A Process for the Emulation of Comparative Oncology Trials with Real-world Evidence (ENCORE)

**Authors**: Janick Weberpals1, Donna R. Rivera2, …, Sebastian Schneeweiss1, Shirley V. Wang1

Author affiliations:

1 Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, USA

2 Oncology Center of Excellence, US Food and Drug Administration, Silver Spring, MD, USA

**Correspondence:**

Shirley V. Wang, PhD

Division of Pharmacoepidemiology and Pharmacoeconomics,

Department of Medicine, Brigham and Women’s Hospital, Harvard Medical School,

1620 Tremont Street, Suite 3030-R, Boston, MA 02120, USA

Phone: +1 617-278-0932

Fax: + 1 617-232-8602

Email: <SWANG1@BWH.HARVARD.EDU>

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# Abstract

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# Background

With 21% of all drug approvals, oncology was the disease area with the most FDA drug approvals in 2023.1 Although randomized controlled trials (RCTs) are considered the gold standard, decision-makers increasingly rely on real-world evidence (RWE) generated from routine-care health data such as electronic health records (EHR) to evaluate the comparative safety and effectiveness of novel cancer therapies.**purpura2022role?** Especially in the field of precision oncology, RWE has many essential use cases and plays a critical role in complementing evidence like in patient populations that are underrepresented in RCTs, to construct external control arms in single-arm trials where active recruitment may not be feasible or in drug/biomarker discovery and label extensions among pan-tumor populations that harbor specific genomic signatures. However, to draw causal inferences from such comparisons in non-randomized data, it is pivotal that endpoints and prognostic information can be measured reliably and at scale, which remains a significant challenge in oncological comparative effectiveness research (CER).

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# Methods

**Systematic process for understanding the validity of RWE for oncology submissions**

# Discussion

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## Conclusions

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# References

**1**. Senior M: Fresh from the biotech pipeline: Record-breaking FDA approvals. Nature Biotechnology, 2024

**2**. Weberpals J, Raman SR, Shaw PA, et al: Smdi: An r package to perform structural missing data investigations on partially observed confounders in real-world evidence studies [Internet]. JAMIA Open 7:ooae008, 2024Available from: <https://doi.org/10.1093/jamiaopen/ooae008>

# Tables

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| Table 1: Criteria .   | Criteria | Definition | Eligible | | --- | --- | --- | | Interventional study | The nature of the investigation or investigational use for which clinical study information is being submitted | Interventional (clinical trial): Participants are assigned prospectively to an intervention or interventions according to a protocol to evaluate the effect of the intervention(s) on biomedical or other health related outcomes. | | Randomized allocation | The method by which participants are assigned to arms in a clinical trial. | Randomized: Participants are assigned to intervention groups by chance | | Interventional study model | The strategy for assigning interventions to participants. | Parallel: Participants are assigned to one of two or more groups in parallel for the duration of the study | | Sponsor/source | The entity (for example, corporation or agency) that initiates the study | Industry | | Study start date | The estimated date on which the clinical study will be open for recruitment of participants, or the actual date on which the first participant was enrolled. | 2011 or later | | Primary purpose | The main objective of the intervention(s) being evaluated by the clinical trial. | Treatment: One or more interventions are being evaluated for treating a disease, syndrome, or condition. | | Primary outcome | A description of each primary outcome measure (or for observational studies, specific key measurement[s] or observation[s] used to describe patterns of diseases or traits or associations with exposures, risk factors or treatment). | Primary or secondary outcome needs to include overall survival | | Overall Recruitment Status | The recruitment status for the clinical study as a whole, based upon the status of the individual sites. If at least one facility in a multi-site clinical study has an Individual Site Status of "Recruiting," then the Overall Recruitment Status for the study must be "Recruiting." | Completed: The study has concluded normally; participants are no longer receiving an intervention or being examined (that is, last participant’s last visit has occurred) OR Active, not recruiting: Study is continuing, meaning participants are receiving an intervention or being examined, but new participants are not currently being recruited or enrolled | | Feasibility and clinical relevance | Are all key variables available to emulate the clinical trial at hand and is the clinical trial considered clinically relevant? | Trials for which there is reasonable believe that key study parameters can be emulated and there is a high enough clinical relevance (e.g., paradigm-changing trials) | |

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| Table 2: Tentative list of randomized controlled trials (RCTs) considered for emulation.   | **NCTID** | **Acronym** | **Clinical setting** | **Line of therapy** | **Treatment comparison** | | --- | --- | --- | --- | --- | | **Non-small cell lung cancer** | | | | | | NCT02296125 | FLAURA | Advanced/metastatic EGFRm+ | 1L | osimertinib versus erlotinib or gefitinib | | NCT01673867 | CheckMate057 | Metastatic non-squamous | 2L | nivolumab versus docetaxel | | NCT03215706 | CheckMate9LA | Metastatic | 1L | nivolumab, ipilimumab, chemotherapy versus chemotherapy alone | | **Breast cancer** | | | | | | NCT01740427 | PALOMA-2 | Advanced postmenopausal ER-positive and HER2-negative | 1L | palbociclib, letrozole versus letrozole | | NCT02819518 | KEYNOTE-355 | Locally recurrent inoperable or metastatic triple negative | 1L | pembrolizumab, chemotherapy vs. placebo, chemotherapy | | NCT01772472 | KATHERINE | HER2-positive | Adjuvant | trastuzumab emtansine versus trastuzumab | | **Colorectal cancer** | | | | | | NCT04737187 | SUNLIGHT | Refractory metastatic | 3L | trifluridine, tipiracil, bevacizumab versus trifluridine, tipiracil | | NCT01374425 | MAVERICC | Metastatic | 1L | bevacizumab, mFOLFOX6 versus bevacizumab, FOLFIRI | | NCT02563002 | KEYNOTE-177 | Metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) | 2L+ | pembrolizumab versus standard of care | | **Multiple Myeloma** | | | | | | NCT01568866 | ENDEAVOR | Relapsing or progressing disease | 2L/3L | carfilzomib, dexamethasone versus bortezomib, dexamethasone | | NCT02252172 | MAIA | Newly diagnosed | 1L | daratumumab, lenalidomide, dexamethasone versus lenalidomide, dexamethasone | | NCT01239797 | ELOQUENT - 2 | Relapsed or refractory | 2L+ | elotuzumab, lenalidomide, dexamethasone versus lenalidomide, dexamethasone | |

# Figures

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| Figure 1: Systematic process to understand effectiveness claims of oncology trials using real-world evidence. |

View figure in higher resolution