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The AI-Guided Clinical Trial Architect: A Genetic Algorithm and MCDM Platform for Adaptive, Multi-Objective Patient Cohort Selection and Trial Simulation

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Abstract

Introduction: Clinical trial design faces a critical challenge in balancing multiple, often conflicting, objectives such as statistical power, patient safety, cohort diversity, recruitment speed, and cost. While Multi-Objective Genetic Algorithms (MOGA) and Multi-Criteria Decision-Making (MCDM) have been applied independently in pharmaceutical contexts, their synergistic potential for clinical trial architecture remains under-explored. This paper introduces the AI-Guided Clinical Trial Architect (AI-CTA), a novel computational platform that integrates a MOGA with a fuzzy MCDM framework for adaptive, multi-objective patient cohort selection and trial simulation. **Methods:** The methodology involves a multi-phase workflow: data encoding via entropy-based weighting, evolutionary exploration of cohort configurations using a fuzzy-enhanced NSGA-II, and final selection through a Fuzzy TOPSIS analysis that incorporates expert-derived linguistic weights to handle uncertainty. **Results & Discussion:** A comprehensive case study for an oncology trial (n=200 from 1,850 candidates) demonstrates the platform's efficacy. The MOGA successfully generated a Pareto-optimal set of cohorts, from which the FMCDM module identified an optimal cohort achieving a superior balance of objectives (Closeness Coefficient: 0.656), validating the platform's ability to derive non-intuitive, robust solutions. **Conclusion:** By unifying the explorative power of MOGA with the deliberative precision of FMCDM, the AI-CTA provides a transformative, transparent, and computationally robust environment for designing more efficient, equitable, and economically viable clinical trials.

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Introduction

The landscape of clinical research stands at a pivotal juncture, pressured by escalating costs, high failure rates, and the pressing demand for more efficient, personalized, and ethically robust therapeutic development. Traditional clinical trial methodologies, often characterized by rigid protocols and homogeneous patient populations, are increasingly recognized as suboptimal for addressing the complex, multi-faceted nature of modern medicine. In response, the integration of advanced computational intelligence paradigms, particularly Artificial Intelligence (AI), is heralding a new era of innovation. This article posits that the synergistic fusion of two powerful computational families Multi-Objective Genetic Algorithms (MOGA) and Multi-Criteria Decision-Making (MCDM)can form the core of a transformative platform for clinical trial design. We introduce the *"AI-Guided Clinical Trial Architect a novel platform engineered for adaptive, multi-objective patient cohort selection and trial simulation, designed to navigate the intricate trade-offs inherent in clinical research.

The philosophical and methodological foundation for such an endeavor is firmly established in the growing body of literature applying MCDM to healthcare and pharmaceutical challenges. Seminal reviews, such as those by Lagana & Colapinto (2022), have meticulously cataloged the application of MCDM in healthcare and pharmaceutical supply chains, highlighting its capacity to manage conflicting criteria. This is complemented by the work of Kolasa, Zah, & Kowalczyk (2018), who systematically demonstrated how MCDM can support the value assessment of pharmaceuticals, providing a critical link between clinical efficacy and health economic considerations. The utility of MCDM as a tangible decision-support tool within institutional settings has been empirically validated; for instance, Roldán et al. (2018) successfully piloted its use in a Pharmacy and Therapeutics Committee, proving its feasibility for drug evaluation. The scope of MCDM is vast, ranging from high-level policy support, as in Schuwirth, Reichert, & Lienert's (2012) study on pharmaceutical removal from wastewater, to direct clinical and operational decisions, underscored by Marsh et al. (2014) in their review of healthcare intervention valuation.

The specific challenge of supplier selection within the pharmaceutical supply chain, a problem analogous to selecting optimal trial sites or partners, has been effectively tackled using fuzzy MCDM approaches. Modibbo et al. (2022) utilized fuzzy TOPSIS for pharmaceutical supplier selection, while Mohamed et al. (2023) adapted a MOGA specifically for healthcare supplier selection, directly bridging MCDM with evolutionary computation. Extending this logic to internal supply chain performance, Khan et al. (2023) employed a hybrid MCDM approach to evaluate the interrelationships of performance factors, a methodology that can be adapted to model the complex dependencies within a clinical trial ecosystem. Furthermore, the management of critical drug shortages in developing countries, as addressed by Moosivand et al. (2021) using an MCDM approach, underscores the real-world impact of these methods on public health and drug accessibility.

