

Comparing five frameworks for defining estimands: friends not foes

Nicholas Bakewell, Doranne Thomassen, Jonathan Bartlett, ...,
Suzanne M Cadarette, Saskia le Cessie, Nan van Geloven

Joint work of STRATOS TG7, TG5, TG4

Following from STRATOS Lorentz workshop Leiden 2024

Estimands

Tukey (1962): *We must give even more attention to starting with an estimator and discovering what is a reasonable **estimand**, to discovering what is it reasonable to think of the estimator as estimating.*

Rubin (2005) defined causal **estimand** as "*the science*"

Our (broad) definition: **estimand** translates the research question into a well-defined target quantity for estimation

Recent surge of interest in defining estimands

Kahan *et al. Trials* (2021) 22:686
<https://doi.org/10.1186/s13063-021-05644-4>

Trials

RESEARCH

Open Access

Estimands in published protocols of randomised trials: urgent improvement needed



Brennan C. Kahan^{1*}, Tim P. Morris¹, Ian R. White¹, James Carpenter¹ and Suzie Cro²

Recent surge of interest in defining estimands

Kahan et al. *Trials* (2021) 22:686
<https://doi.org/10.1186/s13063-021-05644-4>

Trials

Statistics in Medicine



RESEARCH ARTICLE

 Open Access



Estimands for factorial trials

[Brennan C. Kahan](#) , [Tim P. Morris](#), [Beatriz Goulão](#), [James Carpenter](#)

First published: 25 June 2022 | <https://doi.org/10.1002/sim.9510> |

 [VIEW METRICS](#)

Recent surge of interest in defining estimands

Kahan et al. *Trials* (2021) 22:686
<https://doi.org/10.1186/s13063-021-05644-4>

Trials

Statistics

Statistical Methods in Medical Research

Volume 33, Issue 7, July 2024, Pages 1211-1232

© The Author(s) 2024, [Article Reuse Guidelines](#)

<https://doi.org/10.1177/09622802241254197>

Sage Journals

Original Research Article



Demystifying estimands in cluster-randomised trials

Brennan C Kahan ¹, Bryan S Blette ², Michael O Harhay^{1,3}, Scott D Halpern³, Vipul Jairath^{4,5}, Andrew Copas^{1,*}, and Fan Li ^{6,7,*}

Recent surge of interest in defining estimands



Recent surge of interest in defining estimands

Kahan *et al. Trials* (2021) 22:686
<https://doi.org/10.1186/s13063-021-05644-4>

Statistics

Statistical Methods in Medical Research

Thomassen *et al.*

RMC Medical Research

PDS Pharmacoepidemiology & Drug Safety

ispe Official Journal of the International Society for Pharmacoepidemiology

ORIGINAL ARTICLE |  Open Access | 

Tell me what you want, what you really really want: Estimands in observational pharmacoepidemiologic comparative effectiveness and safety studies

[Kim Luijken](#) ✉, [Rik van Eekelen](#), [Helga Gardarsdottir](#), [Rolf H. H. Groenwold](#), [Nan van Geloven](#)

First published: 22 March 2023 | <https://doi.org/10.1002/pds.5620> | [VIEW METRICS](#)

