

Optimizing Clinical Trial Designs with Quantitative Decision Frameworks:
Integrating Pharmacometric, Financial, and Commercial Models to Optimize Value

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Background

R&D Productivity: Biopharmaceutical research and development (R&D) productivity has declined over the past two decades despite rapid technological advancement [1].

$$\text{Productivity} = \text{Efficiency} \cdot \text{Effectiveness} \tag{1}$$

where Efficiency is the ability of the R&D system to translate inputs (e.g., ideas, effort, investment) into clinical outputs, and Effectiveness is the ability of the R&D system to produce clinical outputs that are valued by patients, payers, and society [2]. In essence, R&D productivity represents the aggregate return on investment for drug development activities.

Challenges in R&D Decision-Making: R&D productivity declines are a multifactorial issue driven by the many challenges inherent to drug development: complex science, large capital requirements, long development timelines, market access and pricing uncertainties, competitive dynamics, and cognitive and motivational biases. Value-based decision-making with disciplined risk-management under these conditions represents a formidable challenge for the drug development enterprise.

Quantitative Decision Frameworks: Industry experts recommend four general strategies to improve R&D productivity: (i) proactive use of all data sources; (ii) use of quantitative models to inform all decisions; (iii) removal of organizational silos; and (iv) broad adoption of decision frameworks [1]. A R&D quantitative decision framework (QDF) is a structured approach to combining all relevant data, models, and assumptions about the value and risk of drug development programs to support disciplined decision-making.

Objective

The objective of this work was to demonstrate, using a compelling case study, a framework for integrating quantitative models across several key organizational domains (pharmacometrics, finance, and commercial) to support disciplined decision-making with respect to the value, risk, cost, and timing for a hypothetical trial.

Methods

Program & Organizational Status: A Phase 2 trial for an immuno-oncology candidate is near completion. Preliminary data suggest a generally favorable benefit-risk profile, but budget constraints are such that the asset must compete for financial resources with other assets in the R&D portfolio. Following a recent late-stage clinical failure, the organization is in a relatively risk-averse posture and under pressure to achieve a Phase 3 success to address a future revenue gap.

Integrated Modeling Framework: The QDF was based on a: (i) published model linking tumor-growth to overall survival (OS) following immunotherapy and/or chemotherapy [3]; (ii) financial model quantifying the costs of trial design elements (i.e., the expected cost of carrying out planned trial designs); and (iii) commercial model characterized by indication epidemiology and assumed market uptake, a 3-year time-to-peak sales, and negligible revenue following loss of exclusivity.

Decision Variables & Optimization Objectives: Four trial design decision variables were evaluated: (i) sample size; (ii) study duration; (iii) inclusion criteria (biomarker agnostic versus restrictive); and (iv) number of clinical sites for study recruitment. For these four decision variables, the Non-dominated Sorting Genetic Algorithm (NSGA-II) [4] was used to identify the Pareto front for feasible trial designs based on two competing objectives. The Pareto front represents the set of optimal solutions for which improving one objective requires compromising the other.

Objective 1: Maximize the risk-adjusted net present value of the drug candidate.

$$\text{rNPV}(d) = \text{PoS}(d) \cdot \int_{T_{\text{launch}}}^{T_{\text{lo}}} \text{CF}_{\text{comm}}(t) e^{-rt} dt \tag{2}$$

where $\text{PoS}(d)$ is the estimated probability of success for the planned trial derived using clinical trial simulations, $\text{CF}_{\text{comm}}(t)$ is the net commercial cash flow (revenue minus operating expenses), r is the continuous monthly discount rate, T_{launch} is the total study time plus regulatory review delay, and T_{lo} is the time to loss of exclusivity (i.e., patent expiration). For this example, an annual discount rate of 12% was used for the time-value of money, and probability of success was computed as the proportion of clinical trial simulation replicates ($N=200$) achieving an: (i) OS hazard ratio estimate <0.7 as estimated using a Cox proportional hazards model; and (ii) $P < 0.05$.

