Target Trial Emulation in Health Economics and Outcomes Research: Opportunities and Challenges

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Agenda

1. Overview of the target trial concept and bias control
2. Case example of target trial emulation
3. Potentials, expectations, and challenges using the target trial concept for RWE in the HTA process
4. Q&A

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Felicitas Kuehne

OVERVIEW OF THE TARGET TRIAL CONCEPT

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Focus of this Workshop

- How to gain unbiased causal real-world evidence (RWE)
- Concentrate on target trial emulation concept
- Counterfactual framework guiding the analysis of observational data

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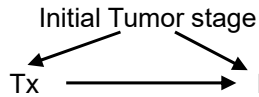
Potential Biases in RWE

Confounding

Unmeasured confounding

Time-independent confounding



Time-independent confounding

Initial Tumor stage is a common cause of prescribed Tx and Death

Time-dependent confounding

Time-dependent confounding

Biomarker is a common cause of Tx and Death and is also affected by Tx

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Quantitative Methods to Control for Confounding

Time-independent Confounding

- Traditional methods
  - Restriction
  - Stratification
  - Multivariate modeling
  - Matching
  - Propensity score
- [g-Methods]

Time-dependent Confounding

- g-Methods
  - g-formula
  - g-estimation
  - inverse probability weighting
- Further approaches:
  - Two-stage method in RCTs with Tx switching
  - Doubly robust methods (TMLE)

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Potential Biases in RWE

Confounding

Time-independent confounding
Time-dependent confounding
Unmeasured confounding

Selection bias

Controlling for collider bias

Immortal time bias

Self-inflicted time zero bias

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Immortal Bias: Example: Oscar Winning

ARTICLE

Survival in Academy Award–Winning Actors and Actresses

Donald A. Redelmeier, MD, and Sheldon M. Singh, BSc

Background: Social status is an important predictor of poor health. Most studies of this issue have focused on the lower echelons of society.

Objective: To determine whether the increase in status from winning an academy award is associated with long-term mortality among actors and actresses.

Design: Retrospective cohort analysis.

Setting: Academy of Motion Picture Arts and Sciences.

Participants: All actors and actresses ever nominated for an academy award in a leading or a supporting role were identified ($n = 762$). For each, another cast member of the same sex who was in the same film and was born in the same era was identified ($n = 887$).

Measurements: Life expectancy and all-cause mortality rates.

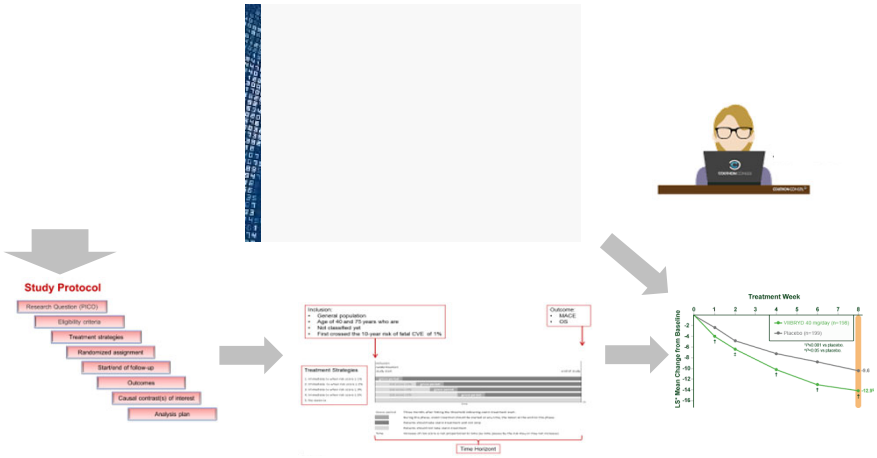
Results: All 1649 performers were analyzed; the median duration of follow-up time from birth was 66 years, and 772 deaths occurred (primarily from ischemic heart disease and malignant disease). Life expectancy was 3.9 years longer for Academy Award winners than for other, less recognized performers (79.7 vs. 75.8 years; $P = 0.003$). This difference was equal to a 28% relative reduction in death rates (95% CI, 10% to 42%). Adjustment for birth year, sex, and ethnicity yielded similar results, as did adjustments for birth country, possible name change, age at release of first film, and total films in career. Additional wins were associated with a 22% relative reduction in death rates (CI, 5% to 35%), whereas additional films and additional nominations were not associated with a significant reduction in death rates.

