

Operationalizing MIDD within R&D Quantitative Decision Frameworks: Identifying Clinical and Biological Drivers of Trial Risk with Global Sensitivity Analysis

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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].

$$\text{Productivity} = \text{Efficiency} \cdot \text{Effectiveness} \quad (1)$$

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 to produce clinical outputs that are valued by patients, payers, and society.

Challenges in R&D Decision-Making: Productivity declines are a multifactorial issue, driven in part by complex science, market access and pricing uncertainties, as well as cognitive and motivational biases in R&D decision-making.

Quantitative Decision Frameworks: Industry experts have recommended four general strategies to improve R&D productivity including use of quantitative modeling to inform all decisions and broad adoption of decision frameworks [2]. 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.

Objectives

The objective of this work was to demonstrate, with a motivating case study, the application of a model-informed drug development (MIDD) model to identify drivers of Phase 3 trial risk and support the development of a Go/No-Go QDR.

Methods

Setting: A Phase 2 trial for an immunotherapy asset with an oncology indication is underway. A semi-mechanistic tumor growth, overall survival (OS) model is being developed in parallel with the maturing Phase 2 data.

TGI-OS Model: The MIDD model was based on a previously published immunotherapy model framework [3]. The model describes the dynamics between the tumor, immune system, and immunotherapy treatment:

$$\frac{dT}{dt} = \rho T \left(1 - \frac{T}{\beta} \right) - \xi \cdot I \cdot T \left(\frac{T}{h_T + T} \right) \quad (2)$$

$$\frac{dI}{dt} = (\alpha + \psi_{\text{eff}}) - \delta \cdot I \quad (3)$$

where the tumor (T) follows logistic growth kinetics with proliferation rate ρ and carrying capacity $\beta = 10^{12}$ cells. Immune-mediated tumor killing by immune cells (I) is quantified by a saturable T-cell killing rate (ξ). Immune dynamics (I) are driven by a zero-order influx rate (α) which is stimulated by immunotherapy potency (ψ_{eff}), and a first-order death rate (δ). Active treatment stimulates immune recruitment via delayed potency ($\psi_{\text{eff}} = \psi \cdot (1 - e^{-k_{\text{on}} t})$), with OS dictated by mortality events occurring when tumor burden reaches an individual threshold $T(t) \geq T_{\text{thresh}}$.

Phase 3 Trial Design: Chemotherapy (control) and chemotherapy + immunotherapy (treatment) arms; 200 subjects with 1:1 randomization; 2-year trial duration.

Latin Hypercube Sampling: A Sobol design matrix was generated using Latin hypercube sampling (LHS) to efficiently sample the plausible parameter space across eight semi-mechanistic parameters. Parameter values were sampled across 1.5x the 95% confidence interval for estimated parameters and across the biologically plausible range for fixed parameters.

Probability of Success: Probability of success (PoS) was determined using clinical trial simulations (CTS) performed with parameter sets obtained from the LHS procedure. PoS was computed as the proportion of CTS replicates ($N = 200$) achieving: (i) a statistically significant difference in OS between treatment and control arms ($P < 0.05$); and (ii) an OS hazard ratio < 0.7 estimated using a Cox proportional hazards model.

Global Sensitivity Analysis: The influence of model parameters on trial risk (i.e., PoS) were evaluated with the first-order (S_i) and total-effect (T_i) variance indices computed using the Saltelli and Sobol methods, respectively [4].

