MSR227

Optimizing Baseline Characteristics in Clinical Trials: Leveraging Machine Learning for Enhanced Trial Design and Cohort Selection

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INTRODUCTION

- The demonstration of a clinical benefit over the control group is a crucial requirement for the approval of new drugs worldwide.[1] This comparative efficacy is the cornerstone of regulatory decisions and is mandated by current drug approval regulations.
- However, for Health Technology Assessment (HTA) bodies and payers, proving efficacy against just a key comparator within the trial is not enough. They demand evidence that demonstrates comparative efficacy across all available treatments.
- This broader assessment is often achieved through indirect treatment comparisons (ITCs) or network meta-analyses (NMAs), which enable a comprehensive evaluation of the new intervention relative to multiple existing therapies, thus providing a holistic view of the new drug's place within the therapeutic landscape.[2]
- In clinical trials, heterogeneity in baseline characteristics (BACs) across study populations often presents significant challenges, particularly in the context of Indirect treatment comparison (ITC). Such variability can impact the comparability of results across trials and complicate the synthesis of treatment effects.
- Variations in trial settings, inclusion/exclusion criteria, and outcome measures can lead to non-comparable trial populations, resulting in inconsistent estimates of treatment effects. This variability complicates the interpretation of comparative efficacy and may obscure the true benefit of the new intervention or the control group. Such inconsistencies can not only impact regulatory decisions but also delay broader clinical adoption and payer acceptance. [3,4]
- Therefore, ensuring comparability and optimizing clinical trial designs—especially at the early stages, such as in the selection of study populations—has become critical for generating evidence that aligns with regulatory and payer expectations. In therapeutic areas like non-small cell lung cancer or breast cancer, where multiple treatment options are available, pivotal trials often exhibit significant heterogeneity in BACs.
- While it may be feasible to anchor new drug development to one or two pivotal trials, this approach becomes increasingly difficult when several pivotal trials with varying comparators are involved.
- The resulting variability in BACs across these trials can pose challenges to maintaining comparability. This inconsistency may lead to potential incompatibility issues between treatments, especially when some BACs serve as key prognostic factors that influence outcomes.
- By focusing on trial design and ensuring more consistent BACs across studies, drug developers can better navigate the complexities of comparative efficacy and meet the high standards set by regulatory agencies and HTA bodies. This strategy not only strengthens the case for a drug's approval but also facilitates its integration into clinical practice.

OBJECTIVES

- We propose a machine-learning (ML) based approach to arrive at optimized (less entropy) marginal distributions for chosen BACs during early-stage trial planning, aiding in cohort selection and accurate subgroup analyses, improving sample specificity and recruitment for future trials.
- The existing heterogeneity of BAC across trials can provide an early assessment of their distribution across different studies. While this doesn't directly impact trial recruitment, knowing marginal distributions for the relevant BAC can still contribute to optimizing recruitment strategies.

METHODS

Data preparation:

- A simulated dataset with 40 studies was generated incorporating six baseline characteristics of lung cancer patients which included: average age, proportion of patients with no smoking history, proportion of male patients, proportion of caucasian patients, proportion of patients with PD-L1 positive expression, and proportion of patients with an ECOG score of 1. Appropriate statistical distributions were applied to model each baseline and trial characteristic, ensuring realistic representation of the study data.

Clustering analysis:

- Following that, a clustering algorithm utilizing the Hartigan and Wong (1979) algorithm was applied and adjusted for the available trial and baseline characteristics.[5]
- This method aims to estimate optimized (lower entropy) marginal distributions of the BACs, represented as a centroid, by minimizing the heterogeneity of BACs across all other trials relative to that centroid.
- This approach aimed to generate clusters of comparable studies, leveraging both baseline and trial characteristics. Within each cluster, the studies are similar based on baseline characteristics.

Relative importance analysis:

- Relative importance analysis was performed to identify pivotal features influencing between-cluster variability and to discern key features responsible for allocating studies to distinct clusters, thereby generating between-cluster variability.

