
- Insufficient clarity in how objectives of clinical trials linked to estimation of treatment effect parameters of interest
- Misalignment between “missing data” analysis methods and treatment effects of interest
- Misunderstanding of the term “sensitivity analysis”

ICH E9(R1) in a nutshell

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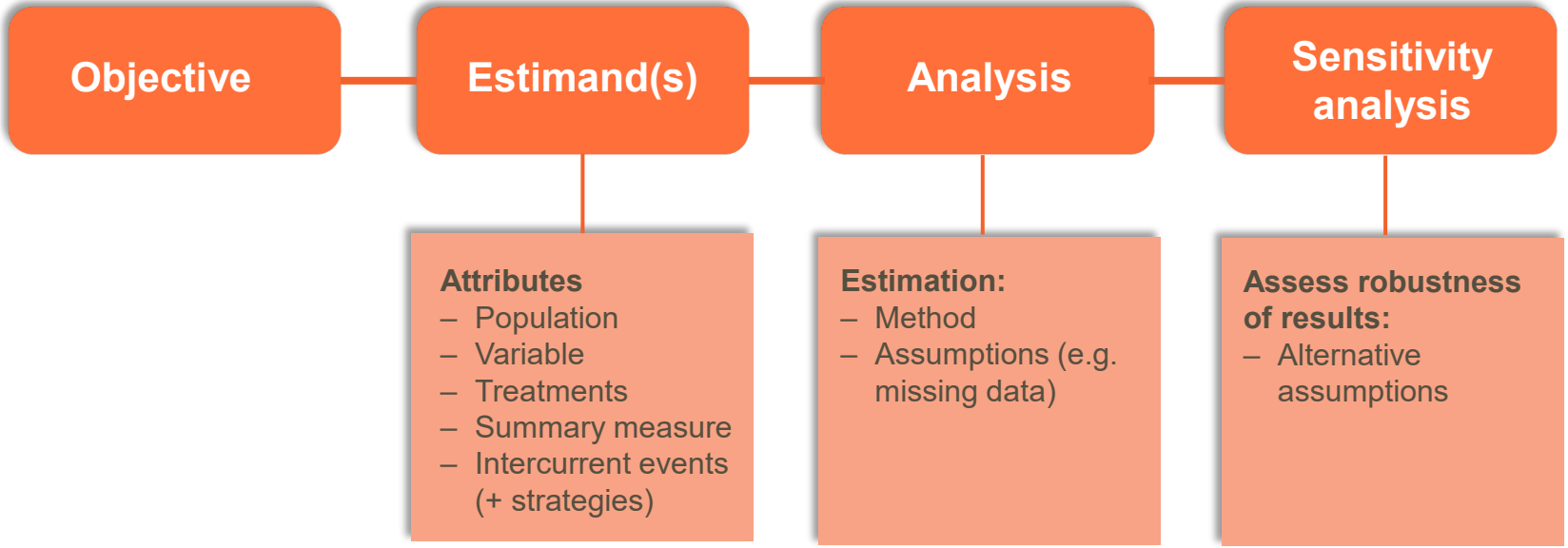
Four key elements that must be aligned



Estimands vs PICO(T)

