

TrialMap: A Principled End-to-End Framework for Guiding and Optimizing Trial Eligibility Criteria Pathways Using Real-World Data

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Background

Clinical trials are designed to generate evidence that informs real-world practice, and eligibility criteria determine the populations in which treatment effects are evaluated under ideal conditions. Although restrictive criteria may improve internal consistency and regulatory confidence, they can limit trial representativeness, reduce recruitment feasibility, and weaken the generalizability of findings to the intended patient population.^{1,2} Conversely, broadly inclusive trials may better reflect real-world practice but can introduce greater clinical heterogeneity and potentially obscure treatment response.

In oncology, many eligibility criteria have historically been shaped by convention and repeated through protocol templates rather than systematically evaluated. Common exclusions, such as brain metastases, have important implications for who is studied, what effects are observed, and how trial results translate to routine care. Between 2020 and 2024, the US Food and Drug Administration issued guidance encouraging modernization and expansion of eligibility criteria in oncology trials.^{3–6} Despite this regulatory shift, eligibility design remains largely qualitative, with limited tools for comparing alternative specifications.

The growing availability of real-world data from electronic health records, registries, and claims, together with advances in artificial intelligence, creates new opportunities for evidence-informed trial design. Prior studies have quantified representativeness gaps or evaluated selected relaxations of individual criteria,^{7–9} but eligibility design requires balancing multiple competing objectives, including treatment benefit, safety, eligible population size, and representativeness. Evaluating many alternative designs also raises concerns about multiplicity and bias in observational data.

To address these challenges, we developed *TrialMap*, an AI- and real-world data-driven framework for systematically evaluating and optimizing clinical trial eligibility criteria using post-market evidence. We demonstrate its application using a nationwide oncology electronic health record database across multiple landmark trials.

Methods

We developed TrialMap as a reproducible framework and interactive software platform to support evidence-informed clinical trial eligibility design. It takes as inputs trial protocols, real-world oncology data, treatment comparisons, and outcomes of interest. Trial eligibility criteria are converted into machine-readable rules and applied to real-world data to construct trial-eligible populations under alternative eligibility specifications. TrialMap then estimates and compares the implications of these eligibility choices for treatment efficacy, feasibility, safety, validity, generalizability, and statistical efficiency.

This study used the US-based nationwide Flatiron Health electronic health record-derived de-identified database from 2011 to 2024, which includes structured and unstructured oncology data from approximately 280 US cancer clinics. We focused on advanced non-small cell lung cancer, advanced melanoma, metastatic renal cell carcinoma, and advanced head and neck squamous cell carcinoma.

We selected 10 landmark phase III randomized trials of first-line immune checkpoint inhibitor or targeted therapies with publicly available protocols, sufficient representation in the Flatiron Health database, and eligibility criteria that could be meaningfully evaluated using routine clinical data. These trials were FLAURA, KEYNOTE-189, KEYNOTE-407, CheckMate 067, KEYNOTE-006, COMBI-v, CheckMate 214, KEYNOTE-426, CheckMate 9ER, and KEYNOTE-048.

TrialMap includes two core functions. The adapting module evaluates the impact of individual eligibility criteria by estimating how enforcing or relaxing each criterion changes the eligible population and treatment effect estimates. The optimization module evaluates alternative eligibility pathways as a multi-objective decision problem, identifies non-dominated pathways across efficacy, feasibility, and safety, and uses an uncertainty-aware stability score to prioritize robust options. The software outputs interactive visualizations of cohort composition, eligibility trade-offs, and ranked eligibility pathways to support transparent, repeatable, and human-in-the-loop trial design. TrialMap is available at <https://clinicalnlp.org/TrialMap/>.

Results

Eligibility criteria restricted trial-accessible populations

Across the 10 landmark oncology trials, applying the original protocol-defined eligibility criteria substantially reduced the proportion of real-world patients who would have qualified for trial enrollment. Among patients receiving the corresponding trial regimens in the specified line of therapy, an average of 62% met all eligibility requirements, with some trials retaining as few as 41% of patients. Exclusions were concentrated in a small number of modifiable criteria. Performance status requirements excluded approximately 14% of real-world patients on average, while central nervous system metastasis exclusions affected an additional 6%. Other modifiable criteria generally excluded smaller proportions when considered individually, suggesting that relaxing selected high-impact criteria could meaningfully expand trial-accessible populations.

