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The Leading European Conference for Health Economics and Outcomes Research

Spotlight Session:

“Navigating Challenges and Seizing Opportunities: Leveraging Multiple RWD Sources in External Control Arms for HTA and Regulatory Decision-Making”

- Academia/HTA Reviewer Perspective -

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UMIT TIROL

4 Key Elements of a Causal Health Decision Framework

1. Understanding Nature

Develop DAGs to understand data-generating process/potential biases

2. Design

Use Target Trial Emulation to avoid self-inflicted biases

3. Analytic Methods

Watch out for time-varying confounding requiring g-methods/TMLE

4. Support Clinical Guidelines/HTA

Feed long-term decision models (Markov models) with causal parameters

1. Understanding Nature & Disease

Use causal diagrams (directed acyclic graphs, DAGs) to define sufficient set of confounders to control for in the analysis

- In ECAs: confounders = prognostic factors
- DAG tells whether an unmeasured confounder is an issue or not
- Multiple RWD sources: use one overall DAG to determine joint set of variables needed for unbiased analysis
- Multiple RWD sources: search “secondary” RWE sources with comprehensive set of potential confounders to identify important factors and determine domains (e.g., for biomarkers, comorbidity)

2. Design

Develop Target Trial Protocol (including DAG) prior to analysis to avoid self-inflicted biases

- Two types of target trials:
  1) Target RCT for approval (e.g., selected patient population)
  2) Target experiment for current decision question (PICOST);
     → may differ from the first regarding subgroup, comparator, outcome, follow-up etc., but also regarding ITT/causal per-protocol
- Multiple RWD sources: perform both types of target trial emulations using different optimal ECAs
- Multiple RWD sources: if SoC is inconsistent over time, prioritise RWE sources reflecting contemporary SoC

3. Analytic Methods (Selection)

- Model specification
  - Correctly specified weight model and outcome model
  - Consider machine learning methods to select functional forms of these models (not variables!) as sensitivity analyses
- Appropriate statistical analysis methods
  - Baseline: time-independent confounding → traditional methods (regression, propensity score)
  - Post-baseline: time-dependent confounding→ g-methods/TMLE
  - Time zero bias (e.g. immortal time bias) → consider cloning – censoring – weighting approach, to be applied to both trial and ECA
- Multiple RWD sources: use influence matrix of confounders to derive information for imputing unmeasured variables in the ECA

4. Support Clinical Guidelines and HTA

- Medical decision making is based on long-term consequences and tradeoffs (benefit-harms-costs)
- Key interest: long-term outcomes beyond follow-up of the trial → plan decision-analytic model along with TTE and selection of RWD sources
- Multiple RWD sources: May inform different parameters
  - E.g. treatment-specific progression, disease-state-specific mortality and quality of life → use decision analytic modeling to link evidence
  - Particularly important for public health interventions (e.g. screening)

IQWiG

Novum: Erste Nutzenbewertung mit unterstützender Modellierung

Im Rahmen der vorliegenden Nutzenbewertung hat das IQWiG ein externes Wissenschaftsteam mit einer Modellierungsstudie beauftragt. Ziel war es, die Abwägung zwischen Nutzen und Schaden zu unterstützen. Expertinnen und Experten der Privatuniversität UMIT Tirol haben daher Daten aus verschiedenen Quellen zusammengeführt und Vorhersagen auch über den Zeitraum hinaus getroffen, der durch die bislang vorliegenden Studien abgedeckt wird.

https://www.iqwig.de/presse/pressemitteilungen/pressemitteilungen-detailseite_61376.html

How Can We Use Multiple ECAs/RWD Sources?

- Use only the best ECA, matching the trial arm best
  - Simple and transparent
- Combine multiple ECAs
  - Increase power
  - “Dilute” known and unknown biases related to one of them
- Use one ECA to derive a causal prediction rule to “expute” unmeasured variables with their predictors in ECA 2
  - Purposeful data synthesis
- Define a hierarchy on using ECA 1, ECA2, ECA 3 etc.
  - Increases success rate
- Combination of the above …

Self-Inflicted Biases in RWE Studies

Table 1. Categories of common ECA critiques.

ECA critique category	Definition
Generalizability	
SoC inconsistent over time	Treatment practices have changed over time, and thus, the generalizability of the external control group is questionable.
ECA nongeneralizable to clinical practice	ECA patient population was derived from outside the country of interest, ECA patient population and market authorization did not match, or other differences in ECA population compared with clinical practice.
Mitigation of confounding	
Unmeasured confounding	All-important known confounders were not available in the data and/or were not included in the adjustment analysis.
Unjustified confounders	Confounders used in adjusting were not justified—no rationale provided regarding why the variable was considered a confounder.
Naive comparison	No adjustment for confounders was executed (eg, propensity score matching).