RESULT

- Effectively managing heterogeneity in BAC significantly enhances clinical trial design, resulting in improved cohort selection, tailored randomization and subgroup analyses, optimized recruitment strategies, reduced bias, and support for adaptive trial designs.(Figure 1)
- The clustering analysis revealed the optimized distribution of baseline characteristics associated with the cluster centroid: 48% of patients were PD-L1 positive, 52% had an ECOG score of 1, 76% were male, 80% were white, and 35% had a smoking history. Mathematically, if a future trial aligns with this distribution of baseline characteristics, the heterogeneity between the new trial and previous trials will be minimized. (Figure 2)
- The RIA revealed that PD-L1 positive (50%) and white patients (20%) are the top BACs contributing to heterogeneity within the cluster. (Figure 3)

CONCLUSIONS

The selection of trials for analysis should be guided by the appropriate decision-making framework. Instead of including all available trials in the baseline characteristic analysis, it's more effective to focus on primary trials of the key comparators. When several pivotal trials with different comparators are involved, this method offers a powerful way to optimize recruitment strategies. ML can be a valuable tool in guiding clinical trial design by identifying critical baseline characteristics that ensure homogeneity and comparability across studies. This approach contributes to more effective and precise evidence-based medical decision-making.

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***Figure 1**: Impact of analysis on future trial design*

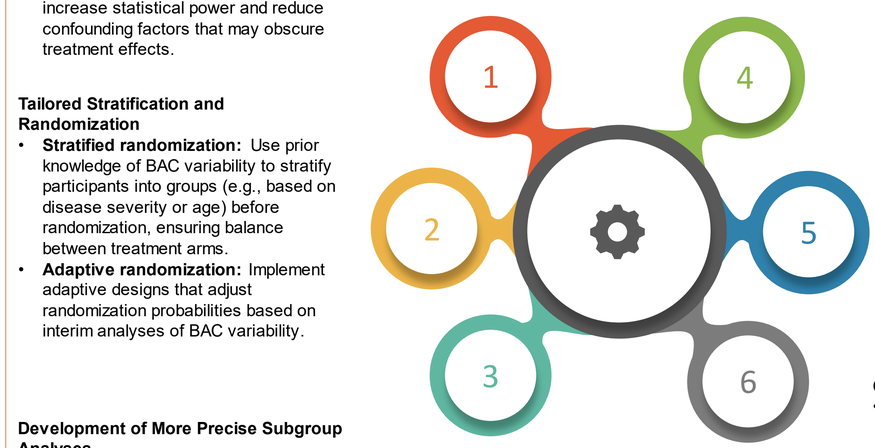


Figure 2: *Cluster plot demonstrating* optimized marginal distributions *of the baseline characteristics*

