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Applications of the Target Trial framework for estimating Comparative Effectiveness using Real-World Data: A systematic review

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Background

The Target Trial (TT) framework was introduced by Hernan and Robins (2016) as an approach for reducing biases associated with using real-world data for estimating comparative effectiveness, utilising the design principles of randomised controlled trials combined with causal inference statistical methods.

The objective of this review was to evaluate applications of the TT framework by investigating:

- The extent of use of the TT framework
- The quality of studies that use the TT framework
- The strengths and weaknesses of studies that use the TT framework

Methods

Our search strategy aimed to identify relevant studies published after Hernan and Robins' 2016 paper* and before June 1, 2021.

The Cochrane CENTRAL, Medline and EMBASE databases were searched using key search terms and a citation search of Hernan and Robins' (2016) paper* was conducted. Two reviewers independently screened the search results.

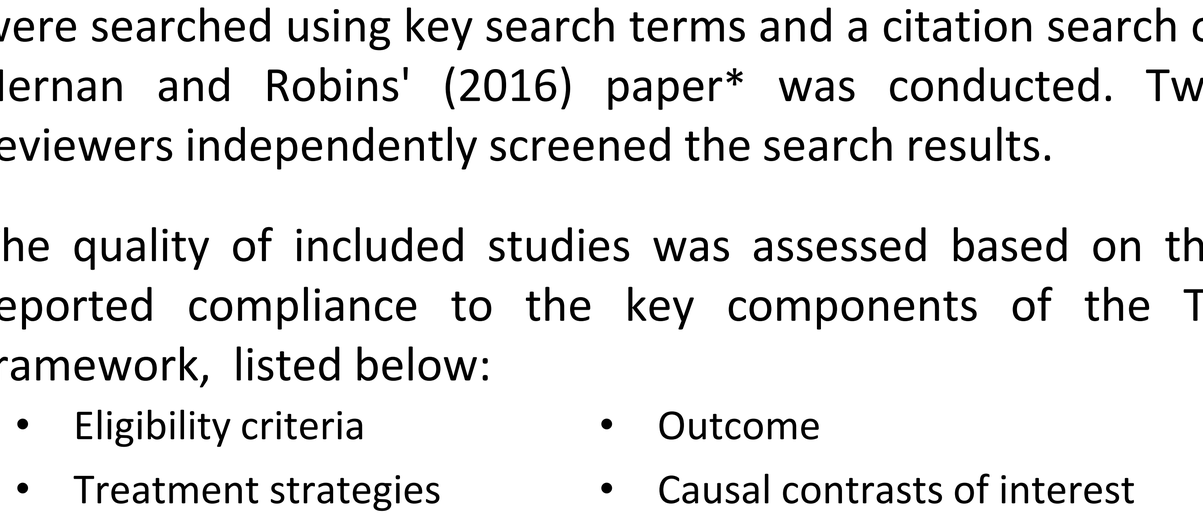
The quality of included studies was assessed based on the reported compliance to the key components of the TT framework, listed below:

- Eligibility criteria
- Treatment strategies
- Assignment procedures
- Follow-up period
- Outcome
- Causal contrasts of interest
- Analysis plan

Additionally, information on baseline/time zero definition and pre-specification of the study protocol/analysis plan were extracted, as well as information on reported challenges.

*Hernán, M.A. and J.M. Robins, Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. Am J Epidemiol, 2016. 183(8): p. 758-64.

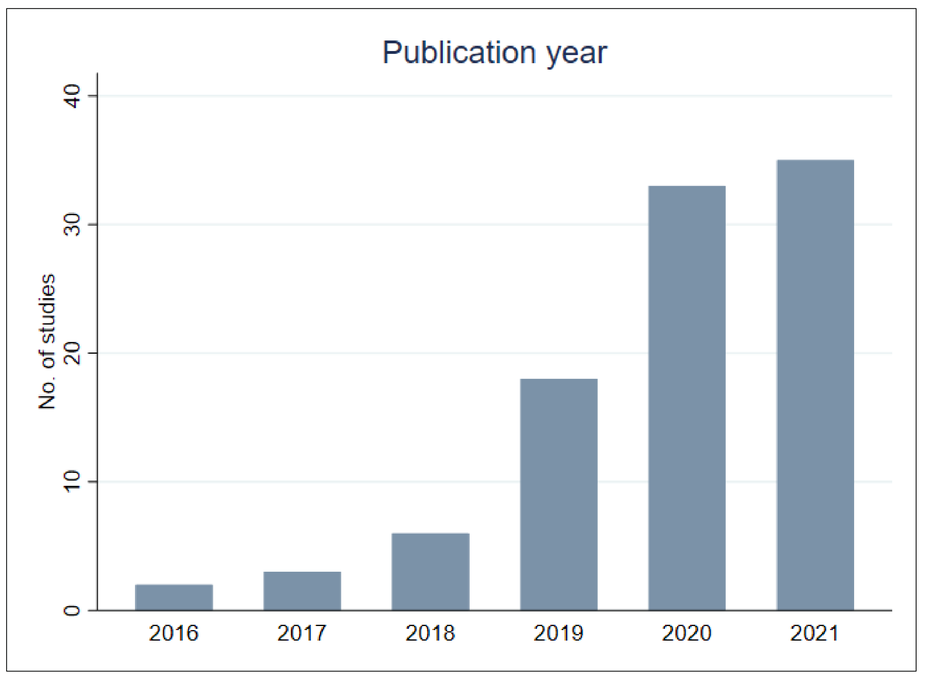
Flow chart



Results

97 studies were eligible for inclusion.

The number of studies using the TT framework has been increasing over time.



Cancer was the most common disease area (19.6%).

Disease area	No. of studies	Disease area	No. of studies
Cancer	19	Mental health	6
HIV	10	Diabetes	4
Cardiovascular disease	9	Urology	4
COVID-19	8	Others	29
Orthopaedics	8	**Total**	**97**

Time-to-event outcomes were reported in 75 (77.3%) of studies.

The most commonly used causal inference statistical methods were:

- Inverse probability weighting: 56 (57.7%)
- Propensity score matching: 19 (19.6%)

Cloning methods and multiple nested trials (14 (14.4%) and 15 (15.5%) studies, respectively) were notable techniques that were used in an attempt to reduce bias.

Most TT components were well defined across studies. However, study baselines (often referred to as "time zero") and causal contrasts of interest were not adequately defined in 13 (13.4%) and 20 (20.6%) studies, respectively. It was unclear whether analysis plans had been pre-specified in 80 (82.5%) studies.

Conclusions

The TT framework is being used regularly to conduct comparative effectiveness analyses using real-world data. However, studies do not always fully comply with all elements of the framework. Analyses could be improved by reporting on all key TT components and through pre-specification of analysis plans.

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