Introduction to the ICH E9(R1) estimand and target trial emulation frameworks and their role in the design and analysis of RWE studies

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December 2nd, 2022

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Agenda

- Motivation (Lisa)

- ICH E9 Addendum: estimand framework (Lisa)

- Target trial emulation highlights (Xabier)

- Correspondence between TTE and the estimand framework, and missing pieces (Xabier)

- Conclusions (Lisa)

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# Question-based approach to transforming RWD into impactful evidence

- Formulate the question first and then consider how RWD will add value for decision making:

  - Will RWD improve our answer to a question ...
  - ... or will RWD answer a new question?
  - Are existing data fit-for-purpose? Are new data needed?
  - Who is asking the question? Different stakeholders may require different levels of evidence.

- Defining the causal effect facilitates the evaluation of data relevancy and / or helps to align the question with study design and data collection.

Imaging
Biomarkers
Clinical trial data
Other data
RWD
Omics
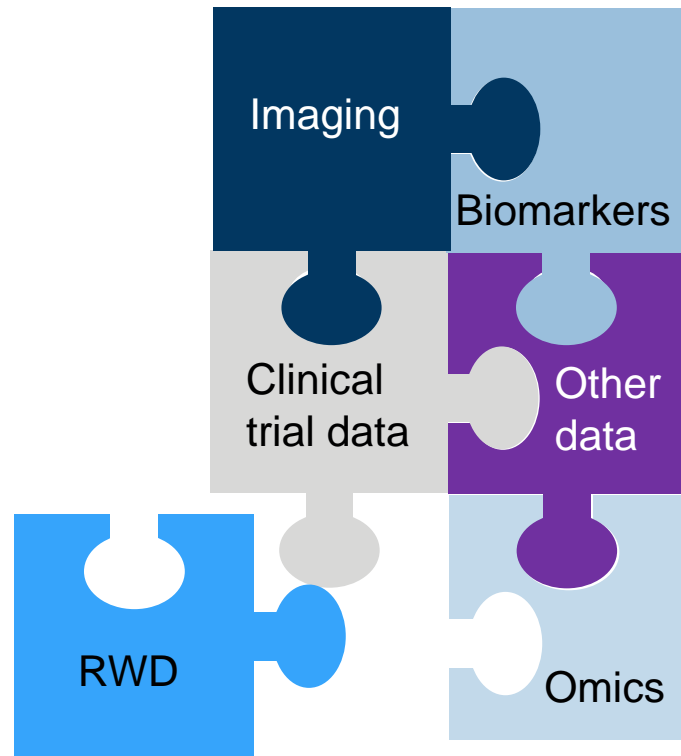
Potential sources of bias when using RWD-based external control arm (ECA)

Single arm trial (SAT)
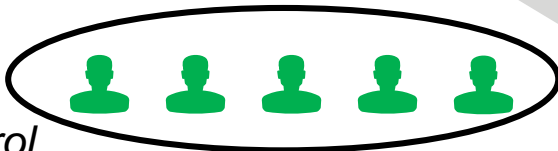*Observed outcomes on drug*

Real-world controls
Observed outcomes on control
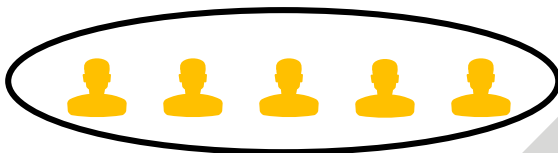
Use real-world controls to understand what the outcomes for the SAT cohort would have been had they received control.

Biases could potentially compromise the comparison of SAT cohort vs external controls

- Confounding
- Selection bias
- Information bias

We can prospectively plan to eliminate or mitigate potential biases through the careful design and analysis of the SAT and ECA. Precisely defining the causal effect of interest can help with this.