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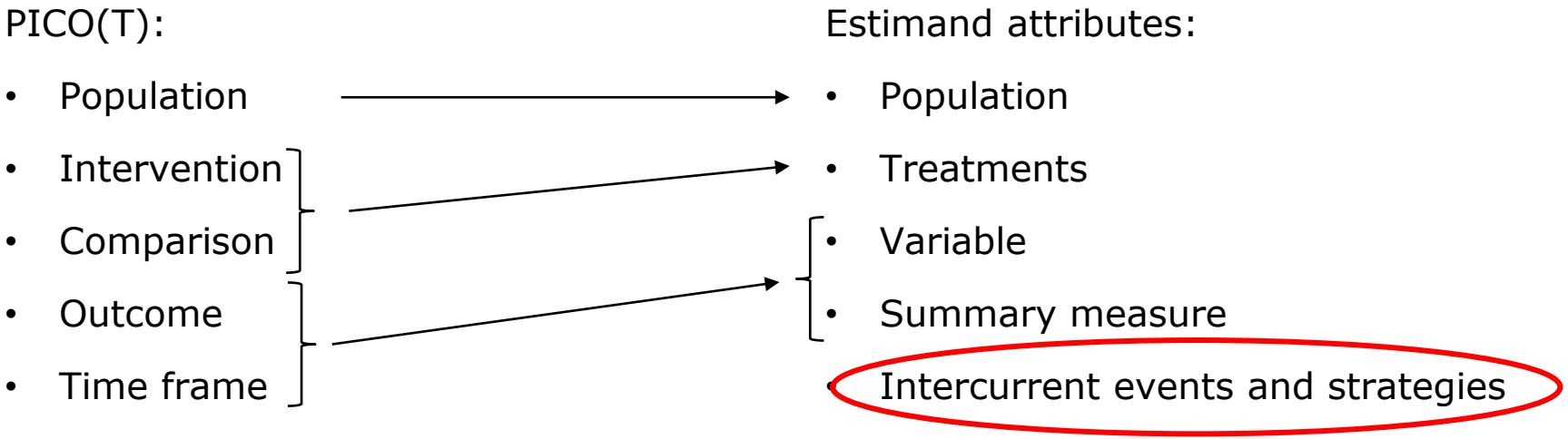
- Causal inference principles shared between Estimands and PICO(T) frameworks



- One can think of Estimands as an evolution of PICO(T)

Based on a true story

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(Example for illustrative purposes inspired in ICH E9(R1) training materials)

In the past, one could find something like this in the study protocol of an RCT:

- Objective: To investigate the efficacy and safety of dapagliflozin for the treatment of type II diabetes mellitus compared to 'control'
- Primary endpoint: Change in glycated haemoglobin (HbA1c) from baseline to week 24
- Analysis method: The primary endpoint will be analysed using an Analysis of Covariance (ANCOVA) model with terms for treatment and baseline HbA1c

The PICO(T) elements can be identified from the above:

- Population: patient with type II diabetes
- Intervention: dapagliflozin
- Control: some 'control' treatment
- Time frame: Week 24 after initiation of treatment

Based on a true story…

(Example for illustrative purposes inspired in ICH E9(R1) training materials)

While assessing the evidence submitted in the MAA

- Applicant: *"Data collected after initiation of rescue medication were excluded from the analysis."* (Single imputation used with last observation carried forward.)

Treatment effect: **dapagliflozin** vs **control** in the absence of rescue medication

- Regulator: (Disagreed with the exclusion of data post-rescue medication) *"I have included a sensitivity analysis in which the primary HbA1c outcomes are used regardless of rescue treatment, and no statistical adjustment is made for rescue."*

Treatment effect: **dapagliflozin** vs **control** regardless of use of rescue medication

Why the misunderstanding?

