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COMMENTARY

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From emulation to evidence: The concepts, limitations, and prospects of TTE and TARGET

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On September 3rd, the TARGET (Transparent Reporting of Observational Studies Emulating a Target Trial) statement was simultaneously published in both *The BMJ* and *JAMA*, marking a milestone in the development and application of target trial emulation (TTE).[1,2] TARGET represents a novel standard guideline for transparent reporting of the design, analysis, and results of observational studies that explicitly aim to estimate causal effects through emulating a target RCT (randomized controlled trial). The TARGET statement consists of a checklist and explanatory materials to guide TTE research reports, targeting researchers, clinicians, and epidemiologists. This commentary introduces and discusses TTE and TARGET, highlighting their critical role in advancing causal inference in observational research.

The main limitation of observational research is its susceptibility to confounding, reverse causation, measurement error, and selection bias, which often generate contradictory or spurious conclusions. These pervasive flaws are further compounded by selective result reporting, undermining the credibility of study findings. Additionally, extensive post-hoc data mining frequently produces technically sophisticated yet clinically irrelevant results, thereby fostering data misuse and divergence from clinical practice. TTE was proposed to incorporate the design principles of RCTs into observational studies. RCTs provide the most credible causal estimates but are often unavailable or infeasible due to ethical, temporal, or financial constraints; applying these principles helps mitigate design-related biases arising from the inappropriate use of observational data.[3] The concept of TTE was proposed by Hernán and Robins in 2016, and its core framework comprises

