Lack of Standardization in Quantitative Evaluations of the Efficacy-Effectiveness Gap for Cancer Therapies: A Targeted Literature Review

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Background

The efficacy-effectiveness gap [EEG] (i.e., differences between RCT-based efficacy and RWE-based effectiveness estimates) has been well described conceptually, but few studies have quantitatively evaluated the magnitude of this gap for different cancer therapeutics.

According to the GetReal consortium, the EEG can be conceptualized as the result of differences between:

- Clinical trials and real-world attributes (e.g., prescribing patterns, clinical guideline adherence) of healthcare systems;
- Complex interactions between biological treatment effects and contextual factors;
- Methods (e.g., study design and analytics) to assess treatment effects.

Various study designs and methodologies have different strengths related to mitigation of biases (selection bias, information bias, and confounding). While RCTs are designed to optimize internal validity, RWE cohort studies may be more representative of real-life patient populations and clinical practices, which can have implications for external validity.

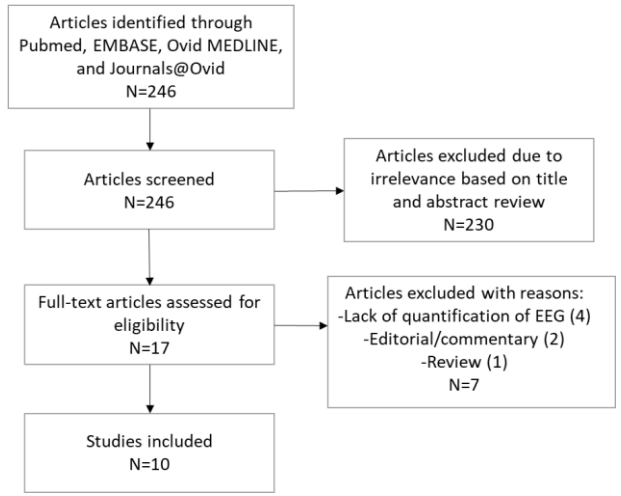
Quantification of EEGs can help us understand how clinical trial results may apply to RW patient populations, how to communicate expected outcomes to patients initiating a given treatment, and what methodological improvements can be made to RCT and RWE studies. Yet few studies formally quantify the magnitude and underlying reasons for EEGs.

The objective of this targeted literature review (TLR) was to briefly summarize the methods and findings of studies that quantified EEG for cancer therapies to help inform future methodological research.

Methods

A TLR was conducted among four databases focusing on English-language studies published between 01/2017–12/2021 that sought to quantify the magnitude of and investigate factors contributing to the EEG for cancer therapeutics (Fig 1).

Fig 1: Article selection process



Results

- Across the 10 included studies, EEG was assessed for:
  - >25 cancers (6/10 studies focused on one cancer type)
  - >45 treatments (systemic, targeted, and immunotherapy)
- Outcomes compared between trials and real-world analyses:
  - Progression-free survival
  - Time to progression
  - Recurrence-free survival
  - Overall survival
  - Adverse event rates
- The most common EEG explanatory factor examined was trial eligibility criteria, but treatment duration/completion and key confounders were also considered.

References

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Results (cont.)

- Poorer performance status and early treatment discontinuation (e.g., due to toxicities) were highlighted as important differences between RCT and RW populations that partly accounted for EEG in some studies.
- There was substantial heterogeneity in EEG quantification methods.
  - 3 studies (overlapping authors) calculated an "efficacy-effectiveness factor" (EEF) to assess the magnitude/direction of the EEG:
    - EEF = patients' overall survival time ÷ median survival from RCT for treatment of interest
    - Multivariable linear regression was used to identify predictors of EEF.
  - Lakdawalla et al. (2017) calculated the percent difference (*f*) between RWE and RCT mortality hazard ratios (HRs), using the βs from Cox regression with an offset of the clinical trial HRs to predict rwHRs.
    - F = 100 x (rwHR-rctHR)/rctHR
  - Some studies used RCT survival data reconstruction to enable direct statistical comparison of trial data to RW data.
  - Schuller et al. (2018) compared trial intervention group data to RW standard of care cohorts (similar to a historical controls analysis) to assess gains or losses in survival time.
- Stratification among trial-eligible subsets of RW populations was a common strategy for investigating influence of eligibility criteria on the EEG.
- Most studies using overall survival as the outcome found lower effectiveness in RWE studies compared to trial-based efficacy.

Conclusion

A heightened understanding of the scope and drivers of the EEG may pave the way for more inclusive clinical trials and innovations in study design and methodology for both clinical trials and RW studies. Research to develop a standardized approach for quantifying EEG is warranted.