Conclusion: The association of high status with increased longevity that prevails in the public also extends to celebrities, contributes to a large survival advantage, and is partially explained by factors related to success.

Ann Intern Med. 2001;134:955-962. www.annals.org
For author affiliations, current addresses, and contributions, see end of text.
See editorial comment on pp 1001-1003.

Redelmeier & Singh, Ann Intern Med 2001

Target Trial Concept



Study Protocol

- Research Question (PICO)
- Eligibility criteria
- Treatment strategies
- Randomized assignment
- Start/end of follow-up
- Outcomes
- Causal contrast(s) of interest
- Analysis plan

Hernan & Robins, Am J Epi 2014

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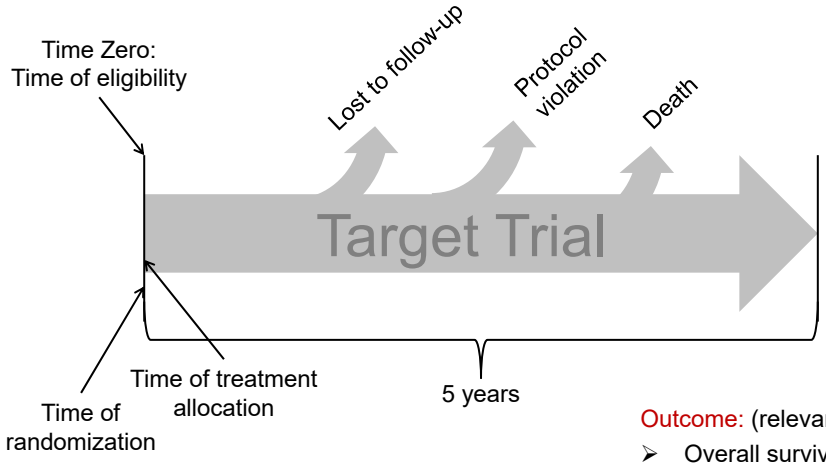
Follow-up Period and Outcome



Outcome: (relevant)

- Overall survival (OS)
- Pain
- Time without chemo

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Target Trial Framework

cloning - censoring – weighting

1. Cloning/replicating all individuals and assign to each comparatice strategy
2. Censor replicates artificially when deviating from the assigned strategy
3. Upweight uncensored individuals to account for potential selection bias induced by analytic censoring

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CASE EXAMPLE OF TARGET TRIAL EMULATIONS AND CHALLENGES IN THE HTA PROCESS

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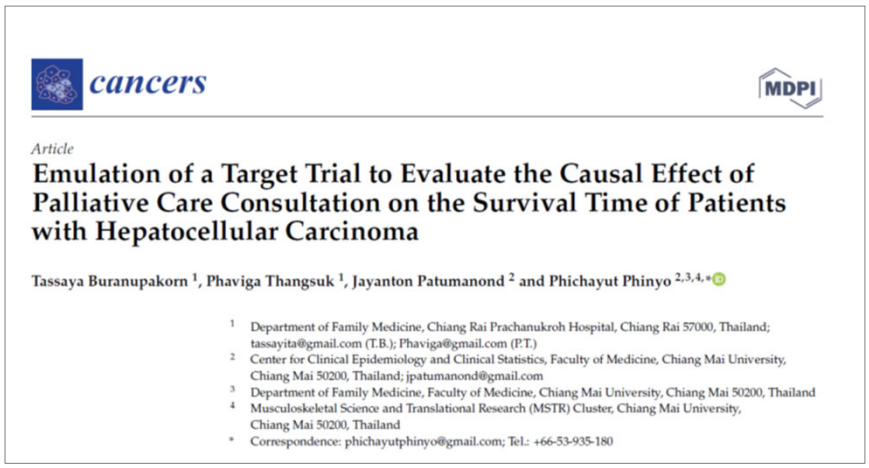
Case Example: Palliative Care Consultation for Patients with Hepatocellular Carcinoma



cancers

MDPI

Article

Emulation of a Target Trial to Evaluate the Causal Effect of Palliative Care Consultation on the Survival Time of Patients with Hepatocellular Carcinoma

Tassaya Buranupakorn [1], Phaviga Thangsuk [1], Jayanton Patumanond [2] and Phichayut Phinyo [2,3,4,*]