The evolution of MCDM is being rapidly accelerated by integration with sophisticated AI and machine learning techniques, enhancing its capability to handle uncertainty and large datasets. Early work by Prasad & Kolla (2014) demonstrated the use of AI-based classification for multi-criteria ABC analysis in a pharmaceutical company. This trajectory has advanced towards more complex frameworks. Ashaduzzaman et al. (2024) proposed a Dual Hesitant Fuzzy Group Decision Making approach for implementing AI/ML in the pharmaceutical sector, highlighting the need for advanced fuzzy sets to capture expert hesitation. Similarly, Aljohani (2025) developed a fuzzy MCDM framework for AI-driven, personalized elderly care, showcasing the direct application to personalized treatment recommendations. The management of interval-based fuzzy uncertainty has been further refined by Jokar et al. (2025), who integrated random forest regression with hybrid MCDM, pointing towards a future of data-driven uncertainty quantification. The most ambitious

integrations are seen in the works of Alsaedi et al. (2024) and Naser et al. (2024), who proposed frameworks combining MCDM with Deep Reinforcement Learning and AI for operational excellence in Iraqi industries, respectively. These works establish a precedent for creating hybrid intelligent systems capable of learning and adapting. A critical perspective on these advancements is provided by Alsaig et al. (2023), whose review of MCDM for big data healthcare applications offers necessary cautions and directions for robust implementation.

Parallel to the advancements in MCDM, Genetic Algorithms (GAs) and their multi-objective variants have proven their mettle in optimizing complex, non-linear systems within the pharmaceutical and healthcare domains. The foundational power of GAs is evidenced by their application to diverse problems, from the classical p-median problem solved with a fuzzy GA by Hassan (2015) to the financial optimization of network pharmacies by Oliinyk et al. (2019). In operational logistics, El Midaoui et al. (2021) utilized GAs for drug logistics chain optimization and scheduling in a Moroccan hospital context, while Chen (2024) focused on optimizing pharmaceutical laboratory course scheduling. The work of Mohammed & Alwan (2024) on improving probabilistic inventory models with GA in a pharmacy department further cements the role of GAs in resource optimization. At a more strategic level, Dao (2025) explored multi-objective genetic algorithms for complex system design, a core inspiration for our multi-objective approach to cohort selection. Even earlier, Mei (2014) demonstrated the efficacy of multi-objective GAs for optimizing fill time and makespan in a central fill pharmacy, directly addressing multi-criteria operational trade-offs. The work of Nowicka (2023) on the multi-criteria optimization of cell classifier circuits in cancer therapy is particularly relevant, as it demonstrates the application of these techniques to a high-precision biomedical engineering task. The algorithmic core itself has been subject to continuous improvement, as seen in the development of fuzzy crossover operators by Jalali Varnamkhasti et al. (2012) and the broader theoretical contributions of Varnamkhasti (2011; 2012) on adaptive neuro-fuzzy inference systems and evolutionary mechanisms.

The confluence of MCDM and GA is not merely theoretical. Bachorz et al. (2025) explicitly highlight the role of Multi-Criteria Decision Analysis in modern drug discovery, a process that is inherently multi-objective. The vision of an AI-supported medical decision-making system, as proposed by Lebedev et al. (2020) using evidence-based medicine and AI, aligns perfectly with the goals of our platform. Foundational work by Sadabadi et al. (2021) on linear programming for fuzzy MCDM problems and the pioneering data mining of pharmacy databases using evolutionary GAs by Ykhlef & ElGibreen (2010) provide the historical and methodological bedrock upon which contemporary research is built.

Despite this rich tapestry of research, a significant gap persists. While MCDM excels at evaluating pre-defined, static options, and GAs excel at searching vast solution spaces for Pareto-optimal frontiers, their integration into a unified, dynamic, and adaptive platform for *clinical trial architecture* remains nascent. Existing applications are often siloed, addressing supplier selection, lab scheduling, or drug evaluation in isolation. There is a lack of a holistic system that leverages the explorative power of MOGA to generate a vast population of potential patient cohort configurations and trial designs, and then employs the discriminative power of advanced, fuzzy-based MCDM to evaluate, rank, and select among these configurations based on a comprehensive set of clinical, ethical, and operational criteria.

This article bridges this gap by introducing the "AI-Guided Clinical Trial Architect." This platform leverages a Multi-Objective Genetic Algorithm to simulate and evolve thousands of potential patient cohorts and trial pathways, optimizing for conflicting objectives such as statistical power, patient safety, recruitment speed, diversity, and cost. Subsequently, a sophisticated MCDM module, informed by the latest advancements in fuzzy set theory and hybrid decision-making (e.g., Jokar et al., 2025; Ashaduzzaman et al., 2024), enables trial architects to interactively evaluate and navigate the

resulting Pareto-optimal solutions. By synthesizing the strengths of MOGA for discovery and MCDM for deliberation, the proposed platform offers a robust, transparent, and adaptive environment for designing more efficient, equitable, and successful clinical trials, ultimately accelerating the delivery of novel therapies to patients in need.

Beyond its algorithmic novelty, the AI-CTA is designed to directly address pressing operational and regulatory challenges in modern trial design. The platform aligns with key principles of ICH-GCP (International Council for Harmonisation - Good Clinical Practice), particularly regarding the justification of patient population selection (ICH E8(R1)) and the ethical imperative of diversity and inclusion (ICH E17). By providing a transparent, multi-criteria rationale for cohort selection, the AI-CTA generates an auditable decision trail that can support discussions with regulatory bodies (e.g., FDA, EMA) regarding trial design validity. Furthermore, it offers a practical tool for pharmacists, clinical pharmacologists, and trial sponsors to interactively model 'what-if' scenarios during protocol development, balancing scientific rigor with feasibility constraints before finalizing the trial architecture.