Objective 2: Minimize the committed capital requirement for the planned trial.

$$\text{CC} = \beta_1 \cdot \text{SS} + \beta_2 \cdot \text{Study}_{\text{Duration}} + \text{NSites}^{\beta_3} + \beta_4 \cdot \text{Study}_{\text{Time}} \tag{3}$$

where CC is the committed capital, SS is the sample size, $\text{Study}_{\text{Duration}}$ is the time in study for each subject, NSites is the number of clinical trial recruitment sites, and $\text{Study}_{\text{Time}}$ is the expected calendar time for the study (i.e., time from first enrollment to study completion). The coefficients for each variable represent the costs associated with unit increases in each variable and were set based on anecdotal experience.

Quantitative Decision Framework: A QDF based on the Decision Quality framework [5] was constructed (Figure 1). Three distinct trial design scenarios were selected from the Pareto front to present to decision-makers. The scenarios included a: (i) "Fast-to-Market", (ii) "Risk-Averse", and "Max Productivity" designs. These scenarios represented feasible trial designs from the Pareto front with minimum time to market, maximum probability of success, and maximum expected productivity index (ePI) [6], respectively.

$$\text{ePI} = \frac{\text{rNPV}}{\text{CC}} = \frac{(\text{PoS} \times \text{NPV}) - \text{CC}}{\text{CC}} \tag{4}$$

where ePI is the expected productivity index, rNPV is the risk-adjusted net present value, and CC is the committed capital requirement for the planned trial.

To assess trade-offs across the scenarios, dimensions of value, risk, cost, and timing were evaluated. For comparison, a reference design was defined using standard parameters: sample size achieving 80% power ($\alpha = 0.05$), 2-year study duration, biomarker-agnostic population, and recruitment from three clinical sites.

References

[1] Deloitte Center for Health Solutions. Measuring the Return from Pharmaceutical Innovation 2024: Navigating the R&D Dynamic. Technical report, Deloitte (2024).

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[5] Spetzler, C., Winter, H. and Meyer, J. *Decision Quality: Value Creation from Better Business Decisions* (John Wiley & Sons, Hoboken, NJ, 2016).

[6] Bayney, R. and Orellana, J. *Decision Analysis and Portfolio Management in the Biopharma Industry* (J. Ross Publishing, Plantation, FL, 2026).

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Improving R&D Productivity with Quantitative Decision Frameworks

Figure 1. Quantitative Decision Frameworks designed to achieve Decision Quality.

A framework for achieving Decision Quality (DQ) was published by Spetzler et al. [5]. R&D Quantitative Decision Frameworks expand on the qualitative DQ framework by providing a structured approach to combining all relevant data, models, and assumptions about drug development programs to support disciplined decision-making.

1. Decision Frame

Decision Variables

Sample size, study duration, patient population, recruitment sites

2. Relevant & Reliable Information

Quantitative Models

Pharmacometric, financial, and commercial models

3. Multi-Stakeholder Input

Multi-Objective Optimization

Identify Pareto front for competing objectives with NSGA-II

4. Distinct Alternatives

Identify Strategic Options

Narrow decision space for decision-maker

5. Clear Values & Trade-Offs

Decision Analysis

Evaluate value, risk, cost, and timing trade-offs across scenarios

6. Decision Quality

Commitment to Action

Increased R&D productivity through better decision-making

Case Study: Quantitative Modeling Framework

Figure 2. Pharmacometric model.

The pharmacometric tumor growth inhibition-overall survival model was used to perform clinical trial simulations to determine the probability of success for potential trial designs. Generally, the probability of success increases with increasing sample size, study duration, and biomarker restriction.