Recent surge of interest in defining estimands

Kahan *et al. Trials* (2021) 22:686
<https://doi.org/10.1186/s13063-021-05644-4>

Statistics
in Medicine

Statistical Methods in Medical Research

Thomassen *et al.*

RMC Medical Research

RESEARCH ARTICLE |  Open Access | 

The Estimand Framework in Diagnostic Accuracy Studies

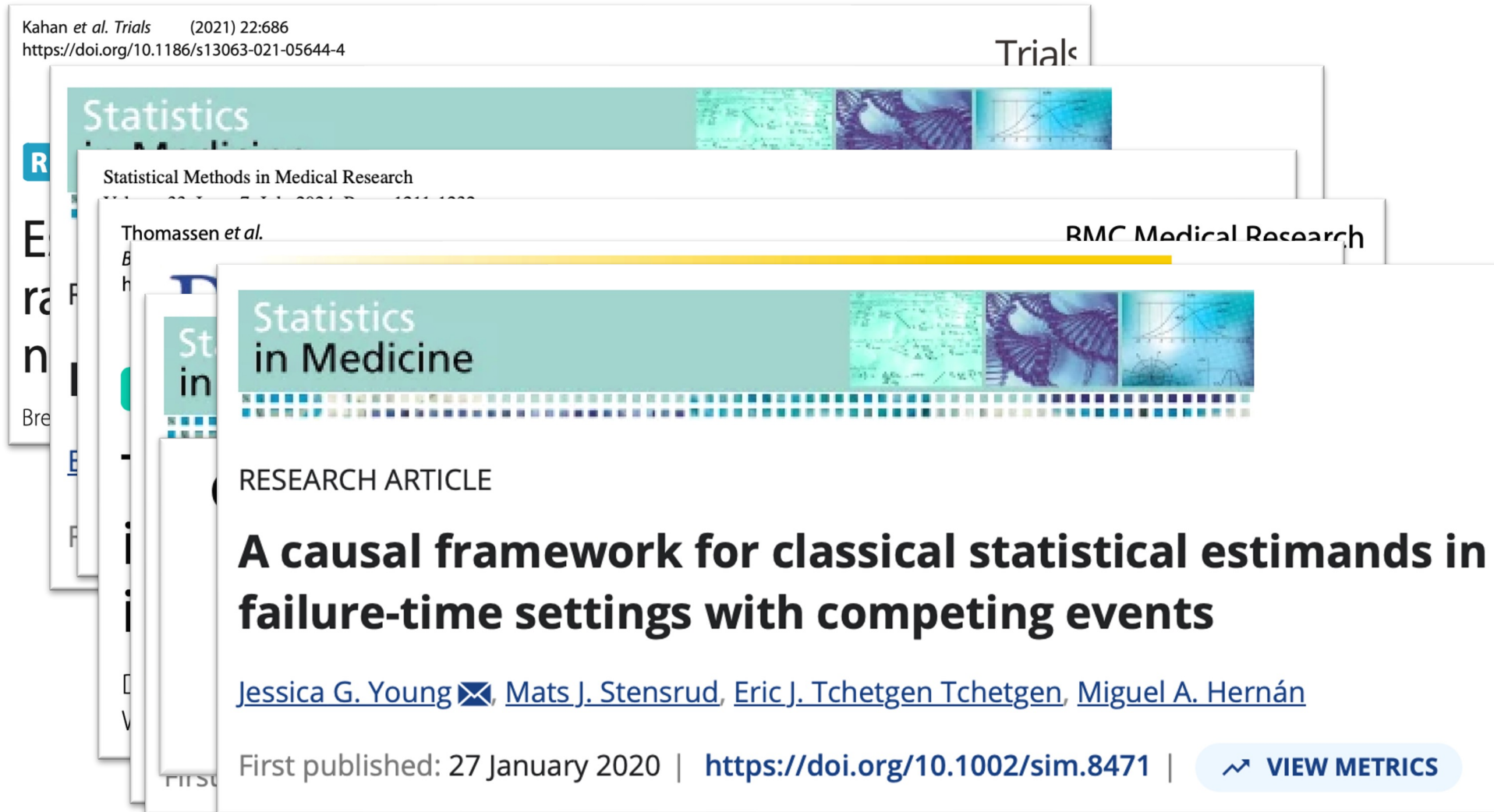
[Alexander Fierenz](#) , [Mouna Akacha](#), [Norbert Benda](#), [Mahnaz Badpa](#), [Patrick M M Bossuyt](#),
[Nandini Dendukuri](#), [Britta Rackow](#), [Antonia Zapf](#)

First published: 17 September 2025 | <https://doi.org/10.1002/sim.70248> |  VIEW METRICS

Recent surge of interest in defining estimands



Recent surge of interest in defining estimands



Frameworks that can be used for defining estimands

- PICOT (Population, Intervention, Comparator, Outcome, Time),
- ICH E9(R1) addendum on estimands
- Target Trial Emulation Framework
- Causal Roadmap
- STRATOS Causal Inference Topic Group (TG7) framework

Discussion about the frameworks

A constructive critique of the *draft* ICH E9 Addendum

[Daniel O Scharfstein](#)   [View all authors and affiliations](#)

[Volume 16, Issue 4](#) | <https://doi.org/10.1177/1740774519853566>

Chasing Shadows: How Implausible Assumptions Skew Our Understanding of Causal Estimands

