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PRESENTED BY EAA AND THE CORE-RWE PROJECT:

HOW TO LEVERAGE RWD FOR EU HTA – conceptual overview & case studies

Brussels, April 16th, 2026

Vlerick Business School

RWE VERSUS RCT FOR REGULATORY DECISION-MAKING: THE DEBATE

Invited Commentary | Oncology

Are Observational, Real-World Studies Suitable to Make Cancer Treatment Recommendations?

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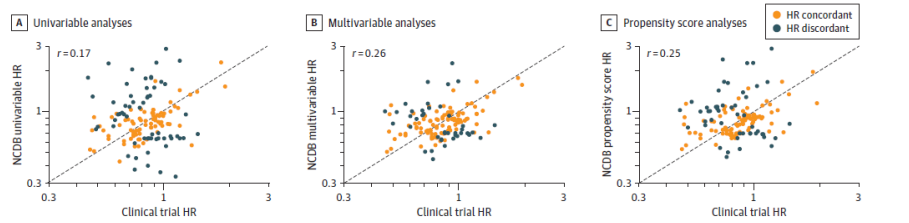
Figure 2. Comparison of Hazard Ratios (HRs) From Randomized Clinical Trials and Analyses With Data From the National Cancer Database (NCDB)



Hazard ratios shown for univariable analyses (A), multivariable analyses (B), and propensity score analyses (C). Each point on the scatter plot represents the HR for overall survival from 1 of the 141 randomized clinical trials in this study and the corresponding analysis within the NCDB. Yellow dots represent NCDB analyses in which the NCDB HR falls within the 95% CI of the HR in the clinical trial (concordant), and blue dots represent HRs from the NCDB analyses that fall outside the 95% CI of the HR in the clinical trial (discordant). The gray dashed line shows where clinical trial HRs equal NCDB HRs. The intersection of the axes represents an HR equal to 1.

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analyses. The authors account for a wide number of potential confounders in these analyses, including Charlson Comorbidity Index and median income. However, neither method was able to move the needle substantially on CER-RCT concordance. Kumar et al[1] found that 44% of unadjusted NCDB analyses yielded overall survival hazard ratios outside of the 95% CI for their RCT counterparts. Incorporation of multivariable regression or propensity score–weighting decreased this proportion modestly to 30% and 36%, respectively. The fact that propensity score–weighting seems inadequate is consistent with prior research.[9] Notably, to our knowledge, no study to date has used the most sophisticated observational method, a target trial simulation,[10] and we encourage future researchers to examine this question.

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Replacing RCTs with real world data for regulatory decision making: a self-fulfilling prophecy?

Real world data are advocated as an alternative approach to RCTs for closing knowledge gaps on drugs, but Beate Wieseler and colleagues argue that this approach is the wrong remedy for current challenges in drug development

Beate Wieseler,[1] Mattias Neyt,[2] Thomas Kaiser,[1] Frank Hulstaert,[2] Jürgen Windeler[1]

Key messages

- Enthusiasm is growing for the use of observational real world data as a basis for regulatory, clinical, and health policy decision making
- But such study designs are ill suited to measure the treatment effects of new drugs
- Promoting the use of observational studies from routine practice data sources might hinder efforts needed to improve the feasibility of randomised controlled trials
- To ensure high quality and efficient healthcare, the conduct of RCTs, including those in routine care, should be made easier, faster, and cheaper

Attempts to accelerate the provision of new treatments have led to evidence that is limited in quantity and quality being submitted for regulatory approval in recent years.[1 2] Approvals based on single arm trials, for example, have become more frequent, such as for lisocabtagene maraleucel, a CAR-T cell therapy for patients with B cell lymphoma. Single arm trials are not informative enough to enable us to select the best therapy for a patient among several options. This lack of robust evidence, especially the lack of comparisons with standard care, has implications for decision making in clinical practice and health policy, as the place of new drugs in the treatment landscape remains unclear, and

The FDA defines real world data as "data relating to patient health status and/or the delivery of healthcare routinely collected from a variety of sources," not restricting study designs. It defines real world evidence as "the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of [real world data]," which can be generated using different study designs "including, but not limited to, randomised trials (eg, large simple trials, pragmatic trials), and observational studies (prospective or retrospective)."[7]

European Medicines Agency (EMA)

The EMA defines real world data as "routinely collected data relating to a patient's health status or the delivery of healthcare from a variety of sources other than traditional clinical trials,"[8] thus restricting the study designs that can be used to generate real world data. The EMA has published inconsistent information on this restriction of study designs—it previously noted that data from pragmatic (randomised) trials would be included if collected under conditions of normal clinical care, citing the randomised Salford Lung Study as an example.[8] But, in a more recent publication, real world data and evidence seem to be restricted to non-interventional preauthorisation or postauthorisation studies or sources other than RCTs.[9] The Data Analysis and Real World Interrogation Network (DARWIN EU), the EMA's main tool for the provision of real world data, is also limited to observational data sources and non-interventional studies.[10]

CORE-RWE METHODOLOGY HIGHLIGHTS

- A **methodological pilot** will be run to explore the application of unanchored indirect comparison methods using real-world evidence (RWE) to determine the minimal clinical effectiveness threshold needed to support timely access to ATMP and Medical Device-based therapies.
- We will use **synthetic real-world** data to stress-test our causal inference algorithms (e.g., proving our method works even with unmeasured confounding) before we touch the real sensitive patient data
- The study will evaluate how to combine RCT & RWD up to **how unanchored indirect designs**—such as matching-adjusted indirect comparisons (MAIC) and simulated treatment comparisons (STC)—when combined with advanced causal machine learning methods, **can inform both regulatory and reimbursement pathways**, even in the absence of head-to-head RCTs.
- The **goal is twofold: (1) to establish evidence thresholds** and identify scenarios where RWE-based causal inference can **reduce evidence uncertainty to acceptable levels for market access**. **(2)** to develop real-world performance-informed **adaptive payment models**