Materials and methods

The methodological framework integrates Multi-Objective Genetic Algorithms (MOGA) and Fuzzy Multi-Criteria Decision Making (FMCDM) into a single adaptive system called the AI-Guided Clinical Trial Architect (AI-CTA). The workflow progresses through four computational layers:

1. Data Initialization and Feature Encoding
2. Evolutionary Simulation via MOGA
3. Fuzzy MCDM-Based Evaluation and Selection
4. Adaptive Feedback and Convergence Validation

Each layer communicates dynamically with a shared Trial Design Knowledge Graph (TDKG) that encodes patient attributes, trial constraints, ethical considerations, and pharmacoeconomic objectives.

Data Initialization and Feature Encoding

Clinical, demographic, and pharmacological attributes are transformed into a normalized decision matrix:

$$\boldsymbol{X} = [\boldsymbol{x_{ij}}]_{\boldsymbol{m\times n}}$$

where
$\boldsymbol{m}$= number of candidate patient profiles, $\boldsymbol{n}$= number of clinical criteria (e.g., age, biomarker, comorbidity, cost, safety index).

Normalization (vector or min–max) ensures commensurability:

$$\boldsymbol{r_{ij}} = \begin{cases} \dfrac{\boldsymbol{x_{ij}} - \boldsymbol{min}\,(\boldsymbol{x_j})}{\boldsymbol{max}\,(\boldsymbol{x_j}) - \boldsymbol{min}\,(\boldsymbol{x_j})} & \text{if higher is better} \\ \dfrac{\boldsymbol{max}\,(\boldsymbol{x_j}) - \boldsymbol{x_{ij}}}{\boldsymbol{max}\,(\boldsymbol{x_j}) - \boldsymbol{min}\,(\boldsymbol{x_j})}, & \text{if lower is better} \end{cases} \quad (1)$$

where $\boldsymbol{x_{ij}}$ is the raw value of criterion *j* (e.g., age) for patient *i*, min($\boldsymbol{x_j}$) and max($\boldsymbol{x_j}$) are the minimum and maximum values of that criterion across all patients, and $\boldsymbol{r_{ij}}$ is the normalized value (between 0 and 1). The formula choice depends on whether a higher value for the criterion is desirable (e.g., safety score) or undesirable (e.g., cost).

Weights $\boldsymbol{w_j}$for each criterion are determined through an entropy-based adaptive weighting:

$$\begin{aligned} \boldsymbol{w_j} &= \frac{\boldsymbol{1 - H_j}}{\sum_{\boldsymbol{j=1}}^{\boldsymbol{n}} (\boldsymbol{1 - H_j})}, \boldsymbol{H_j} \\ &= -\boldsymbol{k} \sum_{\boldsymbol{i=1}}^{\boldsymbol{m}} \boldsymbol{p_{ij}} \boldsymbol{ln}\,(\boldsymbol{p_{ij}}), \boldsymbol{p_{ij}} \\ &= \frac{\boldsymbol{r_{ij}}}{\sum_{\boldsymbol{i}} \boldsymbol{r_{ij}}} \end{aligned} \quad (2)$$

where $\boldsymbol{k} = \boldsymbol{1/ln}\,(\boldsymbol{m})$.

Evolutionary Layer: Multi-Objective Genetic Algorithm (MOGA)

Chromosome Representation

Each chromosome encodes a potential trial configuration $\boldsymbol{C_i}$:

$$\boldsymbol{C_i} = [\boldsymbol{p_1}, \boldsymbol{p_2}, \ldots, \boldsymbol{p_k}]$$

where $\boldsymbol{p_k}$are patient subsets or parameterized inclusion criteria.

Objective Functions

The MOGA simultaneously optimizes multiple clinical and operational objectives:

Maximize: $f_1(C_i) = \text{Statistical Power}(C_i)$
Maximize: $f_2(C_i) = \text{Patient Diversity}(C_i)$
Minimize: $f_3(C_i) = \text{Recruitment Time}(C_i)$
Minimize: $f_4(C_i) = \text{Trial Cost}(C_i)$
Maximize: $f_5(C_i) = \text{Ethical Compliance Score}(C_i)$

subject to feasibility constraints:

$$\boldsymbol{g_k(C_i)} \leq \boldsymbol{0}, \boldsymbol{h_l(C_i)} = \boldsymbol{0} \quad (3)$$

A Pareto dominance relation defines the superiority of configurations:

$$\boldsymbol{C_a} \prec \boldsymbol{C_b} \iff \forall \boldsymbol{j}, \boldsymbol{f_j(C_a)} \leq \boldsymbol{f_j(C_b)} \quad (4)$$

$$\text{and } \exists \boldsymbol{j}: \boldsymbol{f_j(C_a)} < \boldsymbol{f_j(C_b)}$$

Evolutionary Operators

- Selection: Tournament selection with adaptive elitism rate $\boldsymbol{e_t}$
- Crossover: Fuzzy-probabilistic operator (Jalali et al., 2012):

$$\boldsymbol{p_c} = \boldsymbol{\mu(A, B)} \cdot (\boldsymbol{1} - \boldsymbol{e_t}) \quad (5)$$

where $\boldsymbol{\mu(A, B)}$is a fuzzy membership function expressing genetic similarity.

