

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 directive¹, the Food and Drug Administration (FDA) established a framework to increasingly 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.² With 21% of all approvals, oncology was the disease area with the most FDA drug approvals in 2023,³ and especially in the field of precision oncology, RWE has a large potential to complement evidence coming from RCTs. Potential use cases 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 discovery of biomarkers among pan-tumor populations that harbor specific genomic and immuno-pathological signatures.

However, the validity and transportability of results derived between RWE studies and RCTs can depend on many factors and frequently referenced limitations include missing data, small sample sizes, data discontinuity^{4, 5}, rapid changes in guideline treatment patterns and the inability to measure and emulate common eligibility criteria and prognostic factors in real-world data (RWD).⁶ While there are already published examples of oncology trial emulations⁶⁻⁸, 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.

The RCT DUPLICATE initiative⁹ 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.¹⁰ 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**) project¹¹ aims to extend this work to the field of oncology which comes with its own unique set of challenges which must be systematically explored and understood. Building on a process co-developed with the FDA through RCT DUPLICATE⁹, 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^{12, 13} and the conduct of 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 these 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 RCTs and their respective emulations.

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 RCTs and emulations.

Methods

A visual summary of the entire systematic process from trial selection to final results is provided in Figure 1.

Trial selection

The focus of ENCORE is to maximize potential learnings on when RWE studies can or cannot yield similar results compared to RCTs. To that end, the emphasis of the project is on trials of therapies for the most common cancers and/or cancers for which there has been substantial therapeutic development in recent years. After careful review and exchange with clinical and regulatory experts, four cancer indications were identified including lung cancer, breast cancer, colorectal cancer and multiple myeloma. For each cancer we aim to conduct three trial emulations which will be implemented using multiple databases accessible for the scope of this project (i.e. the total number of emulations will equal 12 trials x n databases which are found fit-for-purpose for each trial).

The trial selection will follow a semi-automated process for which we will document the eligibility criteria resulting in a CONSORT diagram showing reasons for excluding RCTs. The search will be conducted using the AACT database which is a publicly available relational database developed and maintained by the Clinical Trials Transformation Initiative (CTTI) which contains all information (protocol and result data elements) about every study registered on ClinicalTrials.gov.¹⁴ To identify eligible trials, we will use a combined search query strategy of the National Library of Medicine (NLM)-controlled *MeSH* term and a free keyword search for the respective cancer indication in the *conditions*, *studies* and *detailed_descriptions* fields of each trial entry on ClinicalTrials.gov.

Eligible trials need to fulfill the following basic criteria:

- Interventional
- Randomized
- Intervention model: parallel assignment
- Industry-sponsored

- Trial start in 2011 or later
- Primary purpose was to study treatment effects
- Overall survival must be one of the endpoints reported
- Recruitment status: ‘Completed’ or ‘Active, not recruiting’
- Feasibility and clinical relevance

The rationale and operationalization of each criterion is listed in detail in Table 1. We will mainly consider pivotal interventional, randomized trials after 2011 since treatment guidelines among studied cancer indications have undergone significant changes in recent years. Due to the rapid adoption of new breakthrough therapies in routine care, it is unlikely to find patients who may be still treated with outdated treatment regimens in the real-world. In parallel, trial results should have also not been published too recently in order to allow for enough data and follow-up time accrual in databases used for this project. An further focus is on trials that have reported overall survival (OS) as one of the pre-specified endpoints in the protocol. Although there have been substantial methodological advancements to increase our understanding on the emulation and comparison of real-world progression-free survival (PFS) and objective response rates (ORR) to a RECISTv1.1¹⁵-based PFS and ORR assessment in RCTs^{16, 17}, imaging-based evaluations still hold a level of granularity which may not be necessarily reflected in chart-abstracted assessments of a patient’s progression in routine care.^{18, 19} Given the large number of other methodological challenges like missing data, small sample sizes, data discontinuity and rapidly changing guideline treatments, the scope of this project was to focus on the emulation of OS as the endpoint of interest.

While most trial-eligibility criteria can be operationalized in an automated fashion, the last criterion on emulation feasibility and clinical relevance involves extensive human review. The critical points considered in this step include a thorough feasibility assessment of the data fitness¹⁹, sample size considerations and the assessment if critical eligibility criteria (e.g., biomarker status) and prognostic factors (e.g., ECOG performance score) are measurable and can be balanced using propensity score matching or weighting methods.²⁰

A list of tentative, shortlisted candidates is presented in Table 2 and the corresponding selection process is illustrated in the CONSORT diagrams (Supplementary Figures 1-4). Naturally, the majority trials will cover advanced or metastatic cancer populations since a large proportion of drug development efforts have focused on these settings in recent years. A key learning that we aim to foster with the shortlisted trials is to achieve a better understanding how different disease settings (early, late), line settings ([neo]adjuvant, first line, advanced lines of therapy), therapy protocols (monotherapy, combination therapy) and population characteristics (simple versus complex genetic or immunological signatures) can be emulated using RWD. If ongoing feasibility assessments indicate that these trials cannot be emulated with high enough confidence, runner-up candidates will be considered instead.

