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

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# 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 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.**purpura2022role?** With 21% of all drug approvals, oncology was the disease area with the most FDA drug approvals in 20231, 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 limitations include missing data, small sample sizes, data discontinuity2, 3, rapid changes in temporal prescribing patterns and the inability to measure and emulate common eligibility criteria and prognostic factors.4 While there are examples of emulations of oncology trials4–6, a systematic and scaled approach to emulate a diverse set of different oncology trials is necessary to gain confidence 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, given the data that is available.

The RCT DUPLICATE initiative7 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.8 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**) project aims to extend this work to the field of oncology which comes with its own unique challenges that are not necessarily comparable with learnings from other disease areas and which must be systematically explored and understood.

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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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# 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)