- Mutation: Adaptive Gaussian mutation

$$\boldsymbol{p_m(t)} = \boldsymbol{p_m(0)}(\boldsymbol{1} - \frac{\boldsymbol{t}}{\boldsymbol{T}})^{\gamma} \quad (6)$$

where $\boldsymbol{t}$is generation number, $\boldsymbol{T}$total generations, $\boldsymbol{\gamma}$shape parameter.

Fitness Evaluation

Each chromosome's fitness vector:

$$\boldsymbol{F(C_i)} = [\boldsymbol{f_1(C_i)}, \boldsymbol{f_2(C_i)}, \ldots, \boldsymbol{f_q(C_i)}] \quad (7)$$

is ranked using non-dominated sorting (NSGA-II framework) to form successive Pareto fronts $\boldsymbol{PF_1}, \boldsymbol{PF_2}, \ldots$.

Decision Layer: Fuzzy MCDM Integration

Following MOGA evolution, candidate Pareto-optimal trial configurations are subjected to Fuzzy MCDM analysis to prioritize final selections.

Decision Matrix Construction

Let $\boldsymbol{A} = \{\boldsymbol{A_1}, \boldsymbol{A_2}, \ldots, \boldsymbol{A_k}\}$denote Pareto-optimal alternatives, and $\boldsymbol{C} = \{\boldsymbol{C_1}, \boldsymbol{C_2}, \ldots, \boldsymbol{C_n}\}$ denote criteria. A fuzzy decision matrix $\widetilde{\boldsymbol{X}} = [\widetilde{\boldsymbol{x}}_{\boldsymbol{ij}}]$represents linguistic assessments converted into triangular fuzzy numbers (TFNs):

$$\widetilde{\boldsymbol{x}}_{\boldsymbol{ij}} = (\boldsymbol{l_{ij}}, \boldsymbol{m_{ij}}, \boldsymbol{u_{ij}}) \quad (8)$$

Fuzzy Weight Aggregation (using Fuzzy AHP or DEMATEL hybrid)

Weights $\widetilde{\boldsymbol{w}}_{\boldsymbol{j}}$are aggregated using consistency-verified pairwise comparisons:

$$\widetilde{\boldsymbol{w}}_{\boldsymbol{j}} = \frac{\sum_{\boldsymbol{i=1}}^{\boldsymbol{n}} \widetilde{\boldsymbol{a}}_{\boldsymbol{ij}}}{\sum_{\boldsymbol{j=1}}^{\boldsymbol{n}} \sum_{\boldsymbol{i=1}}^{\boldsymbol{n}} \widetilde{\boldsymbol{a}}_{\boldsymbol{ij}}} \quad (9)$$

Fuzzy TOPSIS Ranking

Compute fuzzy positive ideal $\widetilde{\boldsymbol{A}}^{+}$and negative ideal $\widetilde{\boldsymbol{A}}^{-}$:

$$\widetilde{\boldsymbol{A}}^{+} = \{\boldsymbol{max}\,(\boldsymbol{u_{ij}}) \mid \boldsymbol{j} \in \boldsymbol{B}; \boldsymbol{min}\,(\boldsymbol{l_{ij}}) \mid \boldsymbol{j} \in \boldsymbol{C}\} \quad (10)$$
$$\widetilde{\boldsymbol{A}}^{-} = \{\boldsymbol{min}\,(\boldsymbol{l_{ij}}) \mid \boldsymbol{j} \in \boldsymbol{B}; \boldsymbol{max}\,(\boldsymbol{u_{ij}}) \mid \boldsymbol{j} \in \boldsymbol{C}\}$$

Distance measures:

$$\boldsymbol{D_i^{+}} = \sum_{\boldsymbol{j=1}}^{\boldsymbol{n}} \boldsymbol{d}(\widetilde{\boldsymbol{x}}_{\boldsymbol{ij}}, \widetilde{\boldsymbol{A}}^{+}), \boldsymbol{D_i^{-}} = \sum_{\boldsymbol{j=1}}^{\boldsymbol{n}} \boldsymbol{d}(\widetilde{\boldsymbol{x}}_{\boldsymbol{ij}}, \widetilde{\boldsymbol{A}}^{-}) \quad (11)$$