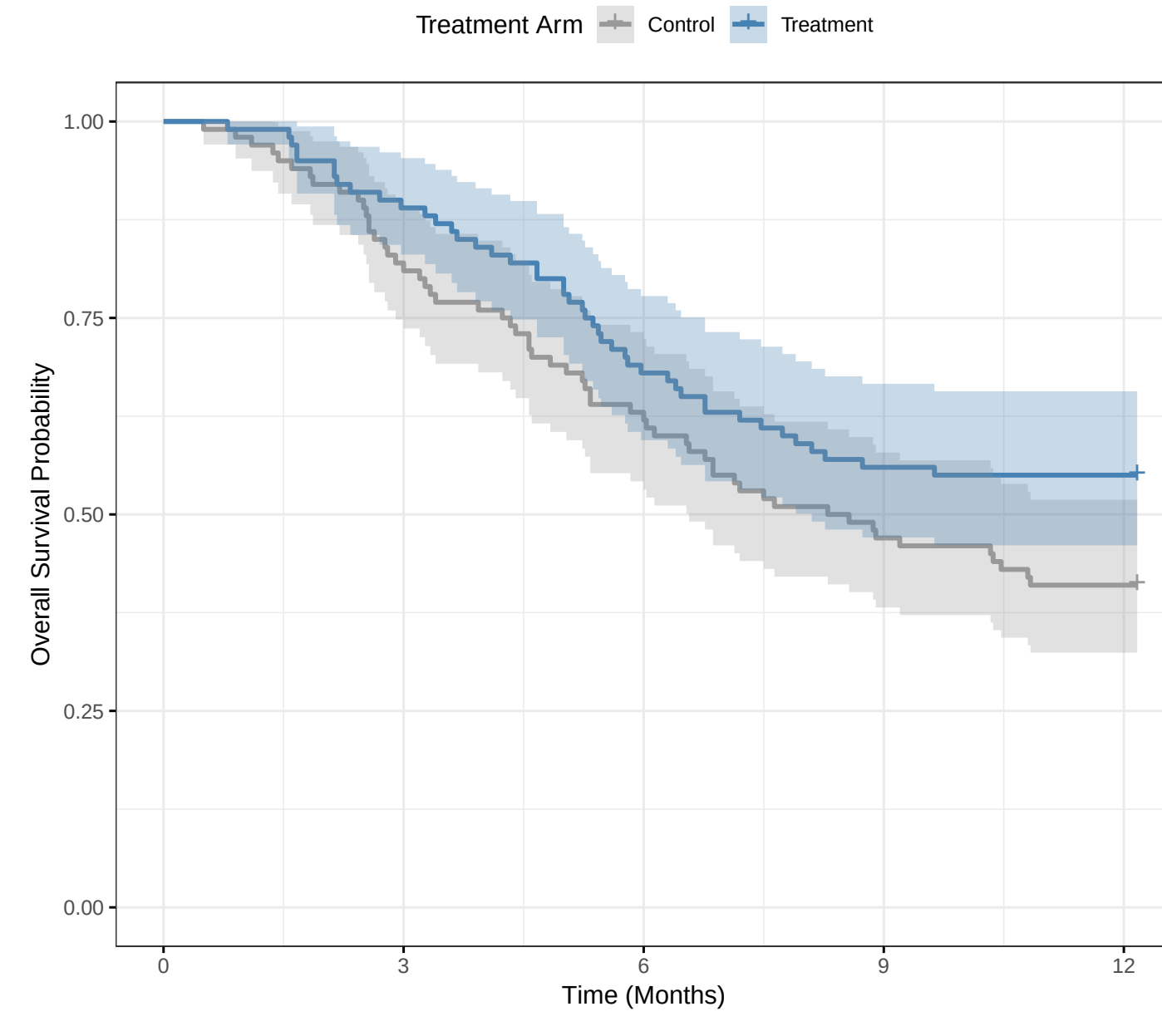


Figure 3. Financial model.

The financial model captures costs associated with trial design elements including enrollment, site activation, overhead, and biomarker screening. Generally, trial costs increase with increasing sample size, study duration, number of clinical sites, slower enrollment, and biomarker restriction.