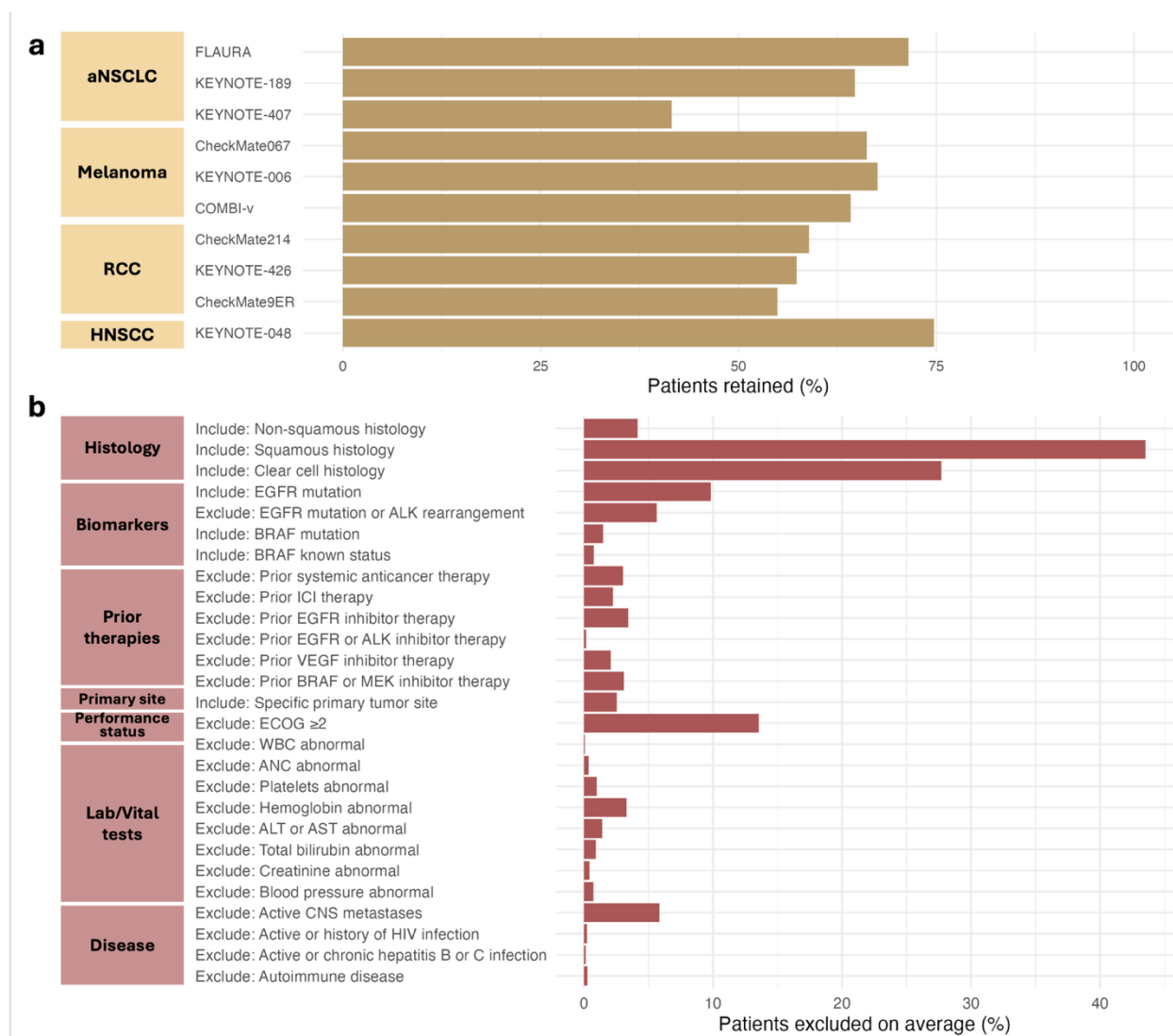


Figure 1. Restriction of trial-accessible real-world populations by eligibility criteria. a, Proportion of real-world patients retained after applying all protocol-defined eligibility criteria for each evaluated landmark trial, stratified by cancer type. b, Average proportion of patients excluded when each eligibility criterion is applied individually across trials.