[Stijn Vansteelandt](#)   & [Kelly Van Lancker](#) 

Pages 507-513 | Received 04 Sep 2024, Accepted 15 Oct 2024, Accepted author version posted online: 30 Oct 2024, Published online: 02 Dec 2024

 Cite this article  <https://doi.org/10.1080/19466315.2024.2421753>



A Perspective on the Appropriate Implementation of ICH E9(R1) Addendum Strategies for Handling Intercurrent Events

 This article relates to: 

[Thomas R. Fleming](#)  [Kevin J. Carroll](#), [Janet T. Wittes](#), [Scott S. Emerson](#), [Mark D. Rothmann](#), [Sylva Collins](#), [Gregory Levin](#)

Discussion about the frameworks

A constructive critique of the *draft* ICH E9 Addendum

[Daniel O Scharfstein](#) 

[Volume 16, Issue 4](#)

Research and Reporting Methods | 18 February 2025

The Target Trial Framework for Causal Inference From Observational Data: Why and When Is It Helpful?

Authors: Miguel A. Hernán, MD, DrPH , Issa J. Dahabreh, MD, ScD , Barbra A. Dickerman, PhD, and Sonja A. Swanson, ScD | [AUTHOR, ARTICLE, & DISCLOSURE INFORMATION](#)

Publication: Annals of Internal Medicine • Volume 178, Number 3 • <https://doi.org/10.7326/ANNALS-24-01871>

The wood and the randomised trials

Richard Hooper^{1*} , Karla Hemming

A Perspective on the E9(R1) Addendum St

 This article relates to: 

[Thomas R. Fleming](#) , [Kevin J. Carroll](#), [Janet T. Wittes](#), [Scott S. Emerson](#), [Mark D. Rothmann](#), [Sylva Collins](#), [Gregory Levin](#)

Re: Are Target Trial Emulations the Gold Standard for Observational Studies?

Vanessa Didelez , Ulrike Haug, Xabier Garcia-Albeniz

[Authors and Affiliations](#) >

Epidemiology 35(1):p e3-e3, January 2024. | DOI: 10.1097/EDE.0000000000001667

Suggested combinations

Pharmaceutical Statistics

The Journal of Applied Statistics
in the Pharmaceutical Industry

The official journal of PSI



VIEWPOINT

The Estimand Framework and Causal Inference: Complementary Not Competing Paradigms

[Thomas Drury](#)✉, [Jonathan W. Bartlett](#), [David Wright](#), [Oliver N. Keene](#)

First published: 23 August 2025 | <https://doi.org/10.1002/pst.70035> | [VIEW METRICS](#)

Start with the Target Trial Protocol, Then Follow the Roadmap for Causal Inference

Lauren E. Dang^a , Laura B. Balzer^a 

[Authors and Affiliations](#) >

Epidemiology 34(5):p 619-623, September 2023. | DOI: 10.1097/EDE.0000000000001637 

Suggested combinations

Pharmaceutical Statistics
The Journal of Applied Statistics
in the Pharmaceutical Industry

VIEWPOINT

The Estimator
Complement

Thomas Drury, J...

First published: 23 August 2025 | <https://doi.org/10.1002/bstc.70035> | [VIEW METRICS](#)

Research Article

Combining the Target Trial and Estimand Frameworks to Define the Causal Estimand: An Application Using Real-World Data to Contextualize a Single-Arm Trial

Lisa V. Hampson ✉, Jufen Chu, Aiesha Zia, Jie Zhang, Wei-Chun Hsu, Craig S. Parzynski, ...show all

Pages 1-10 | Received 11 May 2022, Accepted 11 Feb 2023, Accepted author version posted online: 15 Mar 2023, Published online: 13 Apr 2023

[Cite this article](#) <https://doi.org/10.1080/19466315.2023.2190931> [Check for updates](#)

Four targets: an enhanced framework for guiding causal inference from observational data FREE

[Haidong Lu](#) ✉, [Fan Li](#), [Catherine R Lesko](#), [David S Fink](#), [Kara E Rudolph](#), [Michael O Harhay](#), [Christopher T Rentsch](#), [David A Fiellin](#), [Gregg S Gonsalves](#)

International Journal of Epidemiology, Volume 54, Issue 1, February 2025, dyaf003, <https://doi.org/10.1093/ije/dyaf003>