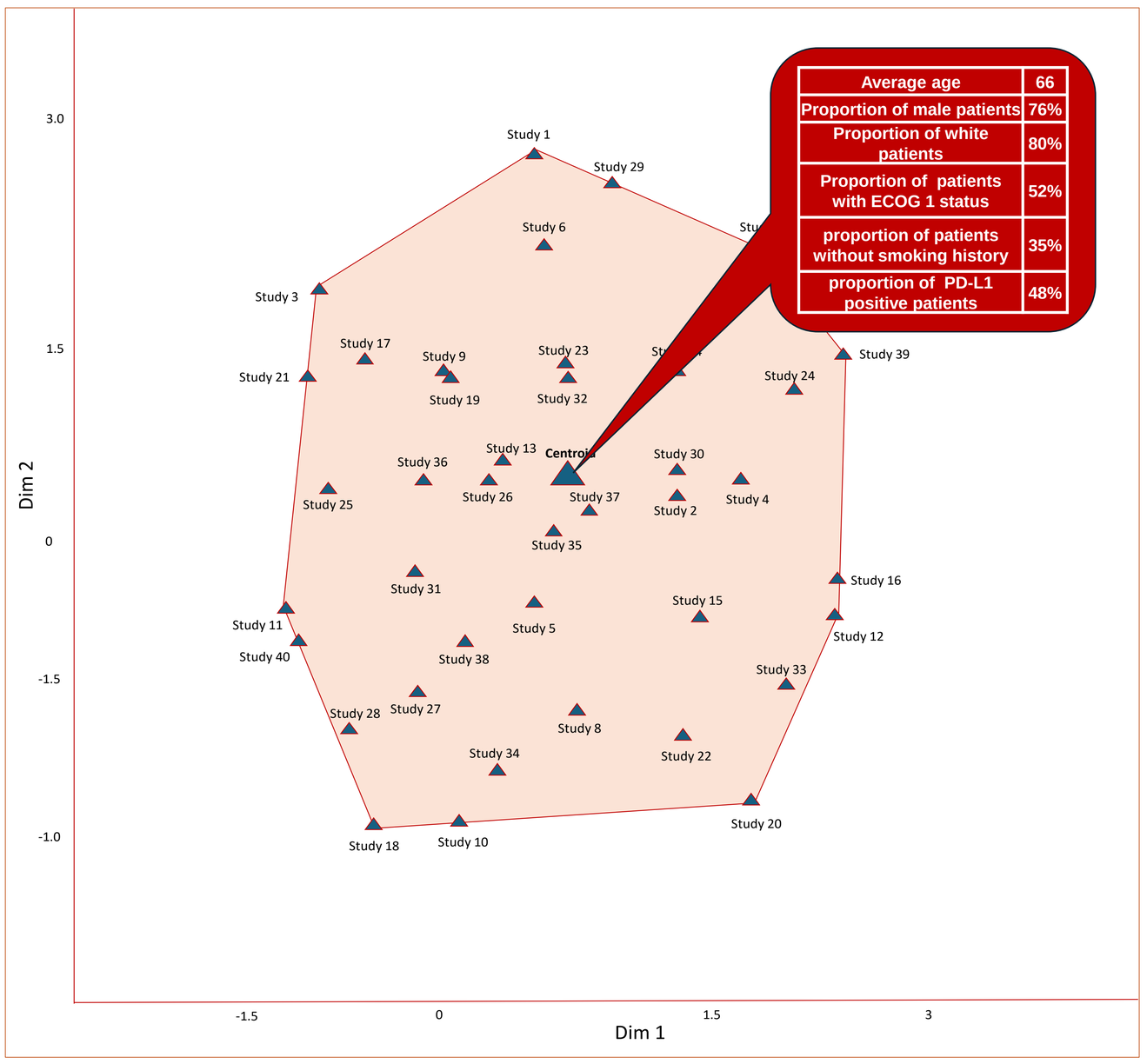
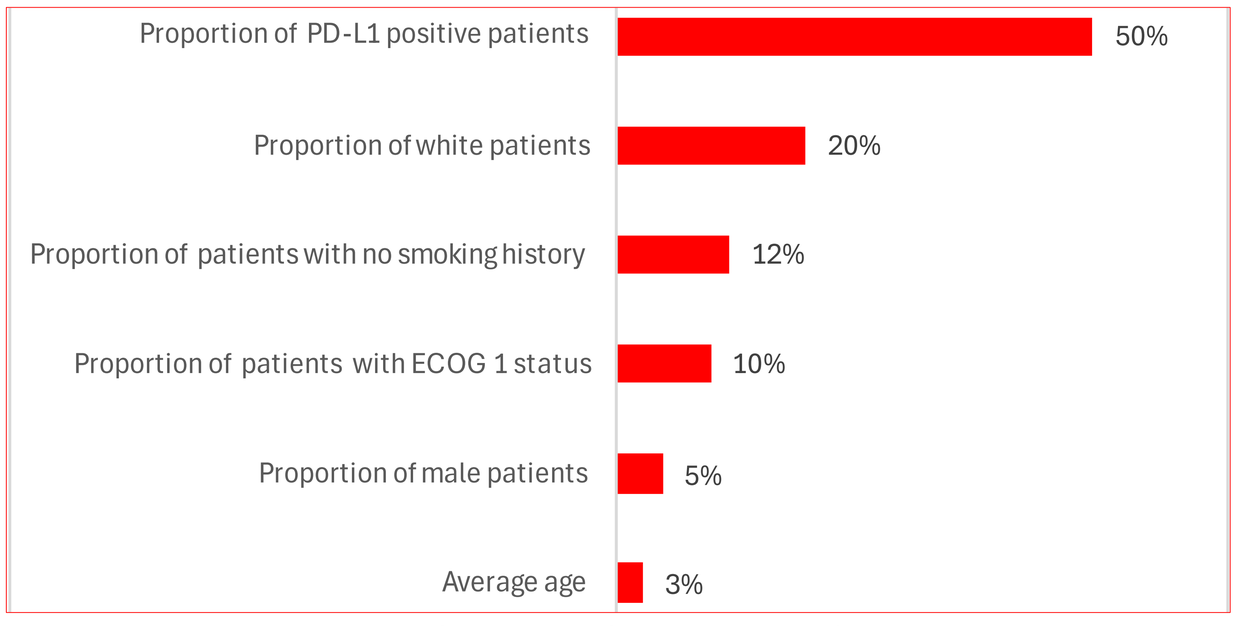


Figure 3: *Relative importance of trial and baseline characteristics*



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