Self-inflicted

Self-inflicted

Self-inflicted

HEALTH POLICY ANALYSIS 1969

Table 1. Categories of common ECA critiques.

ECA critique category	Definition
Other	
Selection bias	Individuals or groups in a study differ systematically from the population of interest leading to a systematic error in an association or outcome. Includes differences related to start of follow-up time (eg, immortal time bias).
Incorrect adjusting methods	Incorrect adjustment methods were used.
Inconsistent outcomes definitions	Outcome variables were defined differently in the clinical trial vs RWD.
Data loss/insufficiency	Due to matching, the power to detect effect was reduced or substantial missing data impacted results.

ECA indicates external control arm; RWD, real-world data; SoC, standard of care.

Self-inflicted

Jaksa A et al. Comparison of 7 Oncology External Control Arm Case Studies: Critiques From Regulatory and HTA Agencies, Health Policy Analysis 2022

Target Trial Emulation to Avoid Self-Inflicted Biases

JAMA Network Open

Original Investigation | Statistics and Research Methods

Reporting of Observational Studies Explicitly Aiming to Emulate Randomized Trials

A Systematic Review

Harrison J. Hansford, BSc(Hons); Aidan G. Cashin, PhD; Matthew D. Jones, PhD; Sonja A. Swanson, ScD; Nazrul Islam, MD, PhD; Susan R. G. Douglas, BExPhys; Rodrigo R. N. Rizzo, PhD; Jack J. Devonshire, BSc(Hons); Sam A. Williams, BSc(Hons); Issa J. Dahabreh, MD, ScD; Barbra A. Dickerman, PhD; Matthias Egger, MD, PhD; Xabier Garcia-Albeniz, MD, PhD; Robert M. Golub, MD; Sara Lodi, PhD; Margarita Moreno-Betancur, PhD; Sallie-Anne Pearson, PhD; Sebastian Schneeweiss, MD, ScD; Jonathan A. C. Sterne, PhD; Melissa K. Sharp, PhD; Elizabeth A. Stuart, PhD; Miguel A. Hernán, MD, DrPh; Hopin Lee, PhD; James H. McAuley, PhD

Introduction

Analyses of observational (nonexperimental) data can be used to estimate the causal effect of interventions when randomized clinical trials are unavailable or infeasible. Bias in observational analyses may be limited by conceptualizing them as attempts to emulate target trials, ie, hypothetical randomized trials that would answer causal questions of interest.[1-3] Hernán and Robins[4] have

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1. Kuehne F, Arvandi M, Hess LM, et al. Causal analyses with target trial emulation for real-world evidence removed large self-inflicted biases: systematic bias assessment of ovarian cancer treatment effectiveness. *J Clin Epidemiol*. 2022;152:269-280. doi:10.1016/j.jclinepi.2022.10.005

2. Dickerman BA, García-Albéniz X, Logan RW, Denaxas S, Hernán MA. Avoidable flaws in observational analyses: an application to statins and cancer. *Nat Med*. 2019;25(10):1601-1606. doi:10.1038/s41591-019-0597-x

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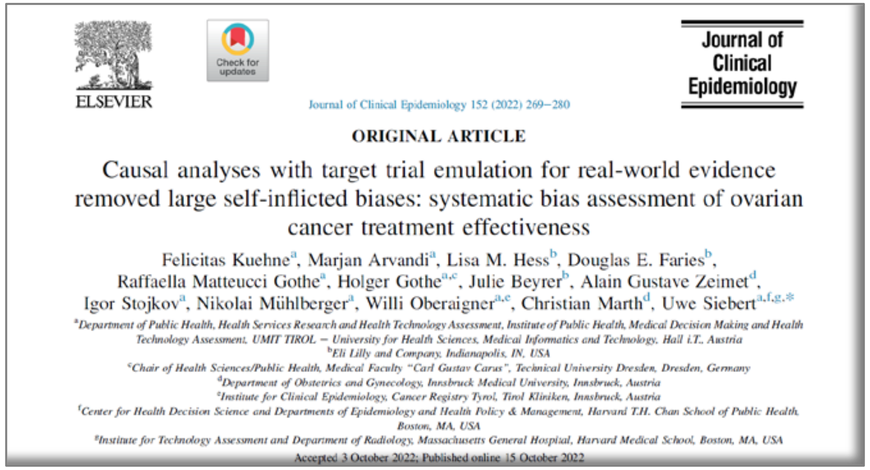
https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2809945