Published: 26 January 2025 **Article history** ▼

Suggested combinations

Pharmaceutical Statistics
The Journal of Applied Statistics
in the Pharmaceutical Industry

Research Article

Combining the Target Trial and Estimand Frameworks to Define the Causal Estimand: An Application Using Real-World Data to Contextualize

VIEWPOINT

The Estimand

Comple

LECTURES AND SEMINARS

Thomas Dr

First publish

2023

nap

Start
for Ca

Lauren E. Dang

Authors and Affil

Epidemiology 34

Causal Estimands for Clinical and Regulatory Decision Making

Miguel Hernán, CAUSALab

International Journal of Epidemiology, Volume 54, Issue 1, February 2025, dyaf003,
<https://doi.org/10.1093/ije/dyaf003>

Published: 26 January 2025 **Article history** ▼

Researcher trying to design a study...





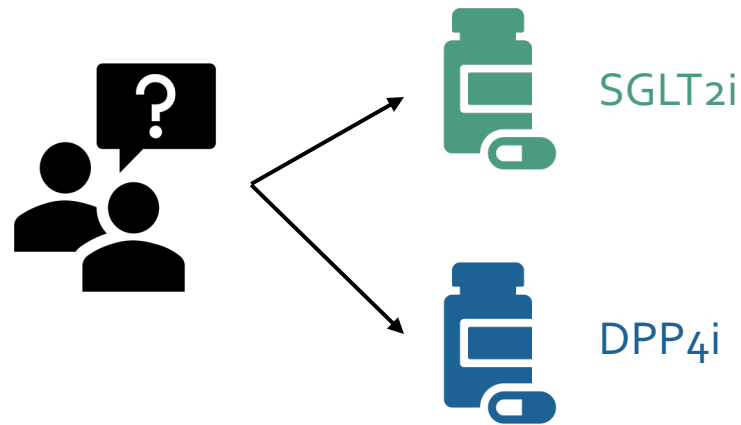
Aim of this work

Comparative overview of five key frameworks used to define estimands

- PICOT
- ICH E9(R1) addendum on estimands
- Target Trial Emulation Framework
- Causal Roadmap
- STRATOS Causal Inference Topic Group (TG7) framework

Example research question

In adults with type 2 diabetes inadequately controlled on first-line oral therapy, does SGLT2i as add-on therapy reduce mortality compared to DPP₄i?



PICOT

Origin

- Developed for guiding literature searches to answer clinical questions
- Intended for comparative studies

Component	Example
Population	Adults ≥ 18 , T2DM, first-line oral therapy, inadequate blood glucose control
Intervention	Add-on SGLT2i
Comparator	Add-on DPP4i
Outcome	All-cause mortality
Time	One year following initiation

PICOT

Advantages

- Provides structure to research question without presupposing a specific design
- Concise, plain language suitable for interdisciplinary exchange
- Comparator made explicit
- Established role in Health Technology Assessment and evidence synthesis

Limitations

- No summary (effect) measure
- Little attention to baseline (time zero)
- Post-baseline events not explicitly considered
- Categorical time-fixed exposures

ICH E9 (R1) Addendum

Origin

- Regulatory document for clinical trials; applicability to single-arm trials and observational studies
- Motivation: description of study design and analysis methods not sufficient for unambiguous interpretation of treatment effects, estimand should precisely describe quantity to be estimated

Component (<i>Attributes</i>)	Example
Population	Same as with PICOT
Treatment(s)	Add-on SGLT2i vs DPP4i
Variable/endpoint	All-cause mortality at one year
Intercurrent events (IE)	Discontinuation of assigned treatment; switching; additional add-on treatments
Strategy for each IE	Ex. 1: Treatment policy: 'effect irrespective of subsequent treatment change(s)' Ex. 2: Hypothetical: 'effect under sustaining assigned treatment throughout'
Population-level summary measure	Risk difference

ICH E9 (R1) Addendum

Advantages

- Explicit consideration of post-baseline events (i.e., IEs), different from missing data
- Population-level summary measure
- Clarifies difference between sensitivity (same estimand) / supplementary (different estimand) analyses
- Language intended for interdisciplinary exchange