- Hernán and Robins. 2020. Causal Inference: What If Link
- Burger HU et al. *Pharmaceutical Statistics* 2021 Link

Several approaches have been proposed to facilitate the precise description of a clinical question

- PICO(T) tool
  - **P**opulation, **I**ntervention, **C**ontrol, **O**utcome, (**T**ime)
  - Commonly used as part of evidence syntheses. For example, to reflect the clinical question in the eligibility criteria for a quantitative systematic review

- Estimand framework
  - Described in ICH E9 Addendum on estimands and sensitivity analyses in clinical trials
  - Aims to align planning, design, conduct analysis and interpretation of clinical trials

- Target trial emulation (TTE)
  - Originally proposed in the context of observational studies
  - Tool for causal inference, where our aim is to estimate the causal effect of interventions

- These different frameworks have commonalities and differences, and are currently used by different communities, within their respective contexts.
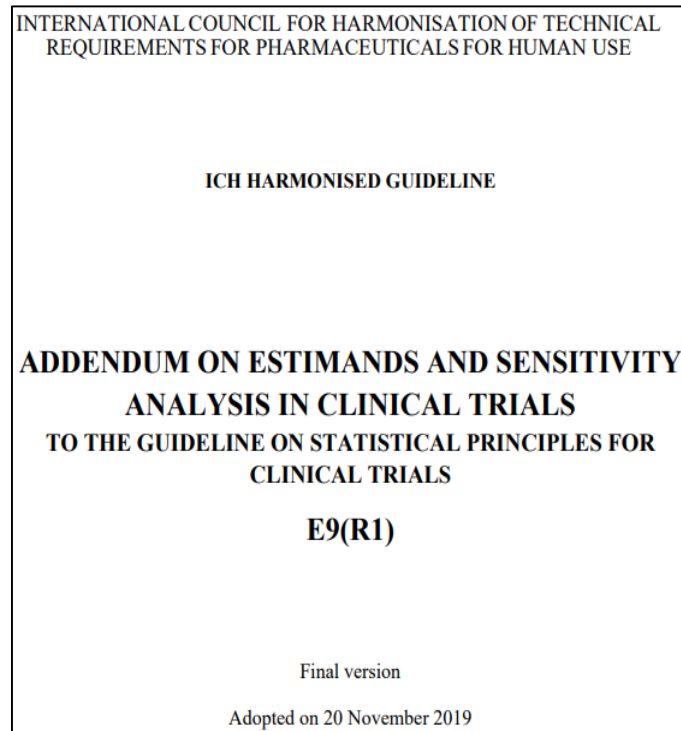
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ICH E9 Addendum – E9(R1)