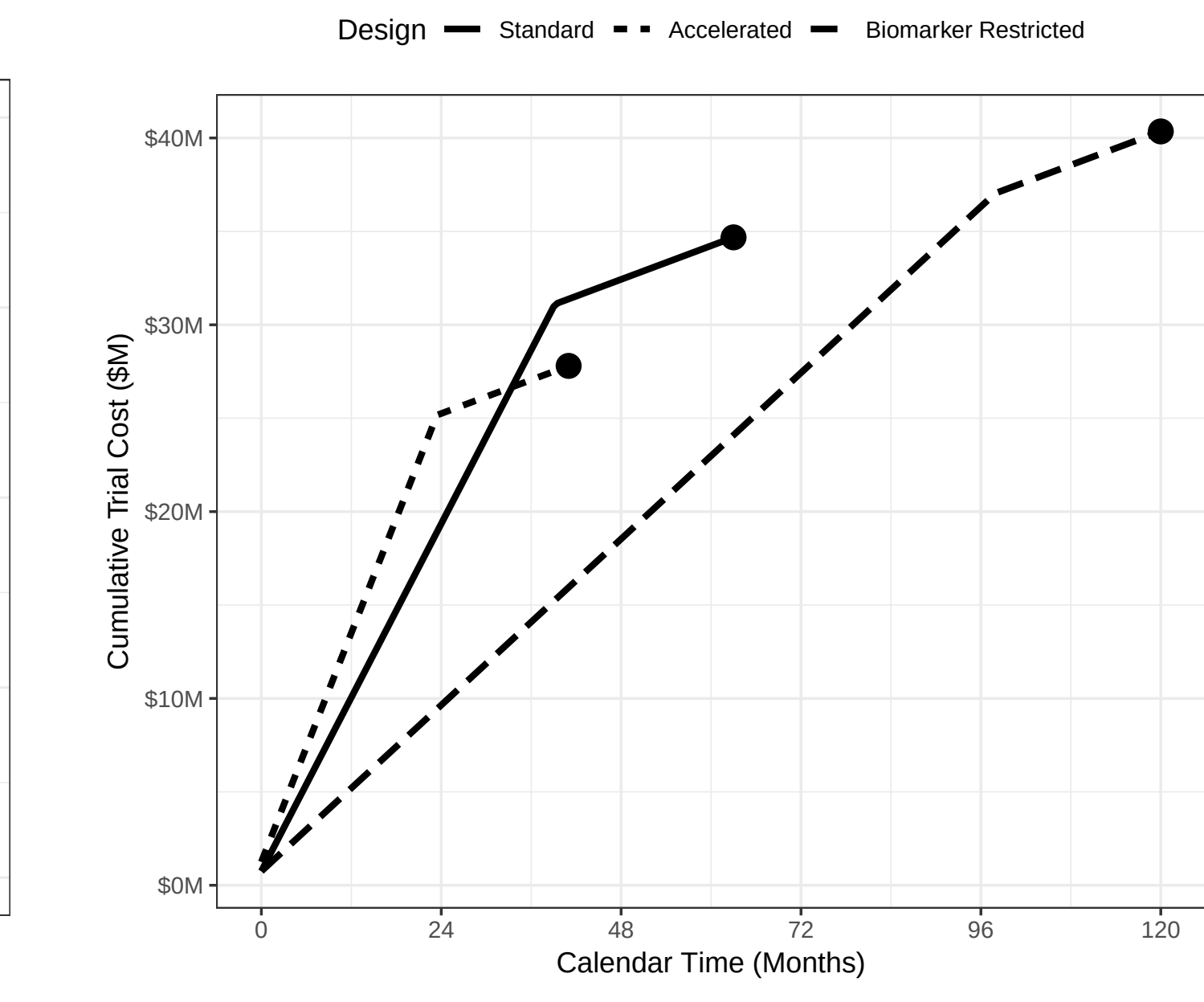