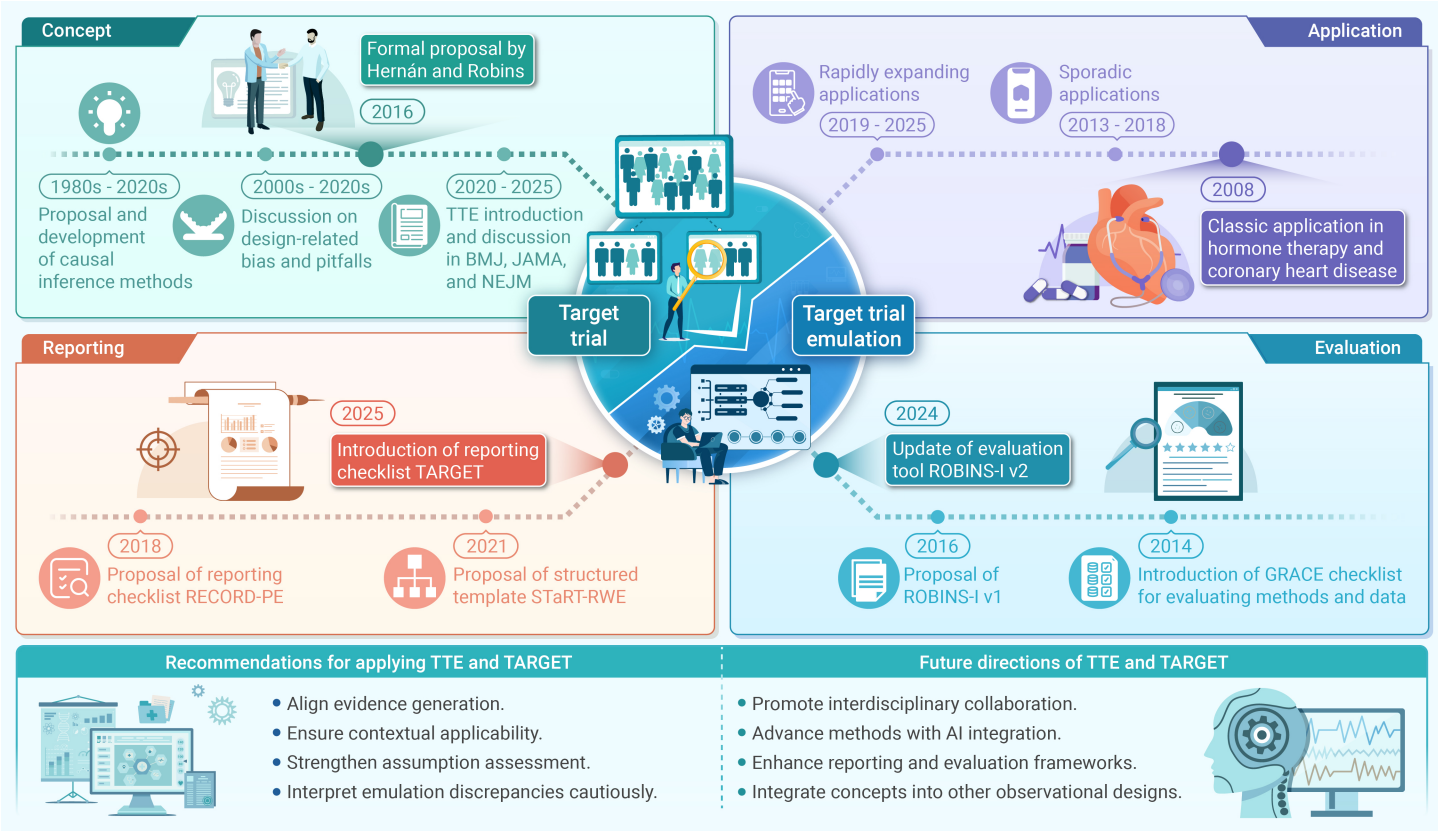

Figure 1. Development of Target Trial Emulation (TTE), including its concept, application, reporting, and evaluation.

two main steps.[3] The first step involves formulating the causal question in the form of a target trial protocol that clearly specifies the causal effect of interest (causal estimand), underlying key assumptions, and analytic strategies (statistical analysis plan). The second step entails mapping each element of this protocol to the corresponding components in available observational data. Under the TTE framework, researchers should clearly specify the scientific question prior to analysis and adhere strictly to the pre-determined protocol during study implementation. Such an approach safeguards study integrity and minimizes the risk of P-hacking or data-driven analyses that are unrelated to the primary clinical question. The development and major milestones of TTE are illustrated in Figure 1. Since 2019, the application of TTE has grown substantially, with nearly 20 applied studies published annually and an exponential rise in recent years, particularly in the areas of infectious diseases (notably COVID-19), cardiology, and oncology. From a regulatory perspective, the TTE approach was explicitly recognized as a method to support causal inference in non-interventional studies in the U.S. FDA guidance *"Real-World Evidence: Considerations Regarding Non-Interventional Studies for Drug and Biological Products"*, issued in March 2024. Thus, the

proposal and application of TTE are expected to advance observational research in clinical medicine and epidemiology.

The introduction of TARGET filled a critical gap, as no specific guidance for reporting TTE was available beforehand. Although STROBE (Strengthening the Reporting of Observational Studies in Epidemiology), RECORD (Reporting of Studies Conducted Using Observational Routinely Collected Health Data), and their extensions have been widely applied in reporting observational research, they do not adequately address the distinctive methodological features of TTE, particularly the mapping of observational data to the target trial. The TARGET statement enhances interpretability for clinicians by requiring explicit specification of the target trial and transparent mapping of observational data to trial components. Through promoting pre-specification and comprehensive reporting of study design, TARGET mitigates the risk that methodological artifacts are misinterpreted as clinically meaningful findings. Moreover, it enables clinicians to assess whether the populations, interventions, and outcomes of an emulation align with their practice context, thereby facilitating the translation of findings into actionable evidence. While TARGET fills an important gap in TTE reporting, it should not be regarded as prescriptive guidance for designing or conducting non-interventional comparative effectiveness studies. Moreover, the TARGET checklist is not intended as a tool for evaluating the quality of TTEs, although clear and transparent reporting is a prerequisite for any such evaluation. There is a need for a dedicated evaluation tool specifically designed for TTE. Such a tool could extend or adapt the ROBINS-I framework (Risk Of Bias In Non-randomized Studies of Interventions) while further capturing biases specific to TTE. In particular, the tool should incorporate a more systematic evaluation of emulation differences, encompassing assessments of data-trial mapping deviations and quantitative indicators of emulation discrepancies. For clinicians, this implies that TARGET cannot be used in isolation to evaluate the credibility of TTE findings. Robust evidence appraisal requires dedicated evaluation tools to assess bias and validity, complemented by close collaboration with biostatisticians. Stepwise documentation, transparent reporting and rigorous evaluation strengthen the reproducibility and credibility of TTE-derived evidence, ensuring its validity for scientific research, its applicability for clinical practice, and its sufficiency to support regulatory decision-making.

The most distinctive feature of the TARGET checklist is the juxtaposition of items 6 and 7. The item 6 ("target trial specification") outlines all design elements of the target trial; item 7 then requires a point-by-point description of how each component of the target trial was emulated using observational data. This side-by-side presentation aligns with most TTE reports, which typically include a table listing the design elements of the target trial in the left column and their emulations in the right column. Such reporting and contrast provide a clear visual illustration of the TTE mapping process. Any biases arising from the study design or observational data, as well as differences introduced through the mapping process, can be identified through detailed reporting. Sub-item 7g ("identifying assumptions") and 7h ("Data analysis plan") are deliberately expanded into two finer sub-items each, thereby highlighting the greater level of detail and specificity. This reflects the central principle that causal inference from TTE is valid only when the underlying assumptions, conditional exchangeability, consistency, and positivity, are explicitly stated and rigorously justified. TTE reports are therefore expected not only to articulate these assumptions but also to evaluate their plausibility and assess their impact through sensitivity analyses using alternative methodological approaches.