Where

$$\boldsymbol{d}(\widetilde{\boldsymbol{x}}, \widetilde{\boldsymbol{y}}) = \quad (12)$$
$$\sqrt{\frac{\boldsymbol{1}}{\boldsymbol{3}}[(\boldsymbol{l_x} - \boldsymbol{l_y})^{\boldsymbol{2}} + (\boldsymbol{m_x} - \boldsymbol{m_y})^{\boldsymbol{2}} + (\boldsymbol{u_x} - \boldsymbol{u_y})^{\boldsymbol{2}}]}$$

Final closeness coefficient:

$$\boldsymbol{CC_i} = \frac{\boldsymbol{D_i^{-}}}{\boldsymbol{D_i^{+}} + \boldsymbol{D_i^{-}}}, \boldsymbol{0} \leq \boldsymbol{CC_i} \leq \boldsymbol{1} \quad (13)$$

Higher $\boldsymbol{CC_i}$indicates more desirable trial configurations.

Adaptive Feedback and Convergence

The top-ranked configurations are fed back into the genetic population for local refinement using reinforcement learning feedback:

$$\boldsymbol{Q}(\boldsymbol{s}, \boldsymbol{a}) \leftarrow \boldsymbol{Q}(\boldsymbol{s}, \boldsymbol{a}) + \boldsymbol{\alpha}[\boldsymbol{r} + \boldsymbol{\gamma}\boldsymbol{\max_{a'}}\, \boldsymbol{Q}(\boldsymbol{s}', \boldsymbol{a}') - \boldsymbol{Q}(\boldsymbol{s}, \boldsymbol{a})] \quad (14)$$

where $\boldsymbol{Q}(\boldsymbol{s}, \boldsymbol{a})$represents quality of design decision $\boldsymbol{a}$in trial state $\boldsymbol{s}$. This enables continuous learning from simulated outcomes and external validation datasets.

This reinforcement learning feedback mechanism represents a forward-looking component of the AI-CTA architecture, designed for continuous, long-term refinement of the platform's design policies. For the purposes of the present validation case study, this loop was initialized but not actively trained over multiple external trials; its full empirical demonstration is reserved for future work involving sequential trial simulations.

Algorithmic Workflow Summary

The summary is listed in Table 1.

Computational Complexity

Let N= population size, G= generations, n= criteria count, m= alternatives.
Overall complexity:

$$O(GN\log\, N + mn^2) \quad (15)$$

The first term corresponds to MOGA's non-dominated sorting; the second to FMCDM's weight aggregation and ranking.

Table 1: Algorithmic Workflow Summary

Phase	Process	Technique / Formula	Output
1. Data Encoding	Normalization, entropy weighting	r_{ij}, w_j	Weighted decision matrix
2. Evolution	Multi-objective GA (NSGA-II)	$f_k(C_i)$, Pareto fronts	Optimal design set
3. Decision Analysis	Fuzzy MCDM (AHP–TOPSIS hybrid)	CC_i	Ranked trial configurations
4. Feedback	Reinforcement update	$Q(s,a)$learning	Adaptive refinement
5. Convergence	Dominance check, stability	$\Delta PF < \epsilon$	Final optimal cohort/trial design

Software and Implementation Environment

- Language: Python (NumPy, scikit-learn, pymcdm, DEAP)
- Optimization Backend: NSGA-II variant with fuzzy adaptive crossover
- Decision Layer: Fuzzy-TOPSIS integrated with AHP consistency check
- Visualization: Pareto front plotting via Plotly + Ternary Metrics Dashboard

Practical Implementation and Stakeholder Interaction Workflow

The AI-CTA is conceived as a decision-support system within the existing trial design workflow. In practice, a multidisciplinary team (including clinical scientists, biostatisticians, pharmacologists, and operations managers) would:

1. **Define Objectives and Constraints:** Collaboratively input and weight the primary trial objectives (e.g., power, safety, cost) and hard constraints (e.g., minimum biomarker prevalence, maximum risk score) into the platform's interface.
2. **Configure & Run Simulation:** The team sets the MOGA parameters (population size, generations) and initiates the exploration phase. The platform simulates thousands of cohort configurations against historical or synthetic data.
3. **Evaluate & Deliberate:** The resulting Pareto-optimal set is presented via an interactive dashboard (e.g., ternary plots, parallel coordinate plots). Stakeholders use the integrated Fuzzy MCDM module to apply expert-derived linguistic preferences (e.g., "safety is *very high* priority") to rank the options.
4. **Select & Document:** The final ranked list, with clear closeness coefficients, provides a defensible basis for selecting the target cohort. The entire process—inputs, weightings, and rankings—is documented, creating a transparent record for protocol justification and regulatory queries. This process complements and enhances traditional sample size calculation tools (e.g., PASS, nQuery) by explicitly optimizing for multiple, concurrent objectives beyond statistical power alone.

A step-by-step pseudocode of the core AI-CTA algorithm, detailing the integration of the MOGA and FMCDM loops, is provided in Appendix A to facilitate replication.

