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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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)
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

2. Design
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)

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

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

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

REFERENCES


https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2809945
Analysis of Self-Inflicted Biases; 2nd-Line Ovarian Cancer Treatment

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
Thank you!

Questions? Contact me:

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