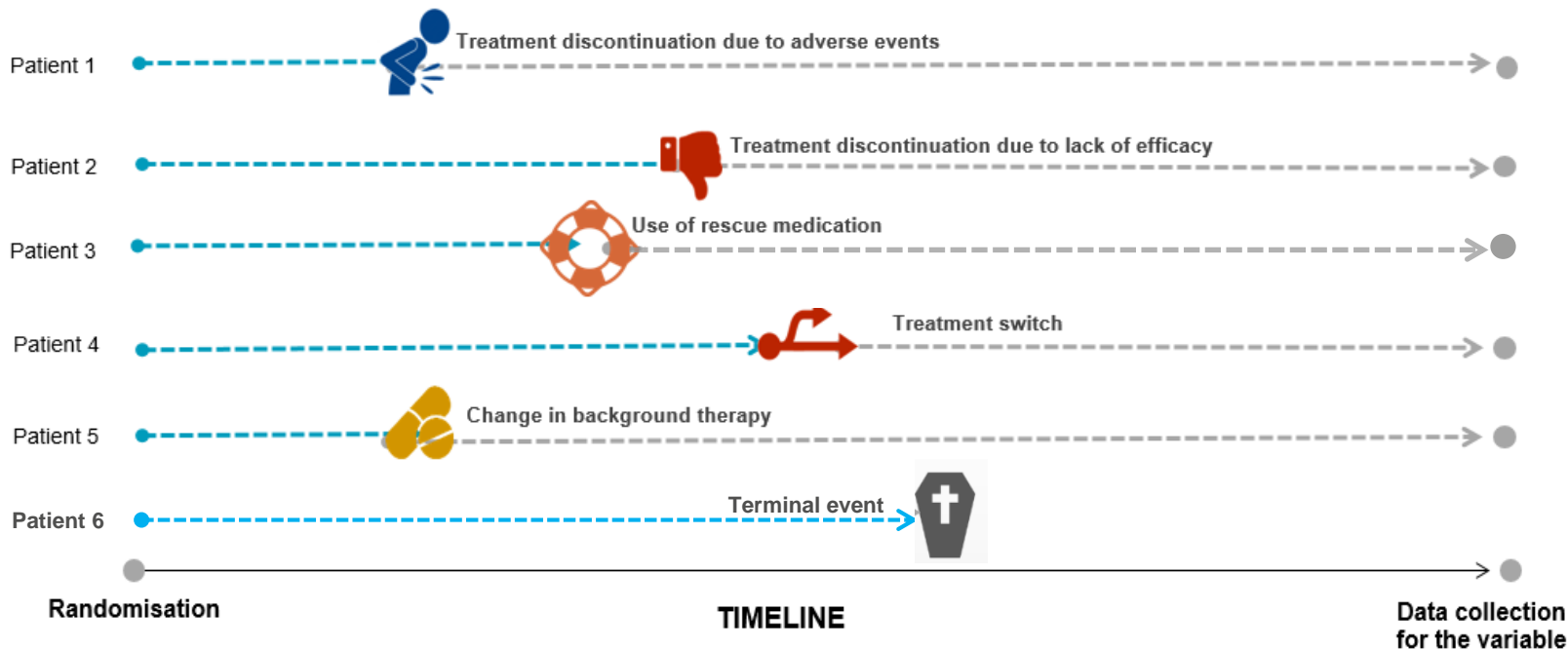**Estimand framework and thinking process**

ICH E9 Addendum: the estimand framework

- **Estimand**: A precise description of the treatment effect reflecting the clinical question posed by the trial objective.

- It summarizes at a population-level what the outcomes would be in the same patients under different treatment conditions being compared.

- While the main focus of E9(R1) is on randomized clinical trials, Burger et al* note these principles "... should be similarly applied for external control studies".

* Burger HU et al. *Pharmaceutical Statistics* 2021 Link

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)

Final version

Adopted on 20 November 2019

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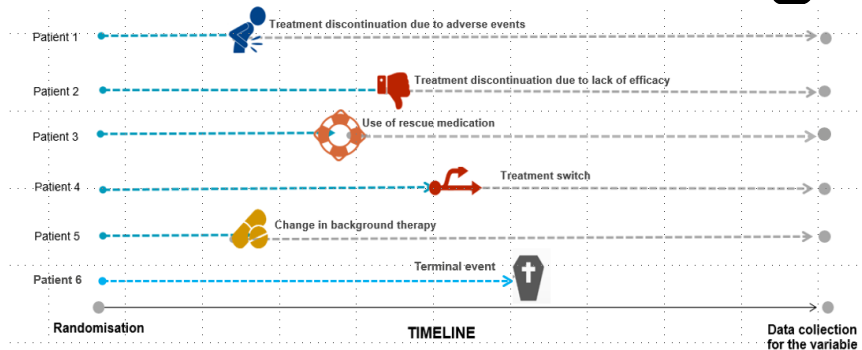# Patient journeys and intercurrent events

An intercurrent event is an event that occurs after treatment initiation that affects the interpretation or existence of measurements associated with the question of interest.

