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 2023[1], 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 discontinuity[2, 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 trials[4–6], 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 initiative[7] 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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References

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

2. Lin KJ, Singer DE, Glynn RJ, et al: Identifying patients with high data completeness to improve validity of comparative effectiveness research in electronic health records data. Clinical Pharmacology & Therapeutics 103:899–905, 2018

3. Joshua Lin K, Jin Y, Gagne J, et al: Longitudinal data discontinuity in electronic health records and consequences for medication effectiveness studies. Clinical Pharmacology & Therapeutics 111:243–251, 2022

4. Rider JR, Wasserman A, Slipski L, et al: Emulations of oncology trials using real-world data: A systematic literature review. American journal of epidemiology kwae346, 2024

5. Merola D, Campbell U, Gautam N, et al: The aetion coalition to advance real-world evidence through randomized controlled trial emulation initiative: oncology. Clinical Pharmacology & Therapeutics 113:1217–1222, 2023

6. Merola D, Campbell U, Lenis D, et al: Calibrating observational health record data against a randomized trial. JAMA Network Open 7:e2436535–e2436535, 2024

7. Wang SV, Schneeweiss S, Franklin JM, et al: Emulation of randomized clinical trials with nonrandomized database analyses: Results of 32 clinical trials. Jama 329:1376–1385, 2023

8. Heyard R, Held L, Schneeweiss S, et al: Design differences and variation in results between randomised trials and non-randomised emulations: Meta-analysis of RCT-DUPLICATE data [Internet]. BMJ medicine 3, 2024Available from: https://doi.org/10.1136/bmjmed-2023-000709

9. Weberpals J, Raman SR, Shaw PA, et al: A principled approach to characterize and analyze partially observed confounder data from electronic health records [Internet]. Clinical Epidemiology 16:329–343, 2024Available from:https://www.tandfonline.com/doi/abs/10.2147/CLEP.S436131

Table 1: Criteria .

Criteria	Definition
Interventional study	The nature of the investigation or investigational use for which clinical study information is
Randomized allocation	The method by which participants are assigned to arms in a clinical trial.
Interventional study model	The strategy for assigning interventions to participants.
Sponsor/source	The entity (for example, corporation or agency) that initiates the study
Study start date	The estimated date on which the clinical study will be open for recruitment of participants,
Primary purpose	The main objective of the intervention(s) being evaluated by the clinical trial.
Primary outcome	A description of each primary outcome measure (or for observational studies, specific key me
Overall Recruitment Status	The recruitment status for the clinical study as a whole, based upon the status of the indivi
Feasibility and clinical relevance	Are all key variables available to emulate the clinical trial at hand and is the clinical trial co

Tables

Table 2: Tentative list of randomized controlled trials (RCTs) considered for emulation.

NCTID	Acronym	Clinical setting
Non-small cell lung cancer		
NCT02296125	FLAURA	Advanced/metastatic EGFRm+
NCT01673867	CheckMate057	Metastatic non-squamous
NCT03215706	CheckMate9LA	Metastatic
Breast cancer		
NCT01740427	PALOMA-2	Advanced postmenopausal ER-positive and HER2-negative
NCT02819518	KEYNOTE-355	Locally recurrent inoperable or metastatic triple negative
NCT01772472	KATHERINE	HER2-positive
Colorectal cancer		
NCT04737187	SUNLIGHT	Refractory metastatic
NCT01374425	MAVERICC	Metastatic
NCT02563002	KEYNOTE-177	Metastatic microsatellite instability-high (MSI-H) or mismatch repa
Multiple Myeloma		
NCT01568866	ENDEAVOR	Relapsing or progressing disease
NCT02252172	MAIA	Newly diagnosed
NCT01239797	ELOQUENT - 2	Relapsed or refractory

Figures

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