Databases

The ENCORE project will utilize data from a total four different oncology-specific electronic health records (EHR)-derived data sources: ConcertAI, COTA, Flatiron Health, McKesson/Ontada. All available databases draw from a comprehensive national sample of patients with cancer in the US with detailed EHR-derived information on the information necessary to study medication effectiveness in oncology. For ENCORE, not all databases will be available for each cancer indication and the names of the databases will be blinded and referred to as ENCORE DataBase (EDB) 1, 2, 3 and 4 for the final reporting of results. If more than one database is considered fit-for-purpose for a respective trial emulation, the best possible analytic model will be employed for each database separately and final treatment effect estimates will be pooled using a meta-analytic approach.

Protocol development

For each shortlisted and selected RCT, a detailed protocol will be developed following the HARPER protocol template²¹ and registered on ClinicalTrials.gov. The protocol will pre-specify key elements of the trial emulation and following the target trial emulation framework, we will provide an explicit statement and rationale on how each element will be emulated including database selection, covariate measurement, operationalization of key eligibility criteria, study design, data analysis and causal contrasts of interest.^{22, 23} Since it is common that oncology RCTs update OS estimates periodically based on accrued follow-up time, the protocol will summarize each emulated RCT and specify which target OS estimates will be used to compare agreement metrics to. All eligibility criteria will be extracted based on publicly available protocols and statistical analysis plans of the selected RCT. Following the *Structured Process to Identify Fit-For-Purpose Data* (SPIFD) framework¹³, tables will outline how eligibility criteria will be measured and operationalized and a color-coded heatmap will indicate the level of confidence on how well each criterion can be emulated in each selected database. As there are general eligibility criteria in oncology trials which either won't be possible to emulate (e.g., physician-assessed survival prognosis of xy months) or that are clinically not relevant for the emulation of the trial (e.g., male patients should be willing to use barrier contraception), the study team will decide on key eligibility criteria for the emulation of the trial. We will additionally provide a definition on how exposure and outcomes are defined and ascertained in each respective database. For most considered databases, the OS endpoint is a composite that is derived from different sources including EHR flags, social security death index, obituary and other linkages. Given that not all relevant sources that provide mortality data are synchronized and updated uniformly, sensitivity analyses with more conservative censoring dates will be considered for each trial emulation to mitigate the impact of potential ghost-time bias.²⁴ Each final protocol draft will be reviewed by a clinical and FDA regulatory expert panel upon registration on ClinicalTrials.gov.

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 to select eligible trials for emulation in ENCORE.

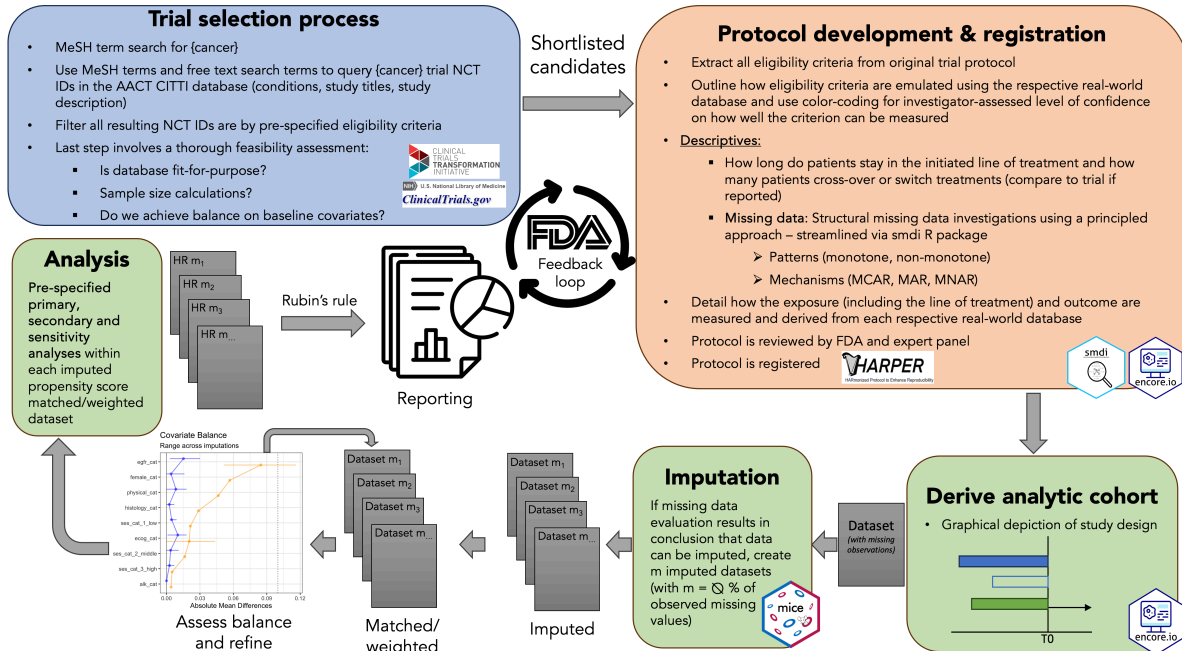
Criteria	Definition	Eligible
Interventional study	The nature of the investigation or investigational use for which clinical study information is being submitted	Interventional (clinical trial): Participants are assigned prospectively to an intervention or interventions according to a protocol to evaluate 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)

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	CheckMate017/057	Metastatic squamous/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

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



[View figure in higher resolution here](#)