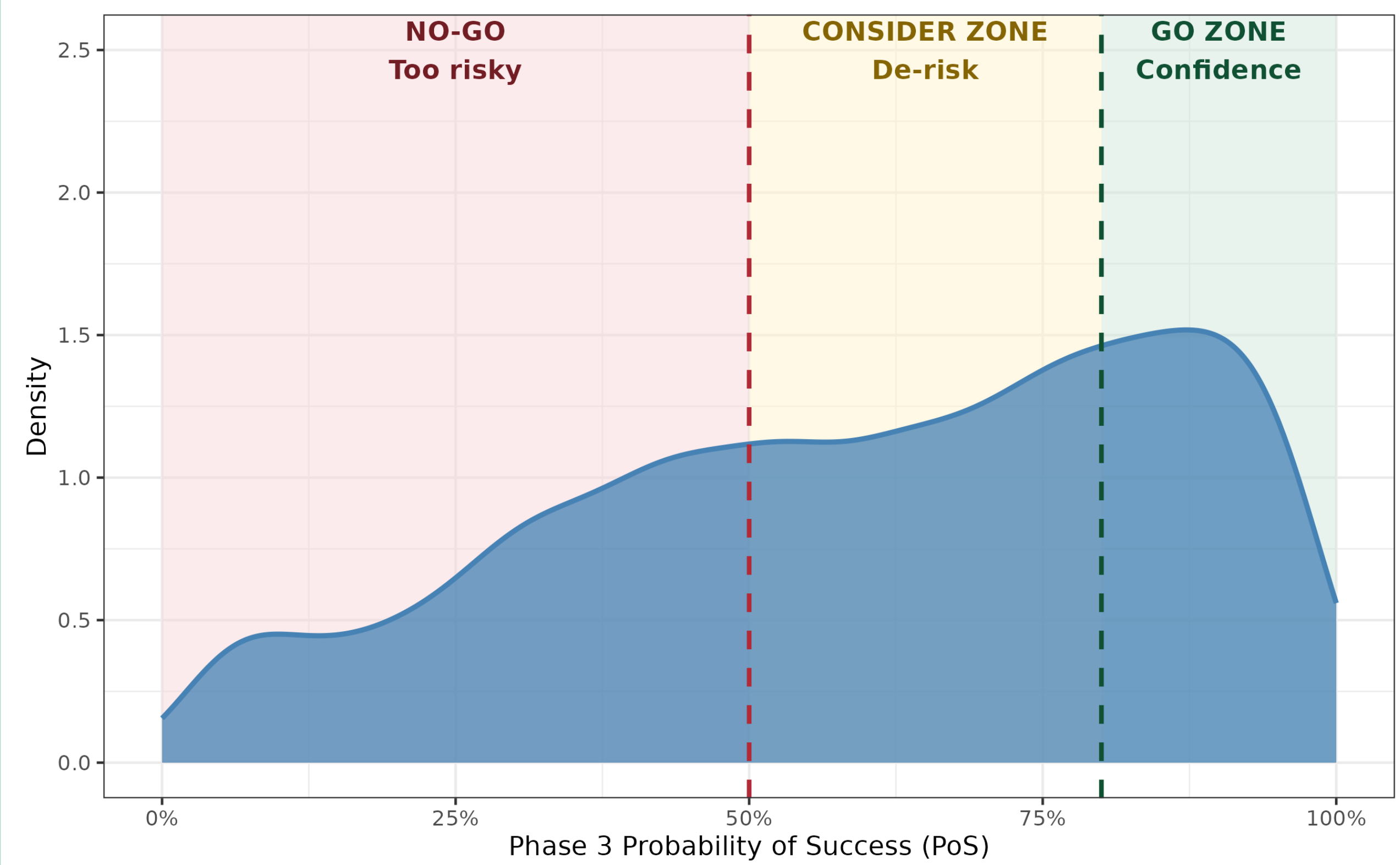
$$S_i = \frac{V_i}{V(Y)} = \frac{V_{X_i}(E_{X_{-i}}[Y | X_i])}{V(Y)} \quad (4)$$

$$T_i = \frac{E_{X_{-i}}(V_{X_i}[Y | X_{-i}])}{V(Y)} = 1 - \frac{V_{X_{-i}}(E_{X_i}[Y | X_{-i}])}{V(Y)} \quad (5)$$

Quantitative Decision Framework: A Go/No-Go decision framework was established by intersecting an organizational risk tolerance threshold ($F(X) = 0.50$) with empirical cumulative distribution functions (eCDF) for key PoS drivers using Monte Carlo Filtering [4]. Minimum Viable Product (MVP) and Target Product Profile (TPP) thresholds were derived from parameter distributions in the "No-Go" (PoS<50%) and "Go" (PoS>80%) decision zones, respectively. These product profile thresholds correspond to parameter values associated with maximum acceptable trial risk ("No-Go" threshold) and a confident Go decision ("Go" threshold). Parameter values between these thresholds warrant consideration of strategic options.

Identifying Drivers of Trial Risk with Global Sensitivity Analysis

Figure 1. Distribution of MIDD CTS probability of success estimates. Probability of success (PoS) estimates are commonly based on drug-agnostic industry benchmarks or internal stakeholder "gut feelings". While industry benchmarks are objective, they neglect drug-specific knowledge accumulated throughout a development program. Internal stakeholders often qualitatively produce PoS estimates, but these estimates are subject to cognitive and motivational biases. MIDD PoS estimates are drug-specific and objective, but model uncertainty, interindividual variability, and trial variability may limit decision confidence [MIDD CTS Estimate: 0.63 (0.12, 0.95)].