Limitations

- Primarily proposed for clinical trials, little attention to issues at baseline (confounding, time zero)
- Listing all possible IEs not always pragmatic
- Categorical time-fixed exposures
- Interpretation of some strategies proposed for handling IEs are debated (principle stratum)

Target trial emulation framework

Origin

- Developed for observational comparative effectiveness and safety studies
- Motivation: prevent design flaws in observational studies (e.g. undefined time zero, immortal time bias), by applying trial design principles

Target trial emulation framework

Component	Example ('target trial' column)
Eligibility	Age ≥ 18 ; recorded T2DM; on first-line oral therapy; inadequate control; assessed at time zero
Treatment strategies	Initiate SGLT2i vs DPP4i as add-on, with some <i>grace period</i> <i>Ex. 1:</i> subsequent decisions left to clinician and patient <i>Ex. 2:</i> sustain SGLT2i vs DPP4i throughout follow-up
Assignment	Randomized, unblinded
Follow-up	From randomization (time zero) to one year
Outcome	All-cause mortality
Causal contrast	Risk difference <i>Ex. 1:</i> ITT, comparison of initiators <i>Ex. 2:</i> Per protocol

Target trial emulation framework

Advantages

- Time zero: aligning start of follow-up, meeting eligibility, treatment assignment
- Addresses post-baseline events within the treatment strategies and causal contrast
- Promotes the role of subject-matter knowledge of data
- Accessible language(?)

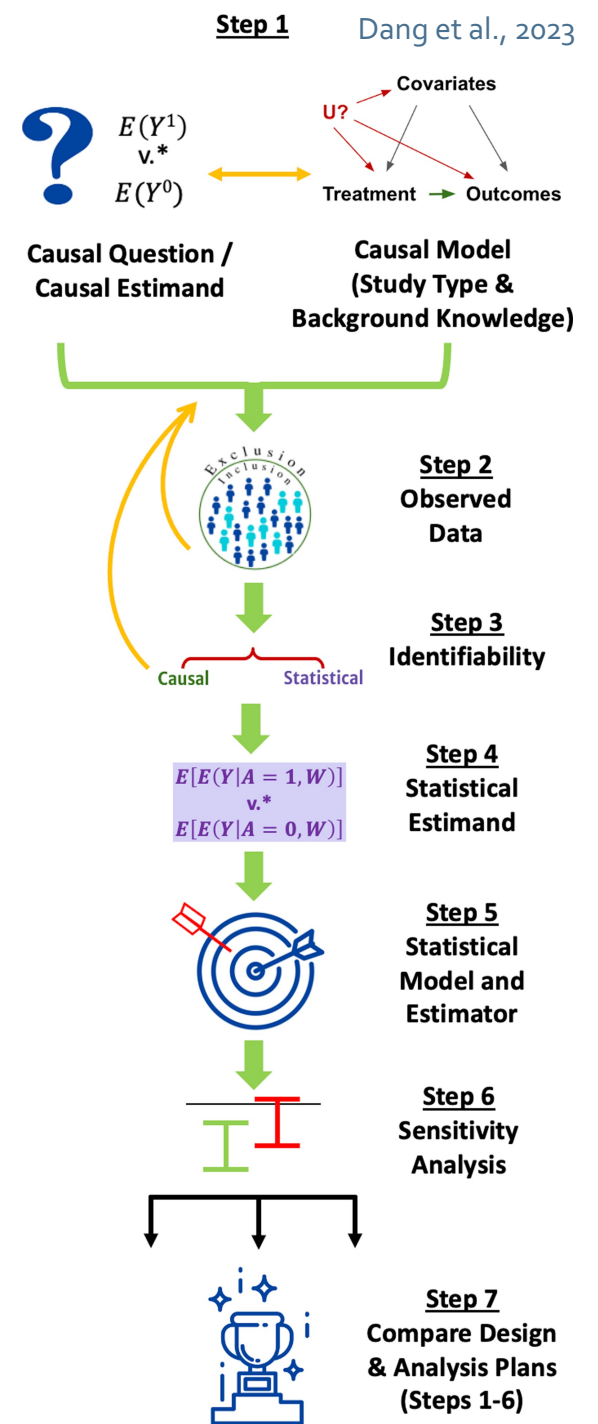
Limitations

- Presumes fluency in trial design
- Estimand not defined explicitly, but implicitly through the defined trial
- Most suitable for categorical exposures