Estimand is defined through 5 attributes

Patient 1 — Treatment discontinuation due to adverse events
Patient 2 — Treatment discontinuation due to lack of efficacy
Patient 3 — Use of rescue medication
Patient 4 — Treatment switch
Patient 5 — Change in background therapy
Patient 6 — Terminal event

Randomisation — TIMELINE — Data collection for the variable

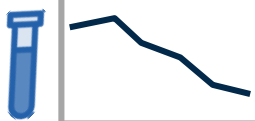**Other intercurrent events** (not included in other attributes)

Strategies for addressing intercurrent events may be incorporated into some or all of these attributes

**Population**

Variable

Incorporates endpoint and time

Treatments

Population-level Summary

ratio

% Σ

Adapted from ICH E9(R1) Training Materials. Link

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Different strategies may be used to address different intercurrent events when defining the question of interest

- Definitions of treatment, population and variable likely address many intercurrent events in line with the clinical question

- Treatment(s) reflect clinical question with regards to changes in background treatment, concomitant medication, ...

- Example: "... specify treatment as intervention A added to background therapy B, dosed as required, with additional medication as required."

- In this example, applying the treatment policy strategy, the intercurrent events are considered part of the treatment.

Estimand Strategies
- Treatment policy
- Hypothetical
- Composite
- Principal stratum
- While on treatment
- ...
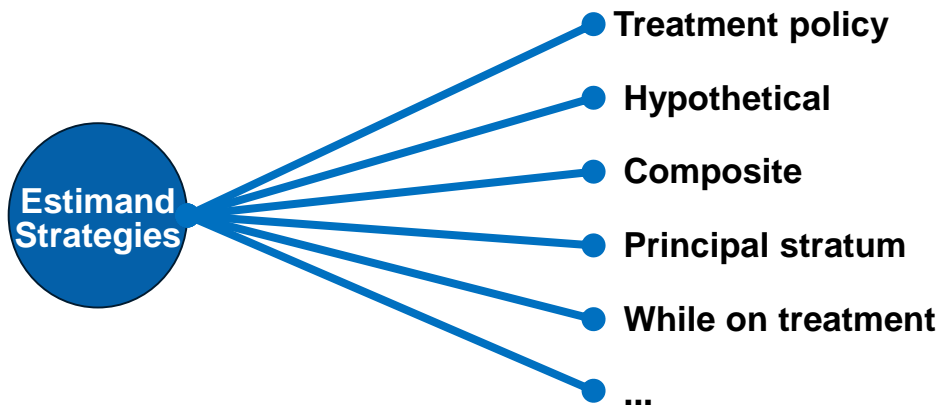
Estimand thinking process

1 **Therapeutic setting** and **intent of treatment** determining a **trial objective**

2 Identify **intercurrent events**

3 **Discuss strategies** to address intercurrent events

4 **Agree on** the Estimand(s)

5 **Align** choices on **trial design**, **data collection** and method of **estimation**

6 Identify **assumptions** for the main analysis and suitable **sensitivity analyses** to investigate these assumptions

7 **Document** the chosen Estimands

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Target trial emulation (TTE)

TTE role in observational research

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

Head-to-head comparisons of COVID-19 vaccines

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, MD; Amy S.B. Bohnert, PhD; Edward J. Boyko, MD, MPH; Denise M. Hynes, MPH, PhD, RN; and Kristin Berry, PhD

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.,

Vaccination Effectiveness: Target Trial Emulation

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

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-

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TTE role in observational research

Safety of COVID-19 vaccines in a large-scale setting

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.,

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 of COVID-19 vaccines in special populations

nature medicine

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

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]

Study design and study population. We conducted an observational cohort
study that emulates a target trial to estimate the effectiveness of the BNT162b2
mRNA COVID-19 vaccine in pregnant women. We used a similar methodology

Effectiveness of COVID-19 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, Isaac S Kohane, Ben Y Reist, Ran D Balicert

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

International Society for Pharmacoepidemiology Annual Conference, 2022

- Hot Topic Session: How Can We Mitigate Publication of Poorly Conducted RWE Studies?
    - Prof. Segal (Johns Hopkins University, School of Medicine), Associate Editor of Annals of Internal Medicine (impact factor = 51.6):
    - "If observational studies are submitted [to *Annals of Internal Medicine*], they [the reviewers] will ask you to frame these as a trial emulation, and they will send it back to you until you do so"
    - [Hot Topic Session and The Final Word (vimeo.com)](vimeo.com) (57:55 minutes)

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What is emulating a target trial?