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Buranupakorn et al., Cancers (Basel) 2021

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Background

- Hepatocellular carcinoma (HCC) aggressive liver cancer
- In Thailand, HCC highly prevalent
  - north and northeast, endemic areas of viral hepatitis
- Often diagnosed at incurable stage
- Great suffering during end-of-life period
- Palliative care can improve quality of life and alleviate symptoms
- Barriers
  - Stigmatization of discipline
  - Palliative sedation perceived as “slow euthanasia”, accelerating death

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Aim, Data & Causal Approach

Aim:	Evaluation of the causal effect of palliative care consultation on the survival time of patients diagnosed with HCC
Data:	Retrospective observational data of a Thai tertiary care center
Causal approach:	Target trial emulation

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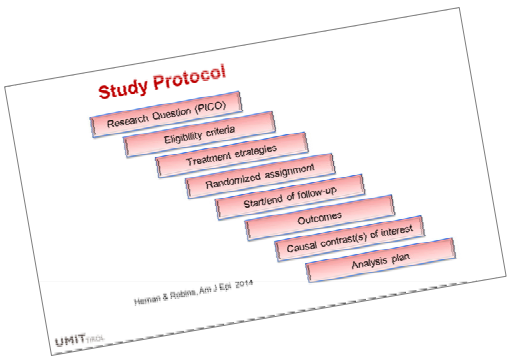
Target Trial Protocol



Buranupakorn et al., Cancers (Basel) 2021

Table 1. Study protocol for target trial emulation comparing to the original patient cohort.

Component	Target Trial	Emulated Cohort	Original Cohort
Design	Randomized controlled, concurrent trial of patients with HCC.	Emulated target trial from observation cohort of patients with HCC.	Retrospective observational cohort of patients with HCC.
Aim	Estimate the effect of palliative care consultation within 12 months of HCC diagnosis on survival time of the patients.	Same as Target Trial.	Same as Target Trial.
Eligibility	Patients with HCC aged ≥18 years old diagnosed at any BCLC stage with any level of performance status.	Same as Target Trial.	Patients with HCC aged ≥18 years old who were diagnosed at CRH during January 2017 to August 2019.
Exclusions	Patients who died from non-cancer specific causes, such as traumatic accidents.	Same as Target Trial..	Same as Target Trial.
Treatment strategies	1. Palliative care consultation within 12 months of HCC diagnosis. 2. No palliative care consultation within 12 months of HCC diagnosis.	Same as Target Trial.	1. Palliative care consultation after HCC diagnosis. 2. No palliative care consultation after HCC diagnosis.
Treatment assignment	Patients were randomly assigned to either strategy.	Trial emulation was performed via cloning of patients in both arms and assigning appropriate censor definition.	Patients were classified into either group on the basis of documented consultation records or ICD-10 code.
Treatment implementation	None.	12 months grace period.	Consulted or never consulted.
Outcome	All-cause mortality at 1 year after HCC diagnosis.	Same as Target Trial.	Same as Target Trial.
Type of outcome	Survival time.	Same as Target Trial.	Same as Target Trial.
Follow-up	Follow-up started at diagnosis, equivalent to treatment assignment and treatment initiation.	Follow-up started at diagnosis, which might not have corresponded with the initiation of palliative care consultation.	Follow-up started at diagnosis, which might not have corresponded with the initiation of palliative care consultation.
Censoring	Loss to follow-up, administrative censoring.	Same as Target Trial.	Same as Target Trial.
Adjustment variables	Age at diagnosis, gender, health insurances, comorbidity, tumor characteristics (etiology of HCC, BCLC staging, tumor size, porto-venous involvement), HCC specific treatment received.	Same as Target Trial.	Same as Target Trial.
Causal contrast	Per-protocol analysis.	Per-protocol analysis. Intended treatment could not be identified from the data. Trial emulation would censor patients, including clones, who deviated from their assigned protocol at the time of deviation.	As-treated analysis. Patients with HCC who did not have any documented record of palliative care consultation during the study period were grouped in the standard oncologic care group.
Statistical analysis (primary endpoint)	Differences in the restricted mean survival time among treatment arms at 90, 180, and 365 days after diagnosis.	Same as Target Trial.	Same as Target Trial.