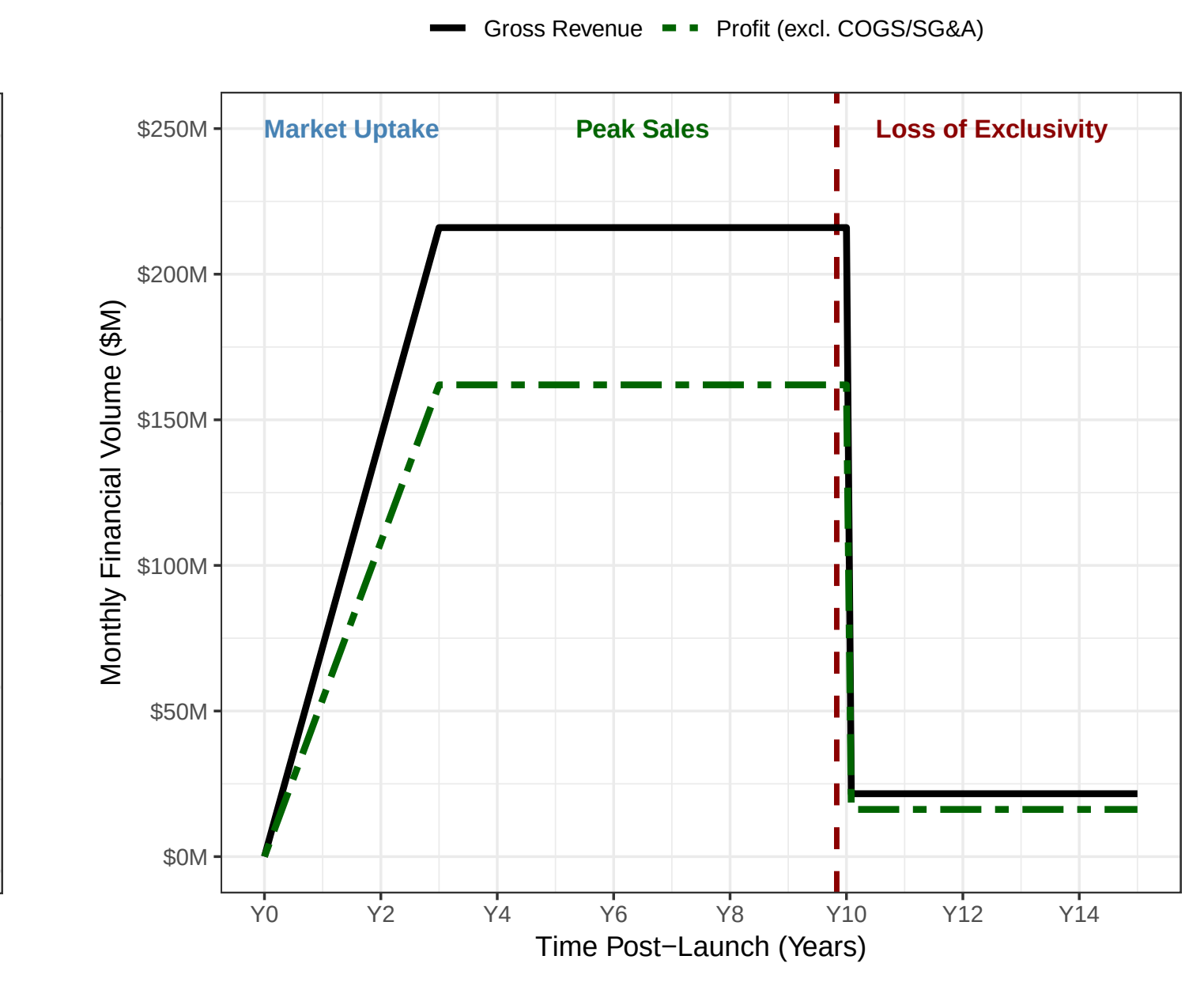