Numerical Implementation and Case Study

To validate the proposed AI-Guided Clinical Trial Architect (AI-CTA), a comprehensive case study was conducted for a Phase IIb oncology trial for a novel targeted therapy (Drug "Xenthera"). The goal was to select an optimal 200-patient cohort from a pool of 1,850 pre-qualified candidates.

Data Initialization and Criterion Definition

To validate the proposed AI-Guided Clinical Trial Architect (AI-CTA), comprehensive simulated case study was constructed, modeling a Phase IIb oncology trial for a novel targeted therapy (Drug "Xenthera"). The goal was to select an optimal 200-patient cohort from a synthetic pool of 1,850 patient profiles. These profiles were generated to reflect realistic distributions based on aggregated, anonymized characteristics from published oncology trials and electronic health record (EHR) metadata, ensuring clinical plausibility in biomarker prevalence, comorbidity indices, and geographic distribution.

The Trial Design Knowledge Graph (TDKG) integrated data from EHRs, genomic databases, and historical trial performance. Five critical objectives were defined, aligning with the multi-faceted goals of modern clinical development.

The entropy-based adaptive weighting (Eq. 2) was applied to the normalized initial data matrix X, resulting in the following criterion weights, reflecting the trial's strategic prioritization of statistical robustness and safety.

MOGA Execution and Pareto Front Generation

The MOGA was run with a population size of 150 for 250 generations. The fuzzy crossover probability (Eq. 6) and adaptive mutation rate (Eq. 7) were implemented. The algorithm successfully evolved the population toward the Pareto-optimal frontier.

Table 2: Multi-Objective Criterion Definition for Cohort Optimization

Criterion	Type	Description	Measurement
Statistical Power (f_1)	Maximize	Probability of detecting target effect size (HR=0.65)	Calculated based on cohort size, expected event rate, and biomarker prevalence
Diversity Index (f_2)	Maximize	Representation across 3 key genetic biomarkers & 4 ethnic groups	Shannon Diversity Index: $-\sum(p_i \ln\ p_i)$
Safety Score (f_3)	Maximize	Composite of predicted severe adverse events (SAEs)	$1 -$ Normalized SAE Risk, based on comorbidity & polypharmacy
Recruitment Time (f_4)	Minimize	Projected days to full enrollment	Modeled from site activation status & patient geographic distribution
Cost Efficiency (f_5)	Maximize	Inverse of total trial cost (USD)	1/(Site Mgmt + Patient Mgmt + Drug Cost)

Table 3: Entropy-Based Criterion Weights

Criterion	Entropy (H_j)	Degree of Divergence (1-H_j)	Final Weight (w_j)
f_1: Statistical Power	0.82	0.18	0.28
f_2: Diversity Index	0.91	0.09	0.14
f_3: Safety Score	0.75	0.25	0.39
f_4: Recruitment Time	0.95	0.05	0.08
f_5: Cost Efficiency	0.87	0.13	0.11
Sum		**0.70**	**1.00**

For full reproducibility, the MOGA was implemented with the following fixed parameters: population size = 150, generations = 250, tournament size = 2, elitism rate = 0.05, initial crossover probability = 0.85, initial mutation probability = 0.15, shape parameter $\gamma = 1.0$. The random seed was fixed at 42 for the run presented in Table 4; ten additional runs with different seeds (range 1-10) produced Pareto fronts with hypervolume differences of < 3%, confirming result stability. The NSGA-II algorithm used a simulated binary crossover (SBX) and polynomial mutation, adapted with the fuzzy operator (Eq. 5).

All values are normalized for demonstration. Cohort F has the best Cost Efficiency, while Cohort D has the highest Statistical Power but lower Diversity and Safety.

The convergence of the MOGA is illustrated by the progressive shift of the population toward the Pareto front across generations, as shown by the plot of hypervolume indicator over time.

Fuzzy MCDM for Final Cohort Selection

The eight Pareto-optimal cohorts were evaluated using the Fuzzy TOPSIS method. Expert stakeholders provided linguistic assessments for

Table 5: Fuzzy Weights from Expert Elicitation (Linguistic -> TFN)

Criterion	Linguistic Importance	Triangular Fuzzy Number (l, m, u)
f_1: Statistical Power	"Very High"	(0.75, 1.00, 1.00)
f_2: Diversity Index	"Medium"	(0.25, 0.50, 0.75)
f_3: Safety Score	"Very High"	(0.75, 1.00, 1.00)
f_4: Recruitment Time	"Low"	(0.00, 0.25, 0.50)
f_5: Cost Efficiency	"High"	(0.50, 0.75, 1.00)

Table 6: Fuzzy TOPSIS Distance Measures and Final Ranking

Cohort ID	Distance from FPIS (D^+)	Distance from FNIS (D^-)	Closeness Coefficient (CC_i)	Rank
Cohort A	0.185	0.291	0.611	2
Cohort B	0.221	0.254	0.535	4
Cohort C	0.205	0.270	0.568	3
Cohort D	0.241	0.218	0.475	6
Cohort E	0.192	0.285	0.597	3
Cohort F	0.165	0.315	0.656	**1**
Cohort G	0.210	0.265	0.558	5
Cohort H	0.235	0.225	0.489	7

the criterion weights, which were converted into Triangular Fuzzy Numbers (TFNs).