Abbreviations: BCLC, Barcelona Clinic Liver Cancer staging; CRH, Chiang Rai Prachanukroh Hospital; HCC, hepatocellular carcinoma; ICD, International Statistical Classification of Diseases and Related Health Problems.

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Target Trial Protocol

Component	Target Trial	Emulated Cohort	Original Cohort
Treatment strategies	1. Palliative care consultation within 12 months of HCC diagnosis. 2. No palliative care consultation within 12 months of HCC diagnosis.	Same as Target Trial.	1. Palliative care consultation after HCC diagnosis. 2. No palliative care consultation after HCC diagnosis.
	FU specified => Treatment strategy defined	☑	*No FU specified => Ill-defined treatment strategy?*

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Target Trial Protocol

Component	Target Trial	Emulated Cohort	Original Cohort
Treatment assignment	Patients were randomly assigned to either strategy.	Trial emulation was performed via cloning of patients in both arms and assigning appropriate censor definition.	Patients were classified into either group on the basis of documented consultation records or ICD-10 code.
	Assignment of patient to exactly one group at Time Zero *Not looking into the future!*	***Cloning*** *=> assignment at Time Zero* ***Artificial censoring*** *=> removing "nonadherent" person time* *Not looking into the future!*	*Assignment of entire patient to exactly one group by "looking into future"* *→ Immortal time bias*
		☑	

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Target Trial Protocol

Component	Target Trial	Emulated Cohort	Original Cohort
Treatment implementation	None. *Immediate implementation*	12 months grace period. *Implementation with time rule* ☑	Consulted or never consulted. *"Ever vs. never" No time specified*

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Controlling for Confounding by IPW

Observational data

⇒ Palliative care assignment may have reasons (confounding)

⇒ Artificial censoring is informative (selection bias)

Solution: Inverse probability weighting (IPW) removes selection bias

Use of a multivariate treatment-specific Cox proportional hazard regression model to predict the probability of censoring for each treatment strategy including all potential confounders (i.e., gender, age, type of health insurance, comorbidity, tumor etiology, BCLC staging, CTP score, tumor size, porto-venous involvement, and HCC specific treatment received).

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Results

Conventional Analysis with Self-Inflicted Biases

Causal Analysis Using Target Trial Emulation

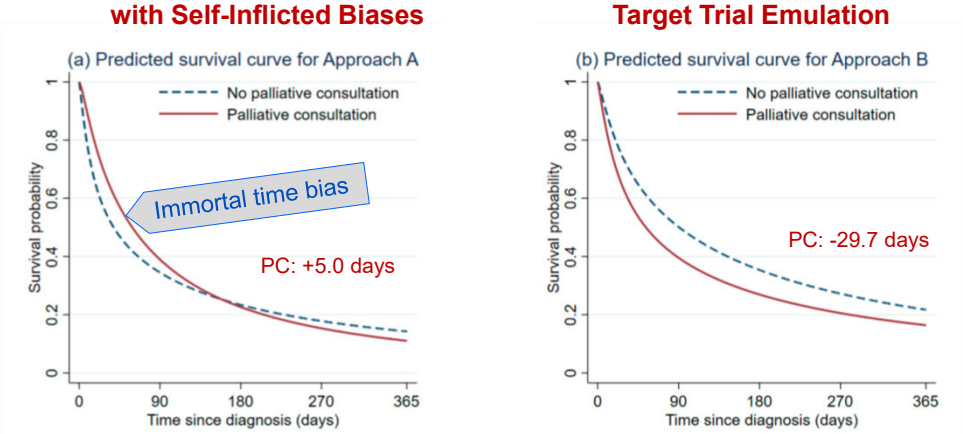

Figure 3. Predicted survival curve based on flexible parametric survival regression for approach A and approach B (limiting the analysis at 1 year after HCC diagnosis).