- Emulating a target trial is one of the main tools of *causal inference*

- For each causal effect of interest, we should be able to imagine a (hypothetical) randomized experiment to quantify it, that is, the "target trial"

- Emulating a target trial using RWD comprises designing a study that is as close as possible to the trial we would have run had we had the opportunity to do so and then using specific epidemiological methods to emulate it

  – Some components may be easy to emulate: eligibility criteria, treatment strategies, outcomes, and causal contrast

  – Others may require more work, including emulation of randomization and of the proper alignment of eligibility, treatment assignment, and start of follow-up

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TTE for Causal Inference

Protocol component	Target trial specification	Target trial emulation
Aim	What is the study objective?	
Eligibility criteria	Who will be included in the study?	
Treatment strategies	What interventions will eligible persons receive?	
Treatment assignment	How will eligible persons be assigned to interventions?	
Outcomes	What outcomes in eligible persons will be compared among intervention groups?	
Follow-up	During which period will eligible persons be followed in the study?	
Causal contrast (or estimand)	Which counterfactual contrast will be estimated using the above data?	
Statistical analysis	How will the counterfactual contrasts be estimated?	

Sources: Hernan MA. New Engl J Med. 2021;385:1345-8; Garcia-Albeniz X, et al. Eur J Epidemiol. 2017 Jun;32(6):495-500.

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Main benefits of framing your observational study as a target trial

1. **Eases discussion**

2. **Bias mitigation:** Alignment of eligibility, time zero and start of follow-up

3. Evaluation of **clinically relevant** treatment strategies

4. Methods to study treatment strategies that are **sustained over time**

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TTE eases study design discussion

- It grounds the discussion on a target trial design and **specification**

- Many agents involved in the project will be more familiar with randomized trials than with observational studies: clinicians, patients, statisticians, market access professionals, data holders, etc.

- Once the target trial is specified, epidemiologists with appropriate training can help with the target trial **emulation**

  – The most important decision points will be settled by then

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Alignment of eligibility, time zero and start of follow-up

1. Avoids prevalent user bias: remember the Women Health Initiative RCT?

    – Observational studies reported a protective effect of HRT on CHD (N Engl J Med. 1996 Aug 15;335(7):453-61)

    – The WHI RCT reported the opposite (N Engl J Med. 2003 Aug 7;349(6):523-34)

    – A target trial emulation using the same observational data reconciled the estimates (Epidemiology. 2008 Nov;19(6):766-79)
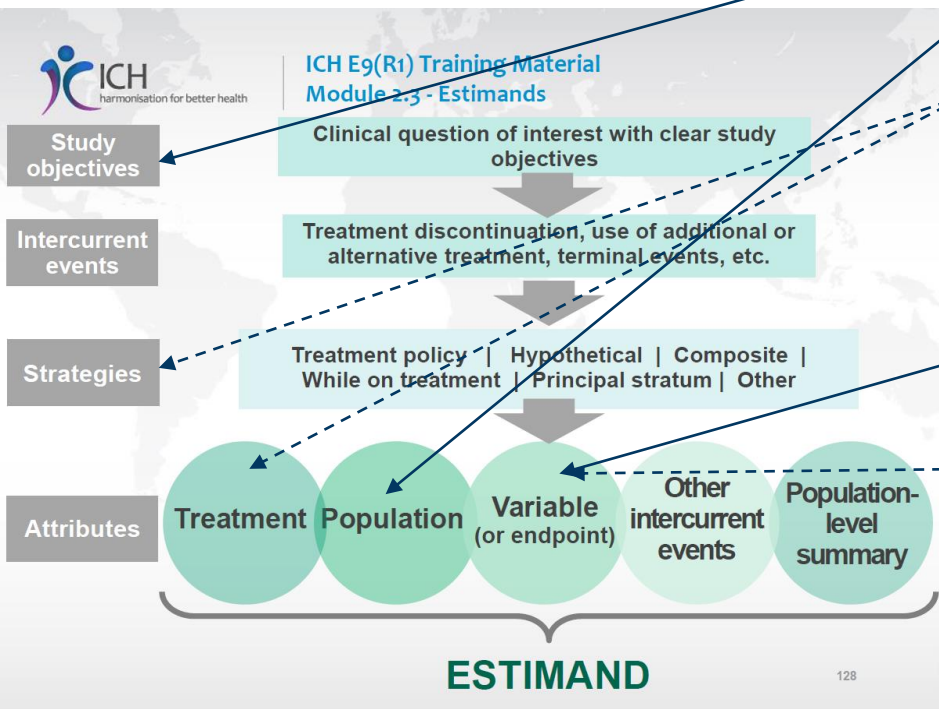
2. Avoids immortal time bias