Despite rigorous theoretical foundations, diverse applications, and well-articulated reporting checklists, TTE is not a panacea or an all-encompassing framework for resolving all challenges in observational comparative effectiveness research. Through the structured TTE approach, investigators could minimize the design-related bias, especially those concerning the definition of time zero, the point at which eligibility is assessed, treatment is assigned, and follow-up begins. By specifying these components synchronously, TTE avoids the existence of immortal time bias, which is closely linked to the misclassification or selection bias. However, significant challenges persist in observational data, including unmeasured confounding, measurement error, and missing information. Addressing these issues effectively requires careful attention and strategies tailored to each specific case. The proposal and implementation of TARGET would help delineate the capabilities and limitations of the TTE framework.

As the first reporting checklist for TTE, TARGET specifies the minimum essential items recommended for reporting. However, its guidance on describing the differences between target trial and its emulation remains limited, being mentioned only vaguely under the "limitations" item in the Discussion section. Emulation differences are the discrepancies arising when replicating a RCT using observational data in TTE. For actual trials that are ongoing or completed, rather than hypothetical ones specified iteratively, full alignment is impossible. These differences reflect structural mismatches from mapping process, including variations in study populations (vague expression of eligibility criteria and incomplete recording), treatment strategies (absence of placebo control, suboptimal adherence, and the differences in dosing and augmentation schedules), and outcome measurements (inconsistencies in definition and identification, and limited availability of long-term follow-up).[4] Enumerating and, where possible, quantifying emulation differences can help disentangle whether and to what extent the observed "efficacy-effectiveness gap" between TTEs and corresponding RCTs arises from biases or limitations of the emulation. The quantification of emulation differences remains exploratory. Existing studies have mainly classified these differences into two or three levels, such as good, moderate, and poor, based on factors including the choice of comparator, outcome definition, medication maintenance, and time alignment.[5] Currently, there is no established guideline, framework, or reporting checklist for assessing emulation differences, which warrants further methodological development. In applications, such distinctions are essential, as TTEs may yield insights that more closely reflect actual clinical practice and complement RCT evidence by extending its relevance to broader populations who are likely to use these interventions in routine clinical care. For clinicians, this discrepancy should be interpreted with caution, paying particular attention to whether the emulated populations, interventions, and outcomes align with their own clinical practice. The potential influence of emulation differences must be explicitly recognized and carefully interpreted before integrating the findings into clinical decision-making. Furthermore, confirmatory RCTs that borrow information from TTEs could be conducted with explicit consideration of the "efficacy-effectiveness gap" to enhance trial efficiency, representing another approach to integrating RCTs and TTEs.

In summary, the TARGET statement, a consensus-based guidance for TTE reporting, is expected to invigorate the development of causal inference using observational data. High-standard reporting guidance enhances the transparency and reproducibility of study designs and methods, enabling more accurate appraisal, interpretation, and translation of research findings into clinical practice. By standardizing evidence generation in observational studies, TTE and TARGET help clinicians apply research evidence more reliably to patient care and ultimately improve the quality of public health services. TARGET is a living guideline that currently focuses on parallel, individual-level TTEs, with future extensions anticipated for more complex and cluster-level designs. Additionally, observational studies encompass various categories. While TTE primarily addresses effectiveness and safety, further efforts are needed to develop reporting guidelines for causal inference in other types of observational studies.

REFERENCES

1. Cashin A. G., Hansford H. J., Hernan M. A., et al. (2025). Transparent reporting of observational studies emulating a target trial-the TARGET statement. *JAMA* **334**:1084–1093. DOI:10.1001/jama.2025.13350
2. Cashin A. G., Hansford H. J., Hernan M. A., et al. (2025). Transparent reporting of observational studies emulating a target trial: The TARGET statement. *BMJ* **390**:e087179. DOI:10.1136/bmj-2025-087179
3. Hernán M. A. and Robins J. M. (2016). Using big data to emulate a target trial when a randomized trial is not available. *Am. J. Epidemiol.* **183**:758–764. DOI:10.1093/aje/kwv254
4. Franklin J. M., Glynn R. J., Suissa S., et al. (2020). Emulation differences vs. biases when calibrating real-world evidence findings against randomized controlled trials. *Clin. Pharmacol. Ther.* **107**:735–737. DOI:10.1002/cpt.1793
5. Wang S. V., Schneeweiss S., Initiative R.-D., et al. (2023). Emulation of randomized clinical trials with nonrandomized database analyses: Results of 32 clinical trials. *JAMA* **329**:1376–1385. DOI:10.1001/jama.2023.4221

DECLARATION OF INTERESTS

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