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Conclusion

- Target trial emulation removed self-inflicted biases
  - Time zero bias
  - Selection bias
  - Ill-defined treatment strategy
- Mean survival time was slightly shorter in the palliative care consultation group (not statistically significance)
- No clear survival benefit or harm of palliative care consultation
- Palliative care consultation led to a significant reduction in life-sustaining intervention, healthcare resource utilization, and cost

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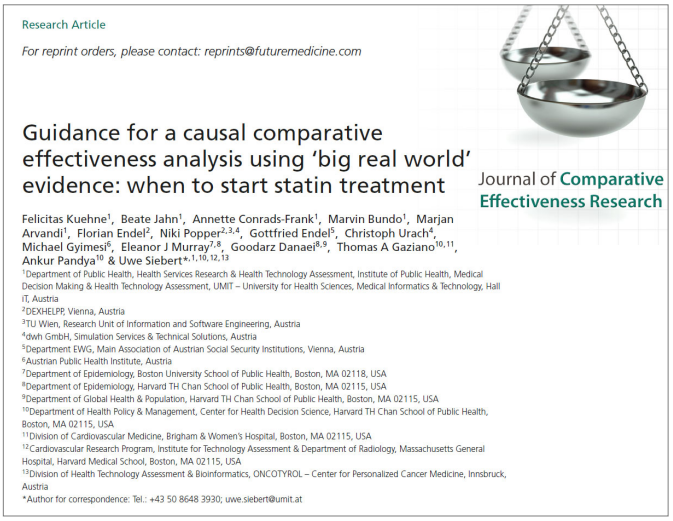
Write and Publish Your Target Trial Protocol



Research Article

For reprint orders, please contact: reprints@futuremedicine.com

Guidance for a causal comparative effectiveness analysis using 'big real world' evidence: when to start statin treatment

Journal of **Comparative Effectiveness Research**

Felicitas Kuehne[1], Beate Jahn[1], Annette Conrads-Frank[1], Marvin Bundo[1], Marjan Arvandi[1], Florian Endel[2], Niki Popper[2,3,4], Gottfried Endel[5], Christoph Urach[4], Michael Gyimesi[6], Eleanor J Murray[7,8], Goodarz Danaei[8,9], Thomas A Gaziano[10,11], Ankur Pandya[10] & Uwe Siebert*[,1,10,12,13]

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Kuehne et al., JCER 2019

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Isao Kamae, University of Tokyo Japan, Former ISPOR President

POTENTIALS, EXPECTATIONS, AND CHALLENGES IN REGISTRY PLANNING AND ANALYSES

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Potentials

- Improve the methods in observational studies to get the evidence less biased
- Strengthen the scientific soundness in research
- Change the rules in informing decisions in government
- Employing the methods in official HTA guidelines
- Provide new information in shared decision making in clinical practice
- Change in core knowledge of HTA literacy

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Expectations

- New additions to scientific knowledge as the standard skills for RWD analyses
- Increasing number of studies and publications with the TTE applied
- The methods may get more familiar to, not only epidemiological community, but also pharmacoeconomics and outcomes researchers
- Employing the TTE methods in official HTA guidelines in the near future (e.g., not described in the PE guidelines in Japan yet)

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Challenges

- Focus on RCTs rather than RWD
- Focus on p-value instead of max likelihood estimates and 95%CI (Cox, prospective model)
- Not all HTA agencies have a formal approach for benefit and harm assessment (e.g. QALY)
- Further investigation in theory for the TTE, focused on the change of relation between befefit (QALYs) and costs when the outcomes with TTE lead to different outcomes with out TTE.
- Assessment of multiple values for patients
- Capability building on TTE literacy (e.g., new mission of ISPOR)

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Registry planning and analyses

- Database design considering the TTE applications
- Need for user-friendly software of the TTE applications
- Availability, reliablity and transparency of the registered data
- Training program on the TTE analyses for a target registry
- International collaboration and sharing the knowledge and skills

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Target Trial emulation in Agencies EU

- NICE (UK)

  Describes target trial emulation in methods guidance

- IQWiG (Germany)

  Relatively reluctant regarding RWE,

  No mentioning of target trial emulation

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Target Trial emulation in Agencies Asia

- Learning stage on the TTE in most Asian countries
- No describes target trial emulation in methods guidance (Japan)
- Quote as the evidence derived from the TTE in literature review of drug approval (e.g., assessment of COVID vaccines in the MHLW committee, Japan, *Dickerman BA, Gerlovin H, Madenci AL, et al. Comparative Effectiveness of BNT162b2 and mRNA--1273 Vaccines in U.S. Veterans. New England Journal of Medicine. Published online December 1, 2021.)*
- Early stage of training program on TTE (e.g., Introduction to TTE, The Society for Clinical Epidemiology The 4th Annual Meeting 2021, Japan)

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