Figure 4. Commercial model.

The commercial model captures longitudinal gross revenue and profits considering the epidemiology of the indication, expected market uptake, launch date, patent life, cost of goods sold (COGS), and selling, general and administrative expenses (SG&A).



Results: Multi-Objective Optimization & Strategic Options

Figure 5. Pareto front for Phase 3 trial designs.

Pareto-optimal (non-dominated) solutions mapping trade-offs between risk-adjusted NPV (rNPV) and Committed Capital (CC) requirement. Navy points represent Pareto-optimal, non-dominated solutions. Light purple points represent population members of the genetic algorithm search that were dominated by other solutions.

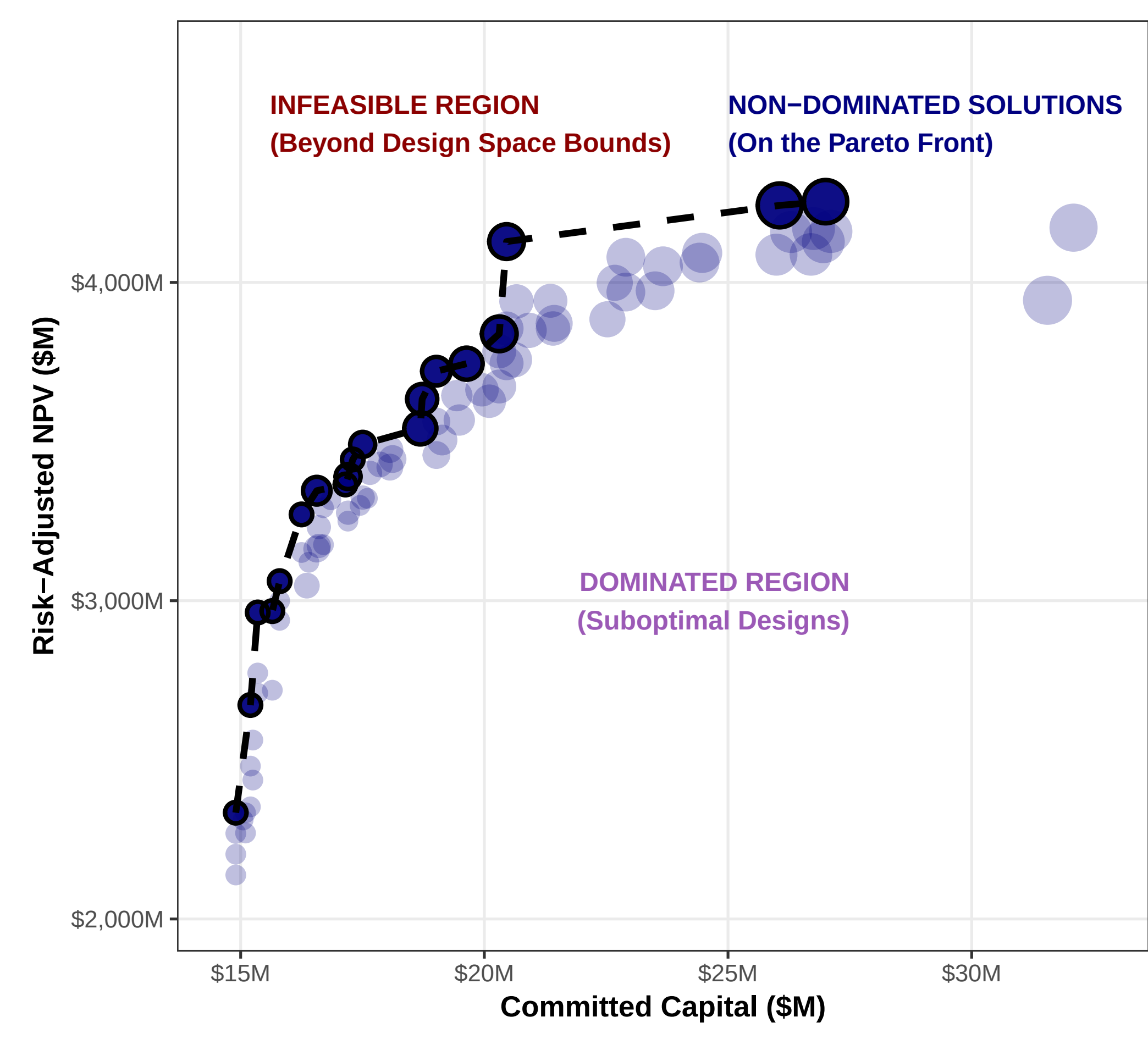
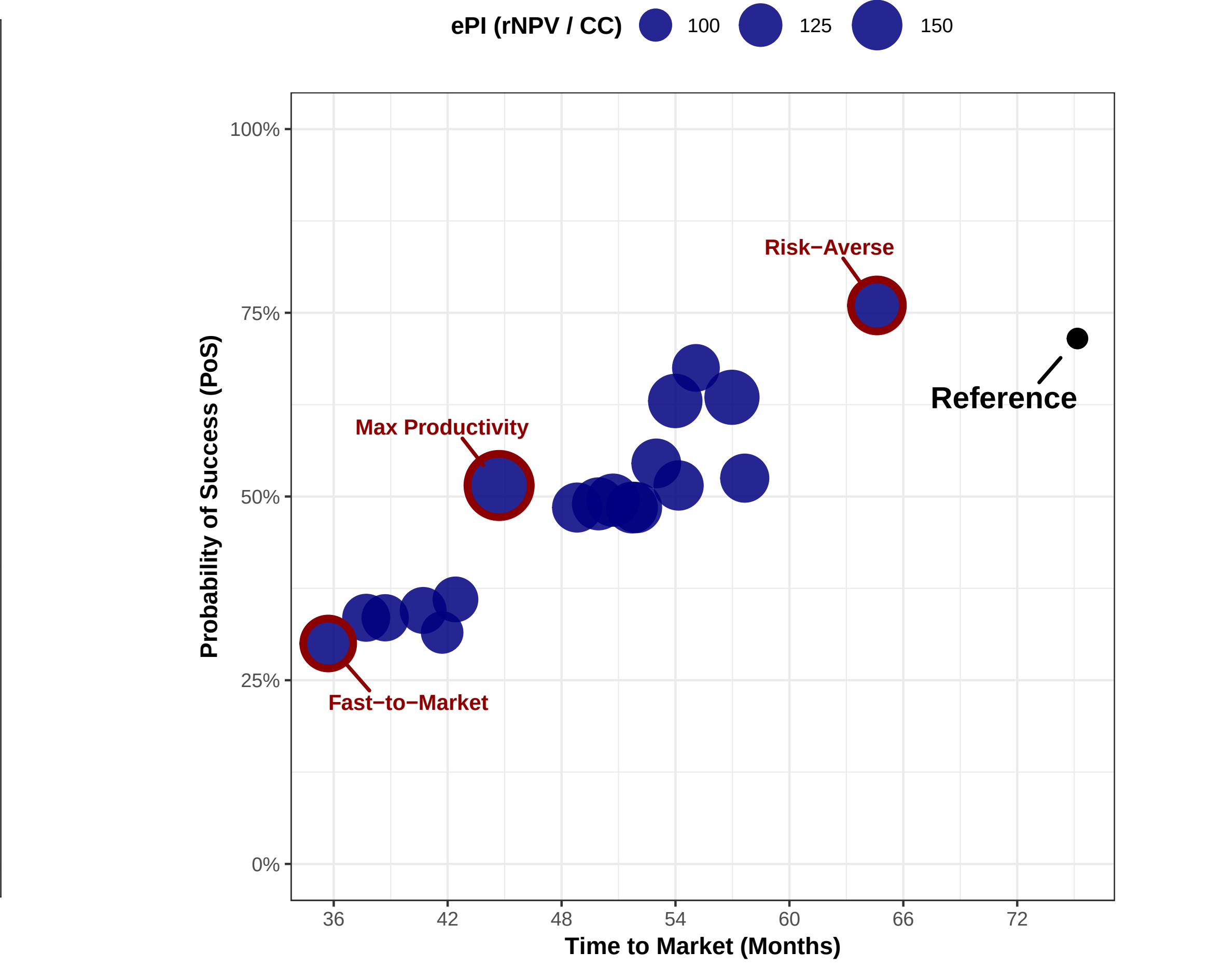