    – Several observational studies reported a protective effect of statins on cancer incidence (e.g., N Engl J Med. 2005 May 26;352(21):2184-92)

    – A meta-analysis of 20 RCT reported a HR of 1.02 (JAMA. 2006 Jan 4;295(1):74-80)

    – A target trial emulation reconciled the estimates (Nat Med. 2019 Oct;25(10):1601-1606)

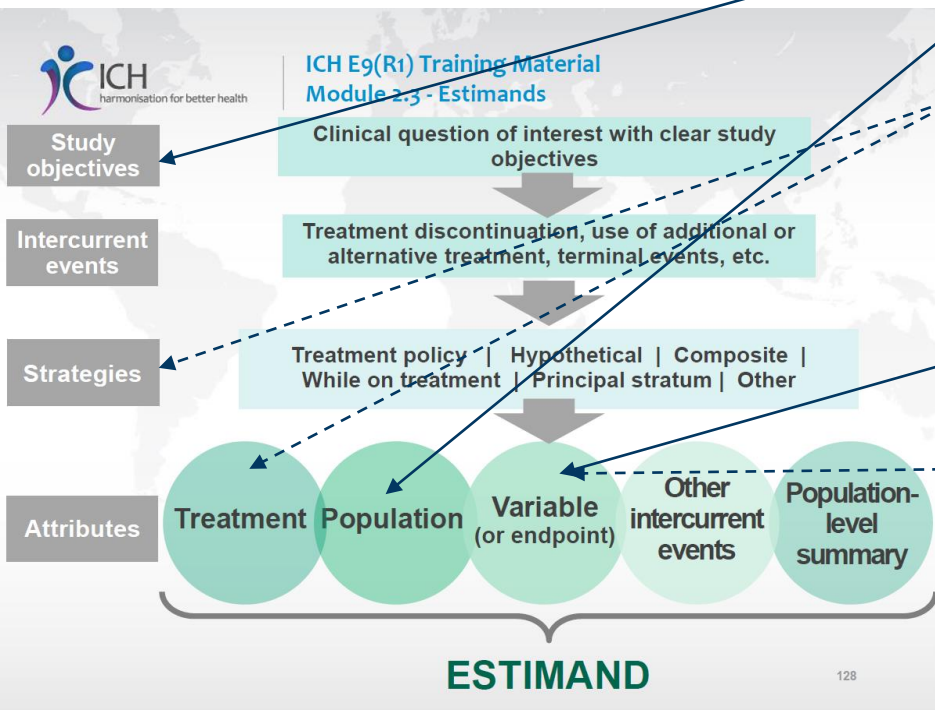NOVARTIS | Reimagining Medicine

Study clinically relevant strategies

- Examples of clinically relevant strategies (Stattin P et al. Real World Outcomes in Patients With Metastatic, Castration-Resistant Prostate Cancer Treated With Radium-223 in Routine Clinical Practice in Sweden. Clin Genitourin Cancer. 2022 Sep 9:S1558-7673(22)00194-X)