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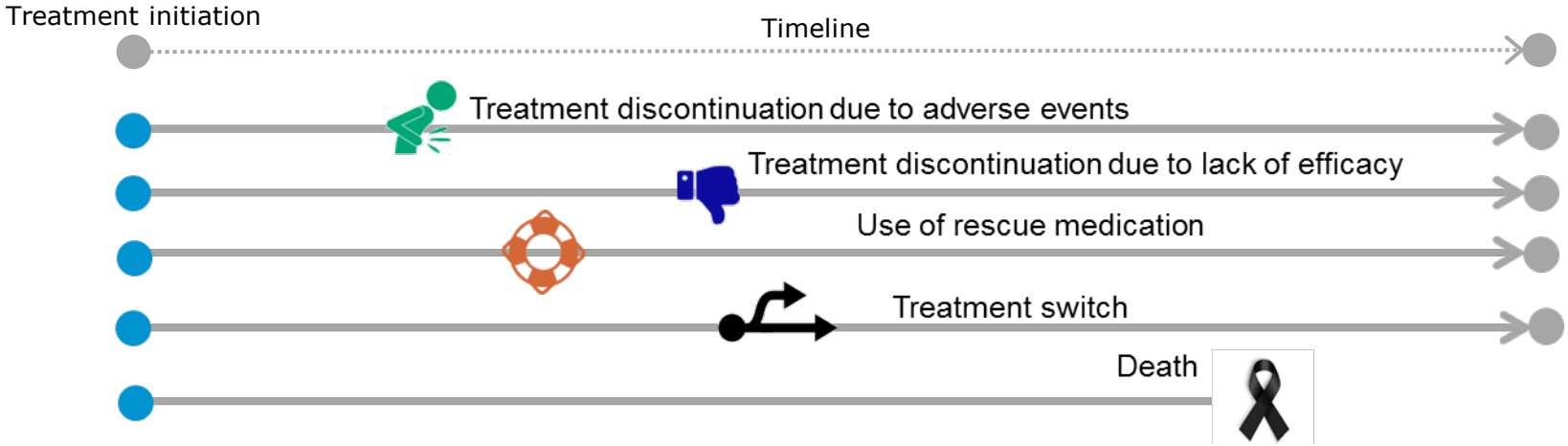
- PICO(T) elements agreed by applicant and regulator
- And yet, applicant and regulator understood different things
  - Applicant:
    Treatment effect: **dapagliflozin** vs **control** in the absence of rescue medication
  - Regulator:
    Treatment effect: **dapagliflozin** vs **control** regardless of use of rescue medication (i.e. *dapagliflozin+rescue* vs *control+rescue*)
- These are two different treatment effects, which are appropriately thought of as **different questions (estimands)** and not two different answers to the same question
- What was missing? The identification of the **intercurrent event** "use of rescue medication" and a strategy to handle it
- This discussion should happen at the design stage, not at the analysis stage

Intercurrent events

Intercurrent events:

"Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest."

Examples of intercurrent events:



Strategies for handling intercurrent events

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Intercurrent events:

"Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest."

Strategies for handling intercurrent events

- **Treatment policy**. Treatment effect regardless of the occurrence of the IE
- **Hypothetical**. Treatment effect in a hypothetical world where the IE would not occur
- **Composite**. Treatment effect considering IE as a bad health outcome on its own
- **While-on-treatment**. Treatment effect before the IE occurs
- **Principal Stratum**. Treatment effect in the stratum of subjects who would (not) experience the IE (not to be confused with the subgroup of subjects who did)

Example – inspired in a RWE study

NIS to investigate selected safety outcomes in patients with spinal muscular atrophy (SMA) exposed to disease-modifying therapies (DMT). Intercurrent events are treatment discontinuation and treatment switch.

Estimand attributes

Population: Patients with SMA

Treatments (Exposures): DMT

Variable: Incidence of selected safety outcomes (based on some list)

Summary measure: Incidence rate

Intercurrent event(s): treatment discontinuation and switch. Two strategies considered leading to two estimands:

- Estimand 1: treatment policy -> interest lies in incidence rates following DMT exposure regardless of treatment discontinuation or switch

- Estimand 2: while-on-treatment -> interest lies in incidence rates only while exposed to DMT

Estimand descriptions
(Research question of interest)

Estimand 1: what is the incidence rate of selected safety outcomes in patients with SMA treated with DMT regardless of treatment discontinuation or switch?

Estimand 2: what is the incidence rate of selected safety outcomes in patients with SMA while treated with DMT?

Discussion

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- PICO(T) framework used to define the research question in NIS. Also used in new legislation for joint European Health Technology Assessment (EU HTA)
- Estimands framework used to define clearly the research question addressed with an RCT. Estimands must be specified in study protocols of RCTs
- Target Trial Emulation offers a bridge between RCT and NIS
- Use of the estimands framework to define the target trial will make the bridge more robust
- Consideration to other elements of ICH E9(R1) would also be beneficial
  - Estimands and estimation are separate discussions
  - Changes in estimands attributes lead to different estimands, not to sensitivity analyses
  - Set the estimand, then choose the estimation method and then consider sensitivity analyses to assess the robustness of the results to assumptions made in the estimation method

Any questions?

Further information

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