Figure 6. Identification of strategic options from the Pareto front.

Pareto-optimal trial designs evaluated across time-to-market, clinical probability of success (PoS), and capital productivity (ePI). Red circles highlight the selected strategic options.



Results: Decision Analysis

Table 1. Decision variables, performance metrics, and productivity index for Pareto-optimal strategic options and reference design.

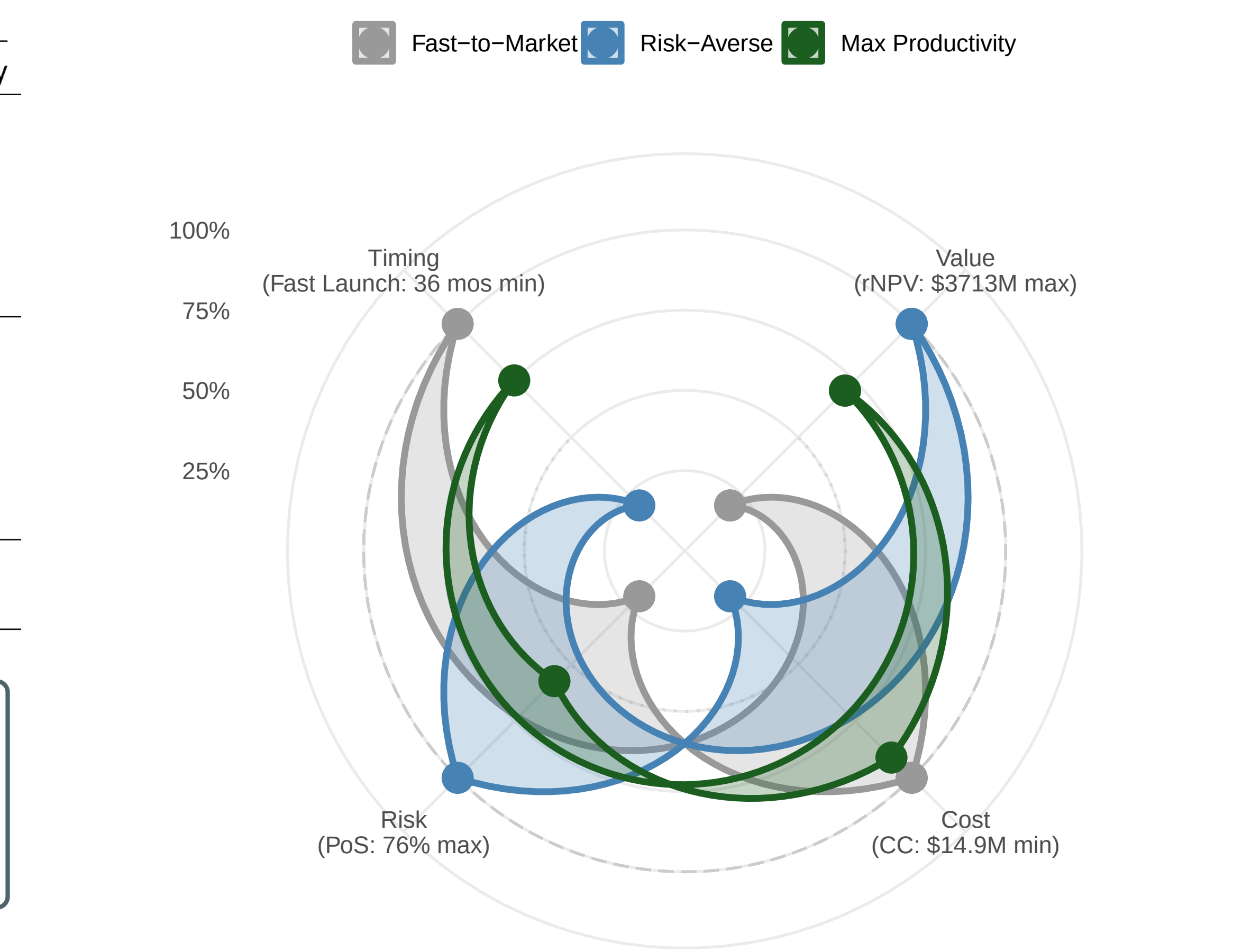
Decision variables, performance metrics, and productivity index (ePI) across strategic options selected from the Pareto front.

Metric	Reference	Pareto-optimal		
		Fast-to-Market	Risk-Averse	Max Productivity
Decision Variable				
Sample Size (N)	240	100	176	100
Protocol Duration (mos)	24	12	32	21
Inclusion Criteria	Agnostic	Agnostic	Agnostic	Agnostic
Clinical Sites	3	5	5	5
Performance Metric				
Committed Capital	\$34.7M	\$14.9M	\$27M	\$16.2M
Risk-Adjusted NPV	\$3140M	\$1940M	\$3710M	\$3060M
Probability of Success	71.5%	30%	76%	51.5%
Time-to-Market (mos)	75.2 mos	35.7 mos	64.6 mos	44.7 mos
R&D Productivity				
Productivity Index	90.5x	130x	137x	188x

Key Result: The Reference design yielded the lowest capital efficiency (ePI = 90.5x), forfeiting 2.5 years of patent life to slow accrual while delivering a lower probability of success (PoS = 71.5%) at higher cost (\$34.7M). Pareto-optimal designs dominated across all metrics—doubling capital efficiency (Max Productivity: ePI = 188x) or raising PoS to 76.0% while saving \$7.7M and launching 10.5 months faster.

Figure 7. Value, risk, cost, and timing trade-offs across Pareto-optimal strategic options.

Normalized strategic performance across value (rNPV), risk (PoS), cost (CC), and timing (time-to-market). Outward expansion toward 100% indicates superior performance along the performance dimension.



Conclusions

This work demonstrates a framework for integrating quantitative models across organizational domains to support capital-efficient R&D decision-making.

Multi-objective optimization of program decisions can support rigorous evaluation of strategic options when a plurality of decision variables and competing objectives make trade-offs intractably complex to evaluate.

Broad adoption of QDFs could improve R&D productivity through better decision-making, thereby supporting a more sustainable R&D enterprise.