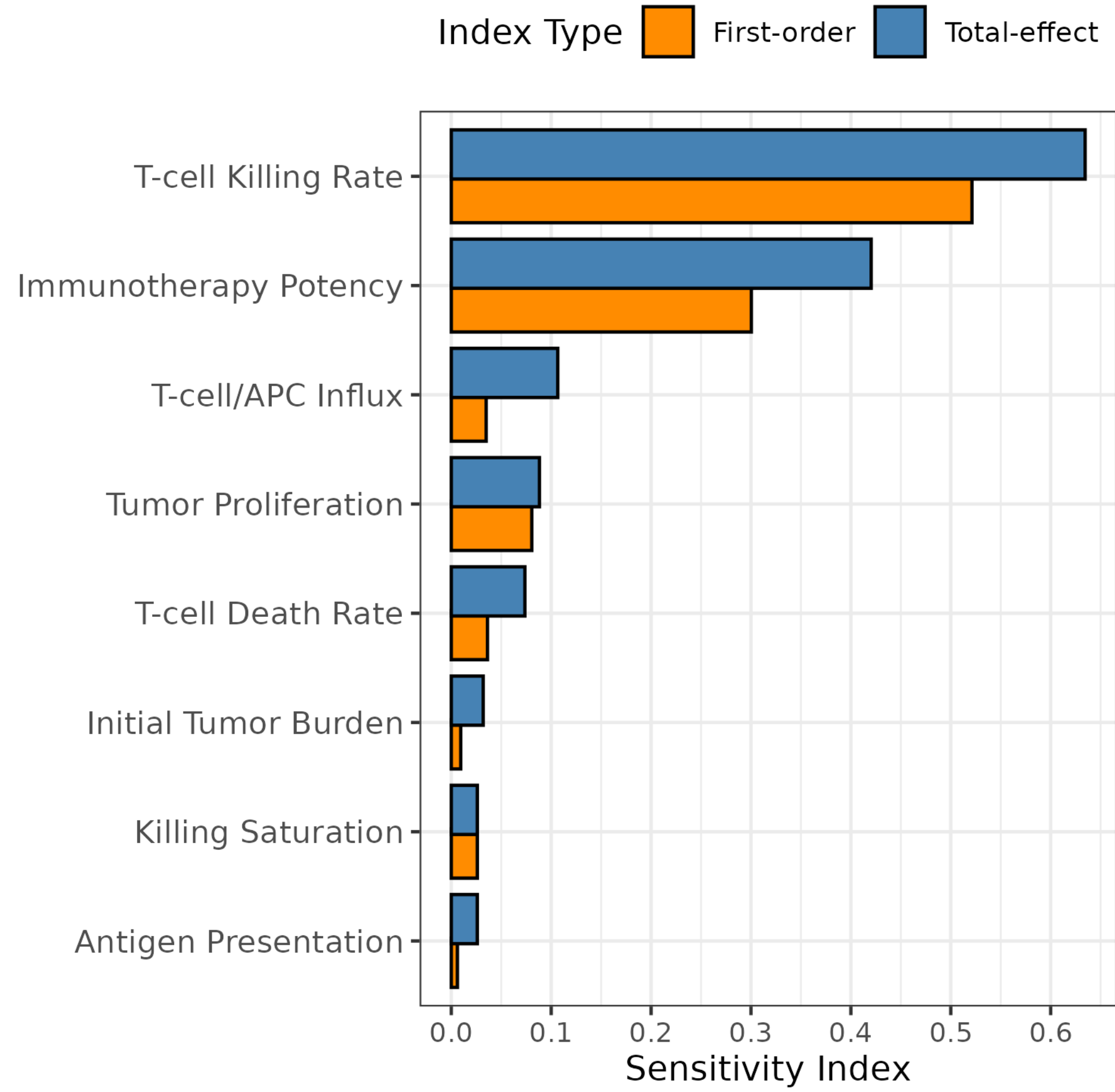
MIDD Application Shift

- From:** What is the predicted probability of success (PoS) and uncertainty level?
- To:** What are the clinical or biological drivers of the PoS? What criteria could support confident Go/No-Go decisions? Can trial risk be mitigated or controlled?

Key Results

- Dominant Risk Drivers:** The Phase 3 trial's PoS is strongly dependent on **T-cell Killing Rate** ($S_i = 0.521$; $T_i = 0.634$) and **Immunotherapy Potency** ($S_i = 0.300$; $T_i = 0.420$). The large S_i indices suggests >80% of the PoS variance is attributable to the values of these parameters. The interaction burden ($T_i - S_i$) suggests a non-linear interplay between drug potency and the patient's immune phenotype.
- Negligible Risk Drivers:** The sensitivity indices for other model parameters suggest the Phase 3 trial's PoS is relatively insensitive to the values and interactions of these parameters. Thus, model and estimation uncertainty for these parameters does not drive operational trial risk; more or deeper research should not be prioritized.