Analysis of Self-Inflicted Biases; 2nd-Line Ovarian Cancer Treatment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Journal of Clinical Epidemiology 152 (2022) 269–280
Journal of Clinical Epidemiology

ORIGINAL ARTICLE

Causal analyses with target trial emulation for real-world evidence removed large self-inflicted biases: systematic bias assessment of ovarian cancer treatment effectiveness

Felicitas Kuehne[a], Marjan Arvandi[a], Lisa M. Hess[b], Douglas E. Faries[b], Raffaella Matteucci Gothe[a], Holger Gothe[a,c], Julie Beyrer[b], Alain Gustave Zeimet[d], Igor Stojkov[a], Nikolai Mühlberger[a], Willi Oberaigner[a,e], Christian Marth[d], Uwe Siebert[a,f,g,*]

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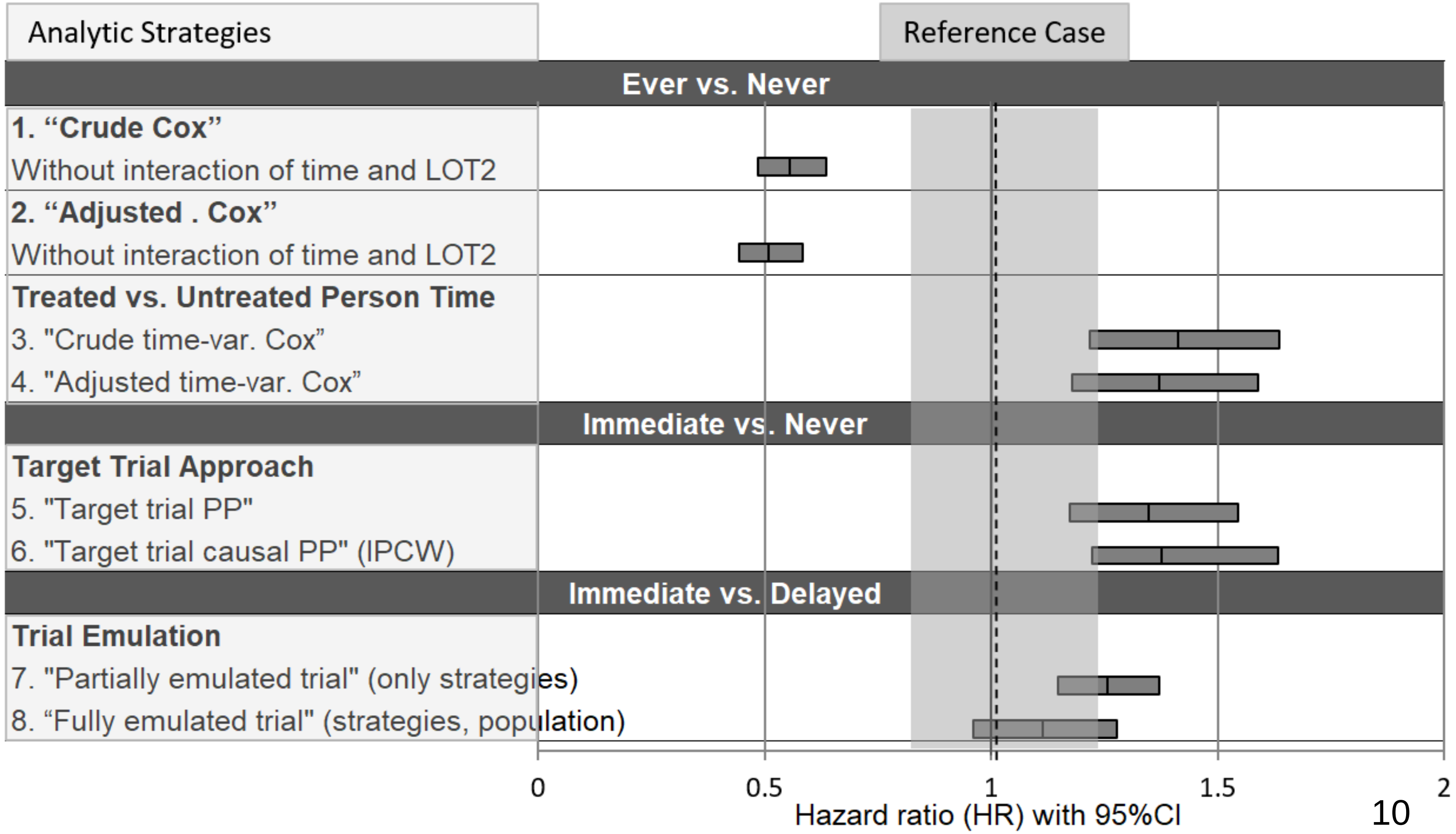
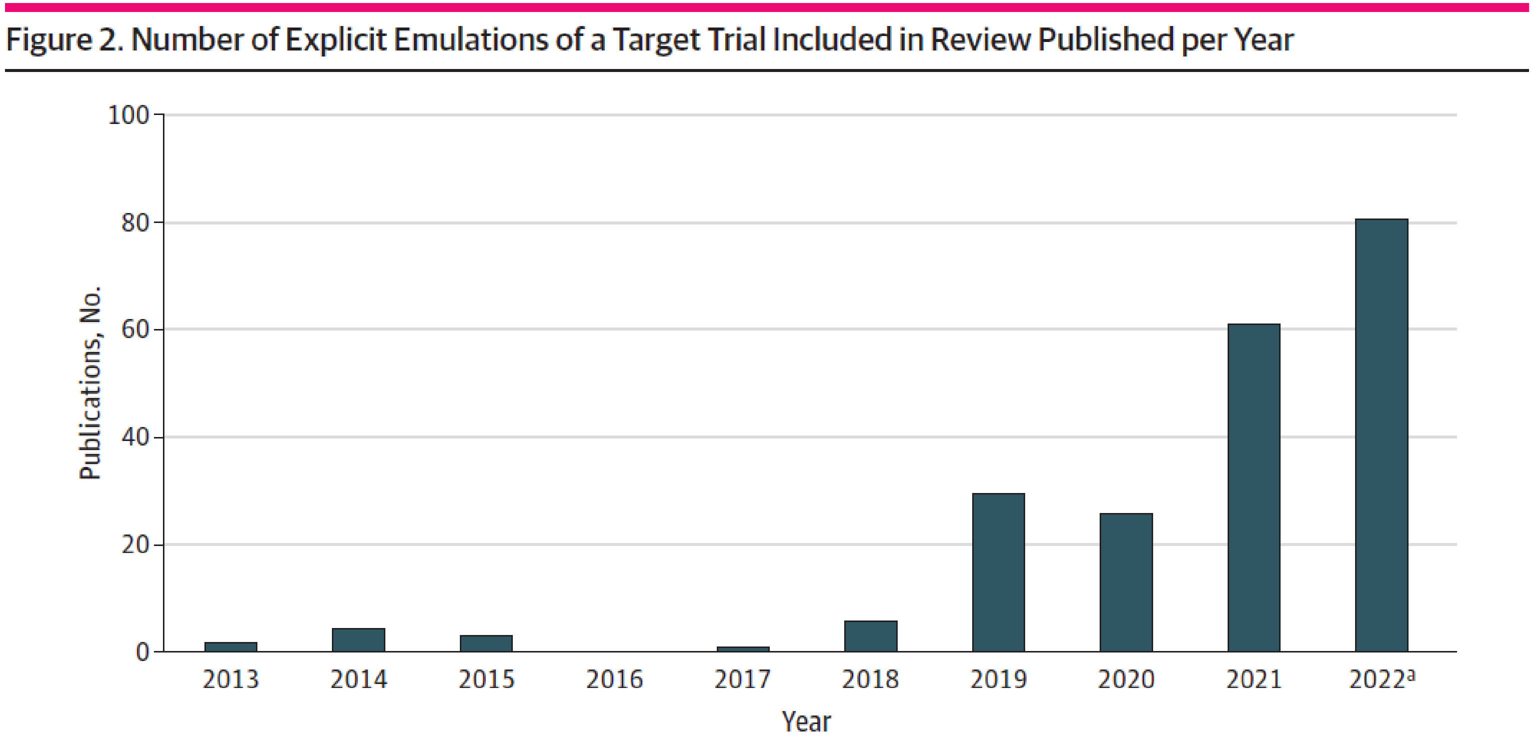
Kuehne F et al, J Clin Epidemiol, 2022



Increasing Application of Target Trial Emulation



Hansford HJ et al., JAMA Network Open. 2023
https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2809945
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NICE describes target trial emulation in methods guidance (June 2022)
www.nice.org.uk/corporate/ecd9

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