1. Initiate **Ra-223**. Patients can stop Ra-223 after 6 cycles or earlier in the event of toxicity, cancer progression, or worsening of the overall health status. Patients can start other systemic drugs for mCRPC after the initiation of Ra-223, when clinically indicated, but they can never be used while taking Ra-223. ADT with first-generation antiandrogens can be used at any time

2. Initiate **other standard of care** (docetaxel, cabazitaxel, enzalutamide, abiraterone, others). Patients are allowed to stop the standard of care and continue with other lines of treatment, with the exception of Ra-223, when clinically indicated. ADT with first-generation antiandrogens can be used at any time.

- Examples of strategies that cannot be implemented in practice (and are thus not relevant for the regulator or clinicians)

  - Receive 6 cycles of Ra-223

  - Receive Ra-223, but no other drugs afterwards

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Correspondence between estimand framework and TTE

Protocol component	Target trial specification
Aim	What is the study objective?
Eligibility criteria	Who will be included in the study?
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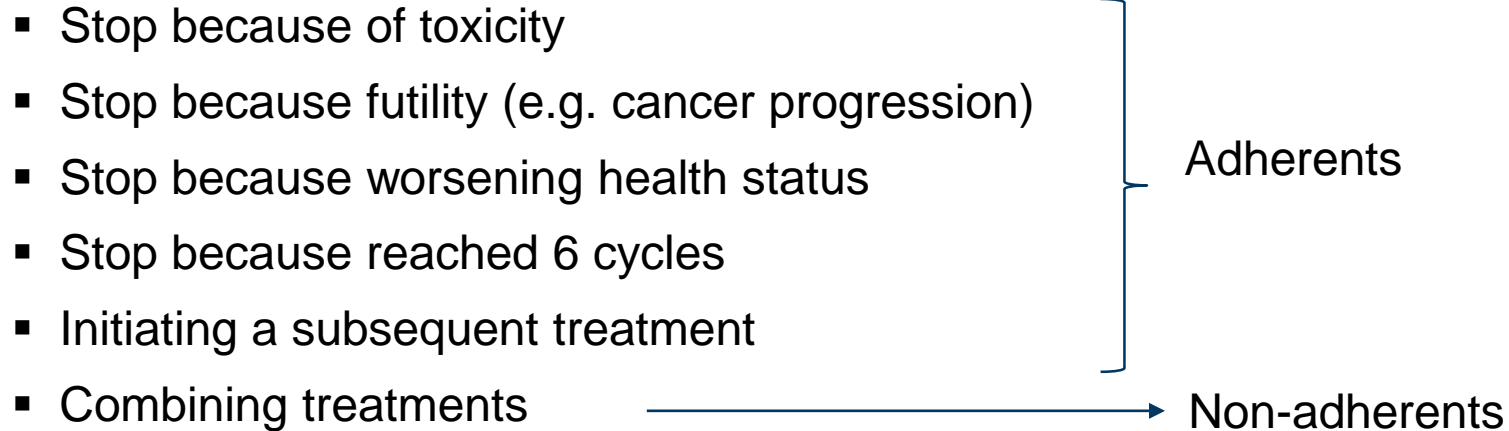| Protocol component	Target trial specification
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ICH E9(R1) Training Material
Module 2.3 - Estimands

Clinical question of interest with clear study objectives

Treatment discontinuation, use of additional or alternative treatment, terminal events, etc.