Causal Roadmap

Origin

- Integrates causal modelling with statistical estimation in observational data
- Motivation: prevent conflation of causal and statistical inference
- Formalized precision using causal inference theory (e.g., structural causal model, counterfactuals)



Causal Roadmap

Component	Example
Causal question, model, and estimand	• A: intervention(s), $a = 1$: SGLT2i, $a = 0$: DPP4i • C: treatment discontinuation, switching, additional add-ons • W: baseline covariates • Y: all-cause mortality at 1 year Structural causal model over (W, A, C, Y), e.g. directed acyclic graph Causal estimand: function of potential outcomes Ex. 1: $P(Y^{a=1} = 1) - P(Y^{a=0} = 1)$ Ex. 2: $P(Y^{\bar{a}=\bar{1}, \bar{c}=\bar{0}} = 1) - P(Y^{\bar{a}=\bar{0}, \bar{c}=\bar{0}} = 1)$ <i>Dang et al (2023) suggest incorporating ICH Eg(R1) or TTE components</i>

Causal Roadmap

Advantages

- Comprehensive sequential workflow, making omissions visible
- Applicable to various types of exposures and study designs
- Explicit observed data step with feedback to estimand

Limitations

- Specialized (although precise!) language
- No specific component for post-baseline events; encoded as variables in causal model

STRATOS TG7 framework

Origin

- Tutorial for formulating causal questions and obtaining answers in non-randomized and randomized studies
- Motivation: methods often chosen before the question is formalized

Component	Example
Treatment and levels	A_1 , initiation of SGLT2i ($a_1 = 1$), DPP4i ($a_1 = 0$) A_2 , sustained use of SGLT2i, DPP4i for 1 year
Outcome	All-cause mortality at 1 year
Population	Adults ≥ 18 , T2DM, first-line oral therapy, inadequate blood glucose control who are eligible for both SGLT2i and DPP4i
Potential outcomes	Ex. 1: Y^{a_1} Ex. 2: Y^{a_1, a_2} ("nested potential outcomes")
Estimand (contrast in potential outcome distributions)	Ex. 1: $P[Y^{a_1=1} = 1] - P[Y^{a_1=0} = 1]$ Ex. 2: $P[Y^{a_1=1, a_2=1} = 1] - P[Y^{a_1=0, a_2=0} = 1]$

STRATOS TG7 framework

Advantages

- Comprehensive sequential workflow, making omissions visible
- Applicable to various types of exposures and study designs
- Attention to levels and versions of exposure, 'exposure chain'

Limitations

- Specialized (although precise!) language
- Post-baseline treatment changes encoded as different versions of intervention, no particular attention to other post-baseline events
- No feedback to estimand after observed data step as in the Causal Roadmap

Discussion

All framework contribute to well-defined estimands; many shared components (**friends not foes**)

Frameworks differ in their original purpose and scope

- Post-baseline events can be incorporated in all frameworks except PICOT, but in different ways
- Some frameworks can more easily deal with continuous or time-varying exposures
- CR promotes explicit feedback to estimand from observed data, recently also proposed for TTE
- Some frameworks use more specialized notation and language (precision vs accessibility)

Discussion

All framework contribute to well-defined estimands; many shared components (**friends not foes**)

Frameworks differ in their original purpose and scope

- Post-baseline events can be incorporated in all frameworks except PICOT, but in different ways
- Some frameworks can more easily deal with continuous or time-varying exposures
- CR promotes explicit feedback to estimand from observed data, recently also proposed for TTE
- Some frameworks use more specialized notation and language (precision vs accessibility)

Our comparative overview:

- helps researchers choose an appropriate framework for their setting, guided by nature of research question, study design and own background knowledge
- helps when combining studies that have used different frameworks, e.g. in meta-analyses
- contributes to exchange and understanding across the cultures

Thanks to all coauthors!

Nicholas Bakewell, Doranne Thomassen, Jonathan Bartlett,
Kelly Van Lancker, Els Goetghebeur, Pamela Shaw,
Emmanuelle Boutmy, Tim Morris, Rima Izem, Susan Halabi,
Daniala L Weir, Marc Vandemeulebroecke,
Suzanne M Cadarette, Saskia le Cessie, Nan van Geloven