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 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 discontinuity[3, 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 trials[5–7], 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 initiative[8] 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**) project[10] 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 DUPLICATE[8], 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 trial[11, 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

...[13]

Agreement metrics

Discussion

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Conclusions

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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