Treatment policy | Hypothetical | Composite | While on treatment | Principal stratum | Other

Study objectives

Intercurrent events

Strategies

Attributes

Treatment   Population   Variable (or endpoint)   Other intercurrent events   Population-level summary

ESTIMAND

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Protocol component	Target trial specification	Target trial emulation
Treatment strategies	1. Initiate **Ra-223**. Patients can stop Ra-223 after 6 cycles or earlier in the event of toxicity, cancer progression, or worsening of the overall health status. Patients can start other systemic drugs for mCRPC after the initiation of Ra-223, when clinically indicated, but they can never be used while taking Ra-223. ADT with first-generation antiandrogens can be used at any time 2. Initiate **other standard of care** (docetaxel, cabazitaxel, enzalutamide, abiraterone, others). Patients are allowed to stop the standard of care and continue with other lines of treatment, with the exception of Ra-223, when clinically indicated. ADT with first-generation antiandrogens can be used at any time.	Same
Causal contrast (or estimand)	Per protocol effect (i.e., effect under complete adherence and under complete follow-up)	Observational analogue of the per protocol effect
Statistical analysis	Censor participants if and when they deviate from their assigned treatment strategy and apply inverse probability weights to adjust for prebaseline and postbaseline prognostic factors associated with adherence	Same per protocol analysis with sequential emulation and additional adjustment for baseline covariates

Methods to study strategies that are sustained over time

Effect of treatment strategies <u>under complete adherence</u> (Ra-223 example):

- Stop because of toxicity
- Stop because futility (e.g. cancer progression)
- Stop because worsening health status
- Stop because reached 6 cycles
- Initiating a subsequent treatment

Adherents

- Combining treatments → Non-adherents

Not adhering to a treatment plan is different from stopping treatment

The definition of adherence and the need for adherence adjustment depends critically on the definition of the treatment strategy

26   Hernán MA, Scharfstein D. Cautions as Regulators Move to End Exclusive Reliance on Intention to Treat. Ann Intern Med. 2018 Apr 3;168(7):515-516.

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TTE

- Makes emphasis on alignment of time zero, eligibility and treatment assignment (not needed in RCTs)

- Makes emphasis on the use of g-methods for the analysis of treatment strategies under complete adherence (not different from RCTs)

- Makes **treatment strategies explicit**
  - It reclassifies some "intercurrent events" as component of the strategies

- In the presence of competing events, it considers different types of treatment effects (Young JG et al. A causal framework for classical statistical estimands in failure-time settings with competing events. Stat Med. 2020 Apr 15;39(8):1199-1236.)
  - Total effect (comparison of risks without elimination of competing events)
  - Direct effect (comparison of risk under elimination of competing events)

- Focuses on clinically relevant treatment strategies in identifiable groups of patients

- Considers that not adhering to a treatment plan is different from stopping treatment if stopping treatment is planned

 Hernán MA, Scharfstein D. Cautions as Regulators Move to End Exclusive Reliance on Intention to Treat. Ann Intern Med. 2018 Apr 3;168(7):515-516.

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Conclusions

Conclusions

- Estimand framework and TTE were originally proposed in different contexts.

- There are many similarities between these approaches ... and some differences too with regards to emphasis, philosophy and terminology:
  - Defining time zero
  - Approach to defining treatment strategies
  - Discussion of intercurrent events and strategies for addressing them
  - Aligning prospective data generation with clinical question vs evaluating fitness-for-purpose of existing observational data for a clinical question

- Both frameworks stress the importance of precisely defining the (causal) treatment effect and aligning the statistical analysis with this.

- Both frameworks could be valuable for informing the design, conduct and analysis of studies using patient-level external controls to contextualize or augment a clinical trial

- Other talks in this session will consider leveraging both frameworks in combination ...

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Thank you

Appendix

Methods to study strategies that are sustained over time

- The effect under complete adherence (i.e. the observational analogue of the per-protocol effect) usually more relevant than the effect of initiating treatment.

- More often than not, treatment strategies are sustained over time

- If adherence does not happen at random (likely), adjustment for baseline and post-baseline confounders is needed
  - This is also the case in RCTs

- If post-baseline confounders can be affected by prior treatment, g-methods may be the best resource for time-varying adjustment.

 Hernán MA, Robins JM. Per-Protocol Analyses of Pragmatic Trials. N Engl J Med. 2017 Oct 5;377(14):1391-1398