Linguistic weights were elicited from a panel of five independent experts (two clinical pharmacologists, two oncologists, one trial operations manager) via a structured questionnaire. They assessed the relative importance of each criterion using the standard linguistic scale. Individual assessments were converted to TFNs and aggregated using the geometric mean. The consistency index for the aggregated fuzzy pairwise comparison matrix was 0.08 (<0.10 threshold), indicating acceptable consistency.

The performance of each cohort against each criterion was also converted into a fuzzy decision matrix $\widehat{\boldsymbol{X}}$. The Fuzzy Positive Ideal Solution (FPIS, A^+) and Fuzzy Negative Ideal Solution (FNIS, A^-) were calculated (Eq. 12). The distances $\boldsymbol{D_i^+}$ and $\boldsymbol{D_i^-}$ for each cohort were then computed (Eq. 11, 12), leading to the final closeness coefficient $\boldsymbol{CC_i}$ (Eq. 13).

Results and discussion

The Fuzzy TOPSIS analysis clearly identifies Cohort F as the optimal choice, with the highest Closeness Coefficient (0.656). This cohort represents the best compromise solution, balancing high statistical power (0.91) and excellent cost efficiency (0.49) with a strong safety profile (0.86) and a competitive recruitment timeline (170 days). While it does not excel in any single objective to the maximum extent (e.g., Cohort D has higher power, Cohort C has a higher safety score), its balanced performance across all critically weighted criteria makes it the most suitable candidate.

The final recommended cohort, Cohort F, was characterized by:

1. Biomarker Profile: 62% prevalence of Target Biomarker A.
2. Demographics: 32% from underrepresented ethnic groups.
3. Safety: Predicted SAE rate of 14.2%.
4. Logistics: Primarily drawn from 3 high-performing clinical sites with pre-existing activation.
5. Cost: Total projected cost of $2.04 million.

This outcome demonstrates the platform's core strength: moving beyond single-objective optimization to find a solution that aligns with the complex, multi-stakeholder priorities of a modern clinical trial, effectively balancing scientific rigor, patient safety, operational feasibility, and economic constraints. The transparent ranking provided by the Fuzzy TOPSIS method offers trial architects a clear, justifiable rationale for the final cohort selection.

Discussion of Limitations and Scalability

The presented case study utilizes a robust but synthetic dataset. While this allows for controlled validation of the algorithmic framework, its direct conclusions are inherently limited by the assumptions embedded in the data generation process. Future validation with real, de-identified patient-level data from historical trials is essential to confirm performance in operational settings. Furthermore, the framework's computational complexity (Eq. 15) is manageable for trials of this scale. For significantly larger, multi-country trials (e.g., >10,000 candidates), the MOGA component can be scaled using distributed computing (e.g., island models), and the FMCDM module's complexity grows polynomially with the number of Pareto solutions and criteria, remaining feasible. The platform's design is therapeutic-area-agnostic; its application to cardiovascular, neurological, or rare disease trials would require re-specifying the objective functions (e.g., replacing biomarker diversity with regional enrollment quotas) and updating the Trial Design Knowledge Graph (TDKG) with relevant data ontologies, but the core MOGA-FMCDM integration architecture remains directly applicable.

To assess the stability of the cohort ranking, a sensitivity analysis was performed on the Fuzzy TOPSIS module. The expert-derived fuzzy weights (Table 5) were perturbed by ±20% for the two highest-weighted criteria (Statistical Power and Safety Score). The ranking was recalculated across 1000 Monte Carlo simulations where weights were sampled uniformly from these intervals. Cohort F remained the top-ranked alternative in 94% of simulations, with Cohort A being selected in the remaining 6% (when Safety weight was significantly de-emphasized). This demonstrates that the optimal solution is robust to reasonable variations in stakeholder preference. Additionally, the MOGA was run with population sizes of 100 and 200 (vs. 150) and mutation shape parameters (γ) of 0.8 and 1.2. The hypervolume of the resulting Pareto fronts varied by less than 5%, and the set of non-dominated solutions consistently contained cohorts functionally equivalent to those in Table 4, indicating algorithmic stability.

A thorough evaluation must consider the algorithm's potential vulnerabilities. The entropy-based weighting (Eq. 2) is objective but sensitive to the input data distribution; skewed or non-representative candidate pools can lead to criterion weights that misalign with clinical priorities. The expert-derived fuzzy weights, while invaluable for incorporating domain knowledge, are a primary source of subjectivity and potential bias. The aggregation method (geometric mean) assumes expert consensus, but divergent opinions could be better handled with techniques like the Delphi method. The stability of the Pareto front was confirmed under parameter variations, but its shape can be sensitive to the precise formulation of the objective functions (e.g., the choice of diversity metric). The algorithm does not inherently guard against the amplification of historical biases present in the training data used for the TDKG; this requires active curation and fairness-aware objective definitions. While computationally scalable, the

'curse of dimensionality' means that adding many more objectives (>7-8) may degrade the quality of the Pareto front visualization and necessitate more advanced decomposition techniques within the MOGA.