Marginal impact of individual eligibility rules on treatment effects

Leave-one-criterion-out analyses showed that relaxing individual eligibility rules usually produced modest changes in estimated overall survival hazard ratios. For eligibility domains emphasized in recent FDA guidance, including performance status, organ function, brain metastases, HIV infection, and viral hepatitis, estimated treatment effects after relaxation remained directionally consistent and of similar magnitude to those under the original criteria. However, effects varied by disease and treatment context. Increasing inclusion of ECOG 2 patients attenuated estimated treatment benefit in melanoma immunotherapy trials, whereas estimates were more stable in several aNSCLC immunotherapy trials. Similarly, relaxation of central nervous system metastasis exclusions generally produced stable estimates, except in the melanoma targeted therapy trial COMBI-v, where greater inclusion of patients with active central nervous system metastases was associated with attenuation of treatment benefit.

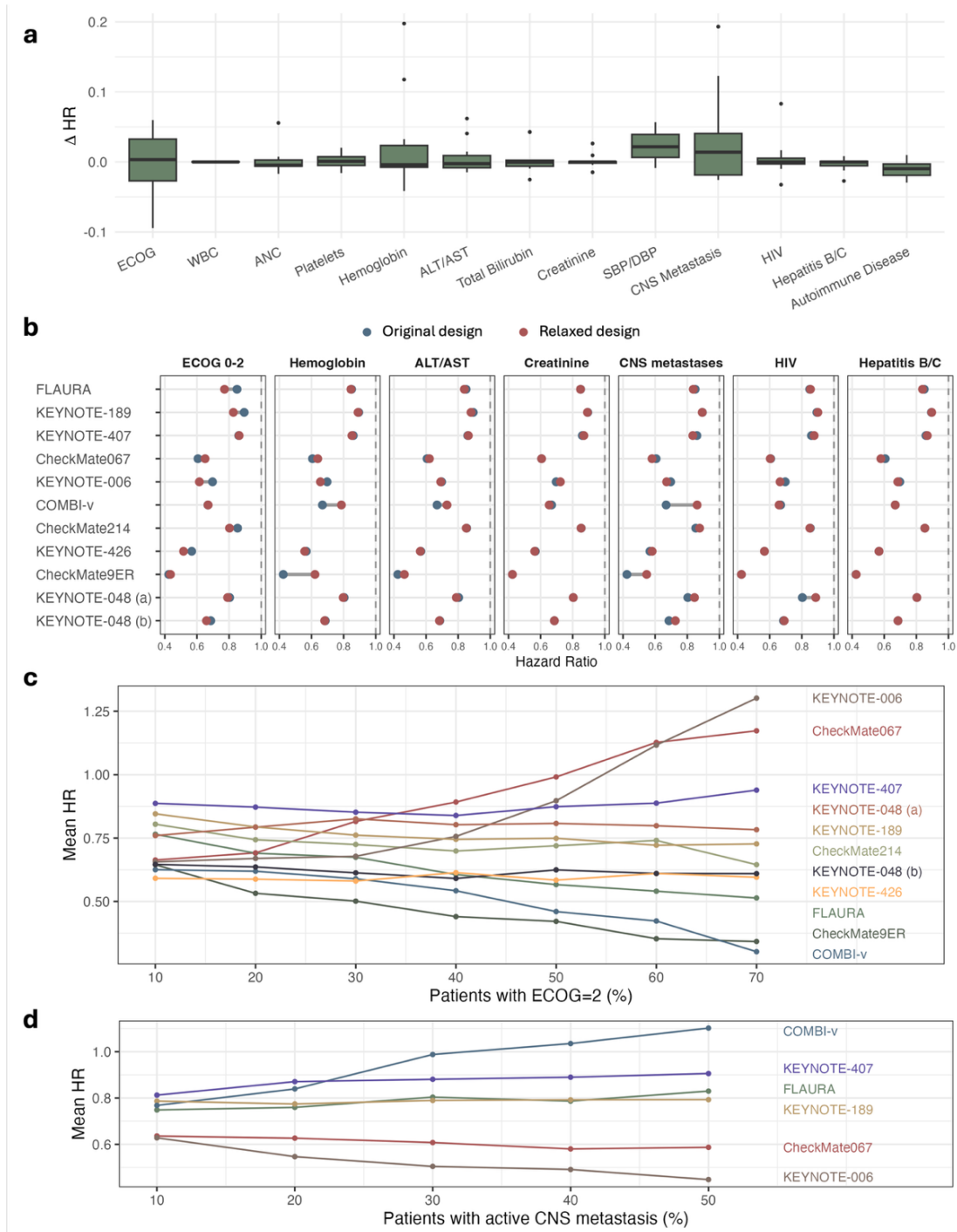


Figure 2. Marginal impact of individual eligibility rule relaxation on estimated treatment effects. a, Distribution of changes in estimated hazard ratios (Δ HR) across trials when each modifiable eligibility criterion is relaxed individually relative to the original protocol design, with all other criteria held fixed. Each box summarizes trial-specific Δ HR values for a given criterion. b, Trial-specific comparison of estimated hazard ratios before and after targeted relaxation of performance status to include patients with ECOG 2 (while continuing to exclude ECOG 3-4). Points represent individual trials. c, Within-trial simulation results showing estimated hazard ratios as the proportion of included ECOG 2 patients increases. Lines correspond to individual trials. d, Within-trial simulation results showing estimated hazard ratios as the proportion of included patients with CNS metastasis increases. Lines correspond to individual trials.

TrialMap identified explicit trade-offs across trial design objectives

In the KEYNOTE-189 example, TrialMap evaluated candidate eligibility pathways across efficacy, feasibility, and safety and identified non-dominated designs along the Pareto frontier. The original protocol-defined eligibility design was not located on the frontier, indicating that alternative eligibility specifications achieved more favorable trade-offs among treatment effect, eligible population size, and adverse event burden. Selected TrialMap pathways represented distinct design priorities: one prioritized treatment effect, population size, and generalizability, while others provided more balanced profiles across efficacy, feasibility, safety, validity, generalizability, and statistical efficiency. Rather than producing a single optimal specification, TrialMap returned a small set of interpretable, evidence-supported eligibility pathways that allow stakeholders to select designs aligned with trial-specific priorities.

