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

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**Article type:** Review

**Word count:** xxx words / xxx words

**Tables:** x

**Figures:** x

**Supplementary material:** Supplementary tables and figures

**Short running title**: …

**Keywords:** Oncology, Real-World Evidence, Trial emulation, EHR

**Funding Statement:** This project was supported by …

**Competing Interests Statement:** Dr. Weberpals is now an employee of AstraZeneca and owns stocks in AstraZeneca. Dr. Wang has consulted ad hoc for Exponent Inc. and MITRE a federally funded research center for the Centers for Medicare and Medicaid Services on unrelated work. Dr. Schneeweiss is participating in investigator-initiated grants to the Brigham and Women’s Hospital from Boehringer Ingelheim, Takeda, and UCB unrelated to the topic of this study. He owns equity in Aetion Inc., a software manufacturer. He is an advisor to Temedica GmbH, a patient-oriented data generation company. His interests were declared, reviewed, and approved by the Brigham and Women’s Hospital in accordance with their institutional compliance policies.

**Data sharing statement:** …

**Analytic code sharing statement:** …

***Proposed target journals:*** *JCO CCI => JAMA Network Open => CPT*

*Manuscript last updated: 2024-11-28 19:39:06.619691*

# Abstract

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# Background

Randomized controlled trials (RCTs) have been the gold standard for establishing the efficacy and safety of medical products. With the advent of the the 21st Century Cures Act directive, the Food and Drug Administration (FDA) established a framework to increasingly include and additionally consider real-world evidence (RWE) generated from routine-care health data such as electronic health records (EHR) to evaluate and contextualize the comparative safety and effectiveness of novel cancer therapies.1 With 21% of all approvals, oncology was the disease area with the most FDA drug approvals in 2023,[2] and especially in the field of precision oncology, RWE has a large potential to complement evidence coming from RCTs. Examples comprise the assessment of effectiveness in patient populations that are underrepresented in RCTs, the construction of external control arms in single-arm trials where active recruitment may not be feasible or the use of real-world data (RWD) for biomarker discovery and label extensions among pan-tumor populations that harbor specific genomic and immunological signatures.

However, the validity and transportability of results derived betwen RWE studies and RCTs can depend on many factors and frequently references limitations include missing data, small sample sizes, data discontinuity3, 4, rapid changes in guideline treatment patterns and the inability to measure and emulate common eligibility criteria and prognostic factors in RWD.5 While there are publsihed examples of emulations of oncology trials5–7, a systematic and scaled approach to emulate a diverse set of different oncology trials in various heterogeneous databases is necessary to gain confidence in the accuracy of RWE studies and to provide an answer as to which questions can be validly answered with which non-interventional study designs and analysis methods.

The RCT DUPLICATE initiative8 increased our understanding of when RWE studies can come to causal conclusions on treatment effects by comparing results against RCTs under the assumption that each RCT finding reflects a causal treatment effect. In settings where the RCT designs could be emulated well, RWE studies came to the same conclusions.9 However, prior work from RCT-DUPLICATE has focused primarily on emulating trials in the cardio-metabolic, renal, and pulmonary clinical areas using claims databases.

The *Emulation of Comparative Oncology Trials with Real-world Evidence* (**ENCORE**) project10 aims to extend this work to the field of oncology which comes with its own unique set of challenges that are not necessarily comparable with previous learnings from other disease areas and which must be systematically explored and understood. Building on a process co-developed with the FDA through RCT DUPLICATE8, this expansion to oncology is going to emulate 12 randomized clinical trials using multiple EHR data sources. The process includes an emphasis on transparency with documented assessment of data fitness of the RWD source for each trial11, 12 and conducting extensive sensitivity analyses to assess robustness of findings and trial eligibility criteria.

The objectives of this project are to develop state-of-the-art methodological approaches and apply those to create insights that may provide guidance on the potential use of RWE for regulatory science in oncology. This includes the systematic evaluation of the suitability of data in relation to the study design and statistical analysis by emulating 12 oncology trials across four cancers and assessing the agreement of treatment effect estimates between trial emulation and RCT.

In this process paper, we describe the design and process for the selection of the 12 oncology RCTs, the assessment of the database quality and selection, protocol development, study design and statistical analysis and final agreement metrics to evaluate the concordance between RCT and its emulation.

# Methods

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

Trial selection

Data feasibility

Protocol development

Application of the target trial emulation framework to study design and statistical analysis

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Agreement metrics

# Discussion

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## Conclusions

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# 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](https://github.com/janickweberpals/encore-process-manuscript/blob/main/figures/process.png)