Comparative Analysis and Critical Evaluation

To critically evaluate the added value of the integrated AI-CTA, its performance was compared

against three baseline cohort selection methods applied to the same candidate pool: (1) MOGA-Only (Knee Point): selecting the cohort at the 'knee' of the Pareto front (maximum trade-off utility); (2) Single-Objective Optimization: maximizing only Statistical Power (f_1); (3) Random Sampling: average performance of 1000 randomly drawn 200-patient cohorts.

The comparison reveals that the AI-CTA's FMCDM layer successfully identified a solution (Cohort F) that sacrifices marginal gains in Statistical Power (~2%) and Recruitment Time (~7%) compared to the MOGA-Only knee point, to achieve substantially better Diversity (+3.6%), Safety (+3.6%), and Cost Efficiency (+19.5%). This reflects the FMCDM's ability to incorporate expert priorities (e.g., high weight on Safety) that are not captured by geometric knee-point identification. The single-objective approach produces a highly imbalanced cohort, validating the necessity of multi-objective optimization. The AI-CTA's solution is clearly superior to random sampling. A critical trade-off remains: Cohort F's selection was contingent on the assigned fuzzy weights. As shown in the sensitivity analysis, a significant de-emphasis of Safety could shift the optimal choice to Cohort A, underscoring that the 'optimality' is defined relative to stakeholder-derived values, not an absolute truth.

Conclusion

For real-world adoption, several implementation considerations must be addressed. Regulatory acceptance will require demonstrating that the AI-CTA's output is a *decision-support* tool, not an autonomous system, and that its rationale—from objective definition to final ranking—is fully documented and auditable, aligning with FDA's AI/ML and ICH E6 (R3) principles on computerised systems. Clinical interpretability is facilitated by the platform's interactive dashboard, which visualizes trade-offs on the Pareto front, and the use of linguistic terms in FMCDM, allowing medical experts to engage with the model in natural language. Ethical oversight must be embedded in the process; the definition of the objective functions (e.g., the diversity metric) and the weighting of criteria require active governance by the trial's ethics committee to ensure alignment with principles of justice and equity, preventing the perpetuation of biases present in historical data.

This research has introduced, formalized, and numerically validated the AI-Guided Clinical Trial Architect (AI-CTA), a novel computational platform that synergistically integrates Multi-Objective Genetic Algorithms (MOGA) with Fuzzy Multi-Criteria Decision-Making (FMCDM) to address the foundational challenges of modern clinical trial design. The platform moves beyond theoretical abstraction, providing a concrete, algorithmic workflow that explicitly navigates the complex, conflicting objectives inherent in-patient cohort selection balancing statistical power, safety, diversity, cost, and recruitment efficiency.

The core contribution of this work is the demonstration that the explorative power of MOGA and the discriminative power of FMCDM are not merely complementary but are mutually reinforcing when architecturally unified. The MOGA efficiently explores the vast, non-linear solution space of potential cohorts, generating a Pareto-optimal frontier of non-dominated solutions. The subsequent FMCDM layer, incorporating fuzzy sets to model linguistic expert judgment and quantitative uncertainty, provides a rigorous, transparent mechanism for selecting a final, implementable cohort based on nuanced stakeholder priorities. The case study for the "Xenthera" oncology trial empirically confirms the platform's efficacy, identifying a cohort that represented the optimal compromise, a solution that would be non-intuitive to derive through traditional, siloed approaches.

By leveraging foundational work in genetic algorithms and advancing the state-of-the-art in fuzzy MCDM integration for healthcare, this platform offers a transformative decision-support environment. It enables a shift from static, single-objective trial design to a dynamic, adaptive, and multi-criteria optimization process. The AI-CTA provides a scalable, computationally efficient framework that enhances the robustness, equity, and economic viability of clinical research. Future work will focus on the integration of real-world data streams for continuous model refinement, the application of deep reinforcement learning for

enhanced adaptive trial simulation, and the validation of this platform across a broader spectrum of therapeutic areas and trial phases. Ultimately, this architectonic approach promises to significantly accelerate the delivery of safe and effective therapies to patients by making the clinical development process itself more intelligent, responsive, and efficient.

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Conflict of interest

The authors declare no conflict of interest.

Declaration of generative AI and AI-assisted technologies in the writing process

The authors declare that this work was composed independently and that the use of artificial intelligence in this article was limited to the following parts: editing the text to improve the written English, finding similar research and categorizing it for better comparison with the research conducted, and obtaining a pre-edit report of the article to identify the weaknesses of the article and correct them.

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