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 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 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 cardiometabolic, 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

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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 individual
Feasibility and clinical relevance	Are all key variables available to emulate the clinical trial at hand and is the clinical trial co

Tables

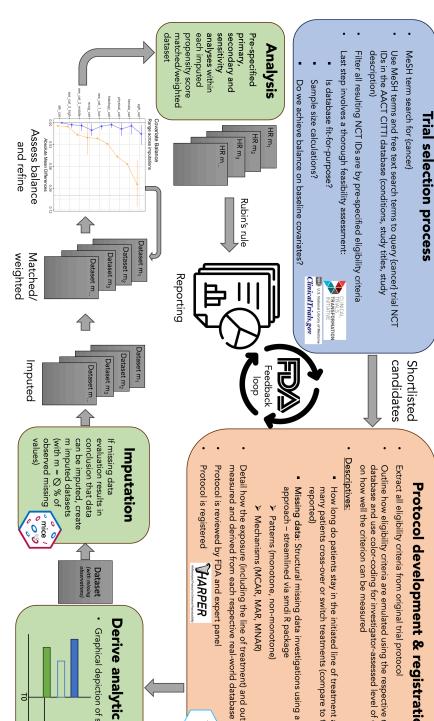
Table 2: Tentative list of randomized controlled trials (RCTs) considered for emulation.

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

Figures

View figure in higher resolution

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



Protocol development & registration

- Extract all eligibility criteria from original trial protocol
- Outline how eligibility criteria are emulated using the respective database and use color-coding for investigator-assessed level of on how well the criterion can be measured
- How long do patients stay in the initiated line of treatment many patients cross-over or switch treatments (compare to reported)
- Missing data: Structural missing data investigations using a approach streamlined via smdi R package
- Detail how the exposure (including the line of treatment) and out measured and derived from each respective real-world database
- Protocol is reviewed by FDA and expert panel