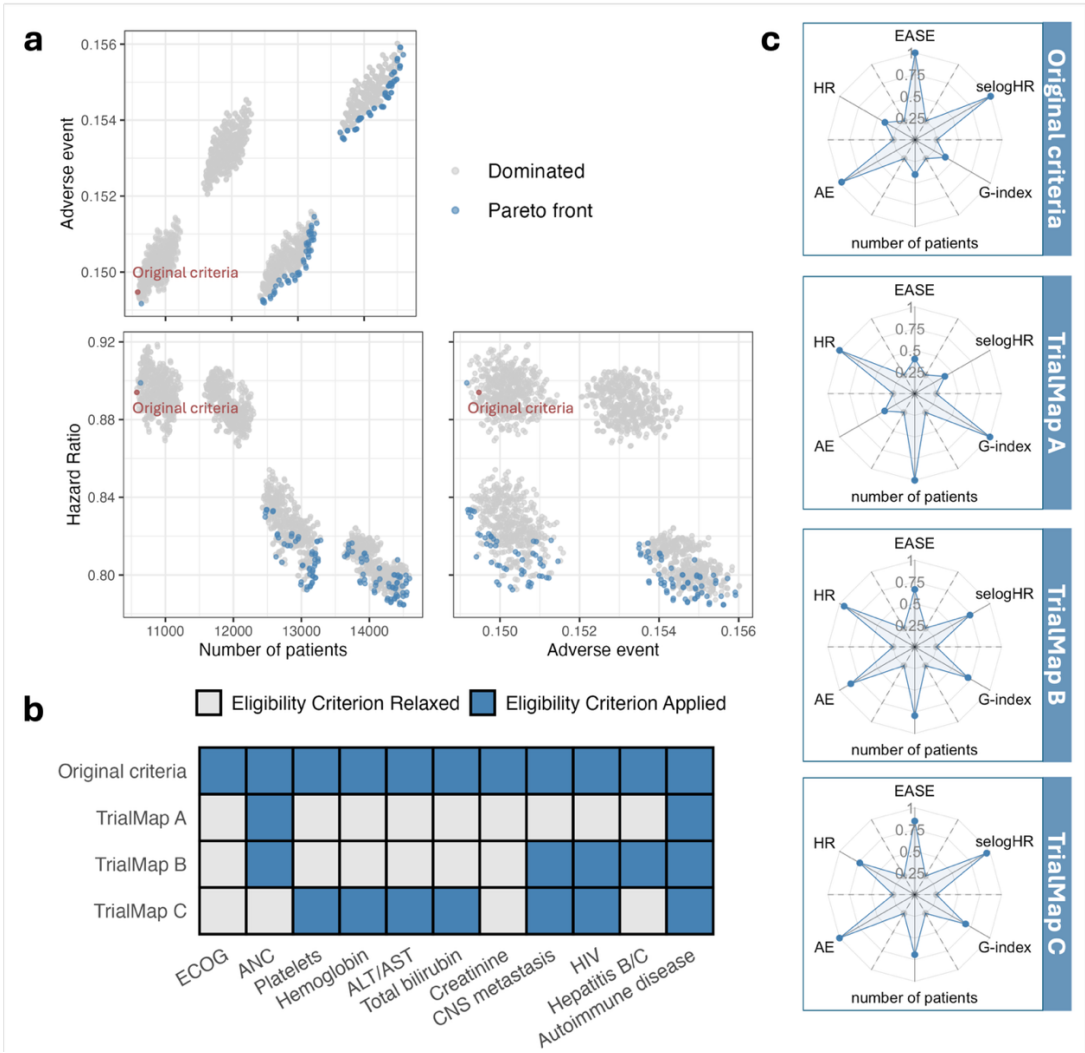


Figure 3. Multi-objective trade-offs illustrated using the KEYNOTE-189 trial. a, Two-dimensional projections of the Pareto frontier of candidate eligibility pathways. Non-dominated pathways (blue) achieve optimal trade-offs across efficacy, safety, and feasibility. b, Criterion-level composition of selected pathways, indicating which eligibility criteria are applied (blue) or relaxed (grey) relative to the original trial specification. c, Origami plots. Each summarizes six metrics: overall-survival hazard ratio (HR), standard error of logHR, number of patients, adverse events (AE), expected absolute systematic error (EASE), and G-index, for four design scenarios: the original trial criteria and three TrialMap-selected pathways (A-C). Larger polygon areas indicate more favorable trade-offs across objectives.

Conclusion

TrialMap demonstrates how real-world oncology data can be systematically repurposed to support more transparent, reproducible, and evidence-informed clinical trial eligibility design. Across landmark oncology trials, protocol-defined eligibility criteria excluded substantial proportions of real-world patients, while selected relaxations of individual criteria often expanded the trial-accessible population without materially changing estimated treatment effects. By evaluating eligibility specifications across efficacy, feasibility, safety, validity, generalizability, and statistical efficiency, TrialMap reframes eligibility design as a multi-objective decision problem rather than a set of convention-driven rules.

For the OHDSI community, this work highlights an important opportunity: large-scale observational data networks can inform not only post-market safety and effectiveness studies, but also the prospective design of more inclusive and generalizable clinical trials. TrialMap provides a repeatable framework for translating real-world evidence into actionable trial design options, making trade-offs explicit while preserving stakeholder judgment. More broadly, this approach supports a shift toward learning health systems in which routine clinical data, causal inference, and interactive software tools are used together to improve the design, conduct, and relevance of future trials. Future work will extend validation across additional trial protocols, therapeutic areas, and OMOP data sources.

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