Figure 2. Probability of success sensitivity indices by model parameter. The First-Order index (S_i) describes the sensitivity attributable to the parameter value itself. The Total-Effect Index (T_i) describes the sensitivity attributable to the parameter value and all interactions with other model components.



Quantitative Decision Framework

Figure 3. Probability of success versus parameter value for key drivers of trial risk. The relationship is generally nonlinear for T-cell Killing Rate and linear for Immunotherapy Potency. The blue line represents a LOESS smooth through the data. Green and red horizontal lines denote PoS values of 0.80 and 0.50, respectively.

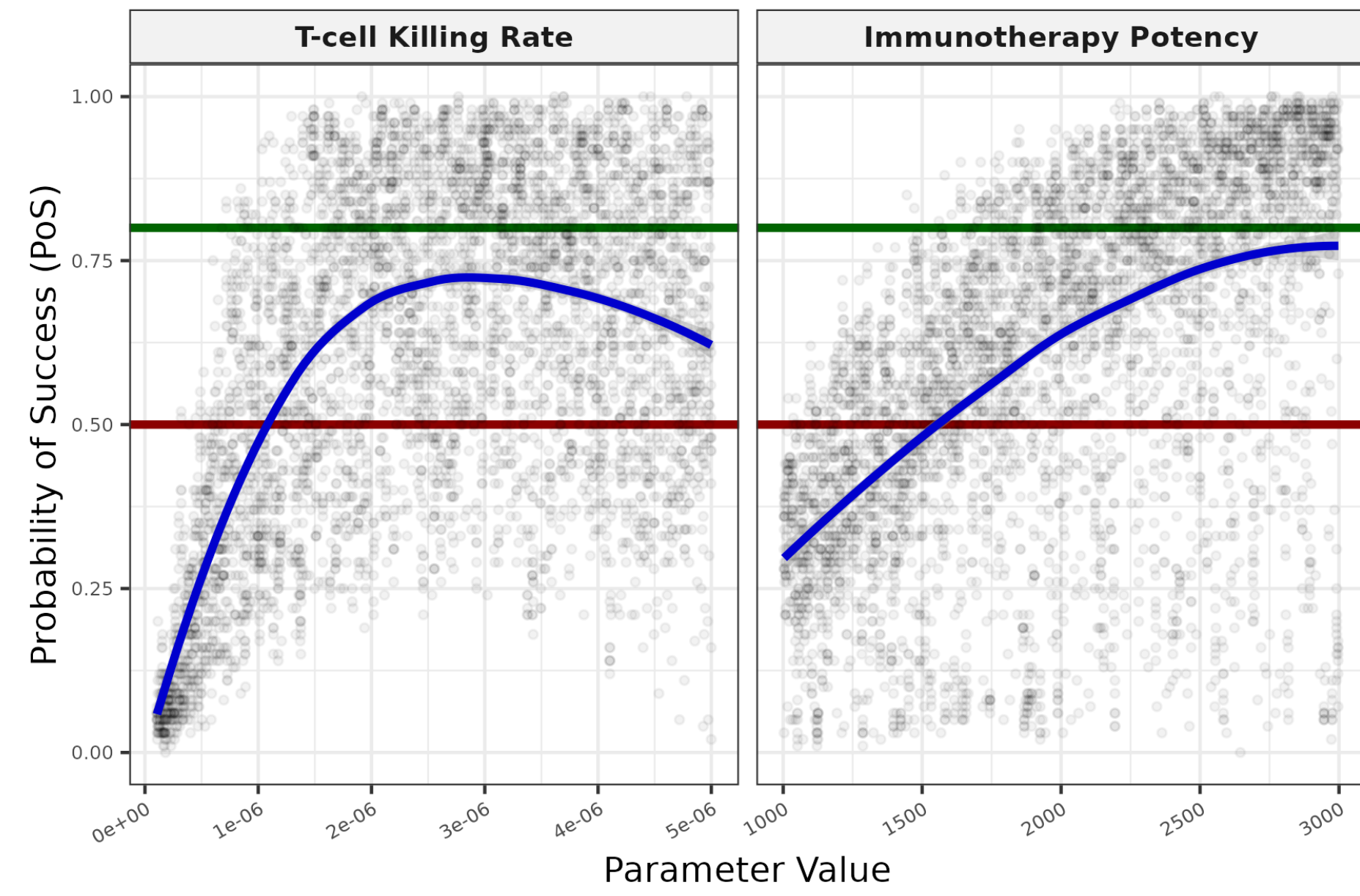


Figure 4. Probability of unacceptable trial risk versus immunotherapy potency. Horizontal dashed lines depict organizational risk tolerance thresholds. The Minimum Viable Product (MVP) threshold is identified at the intersection of the decision probability curve and organizational risk tolerance threshold ($F(X) = 0.50$).

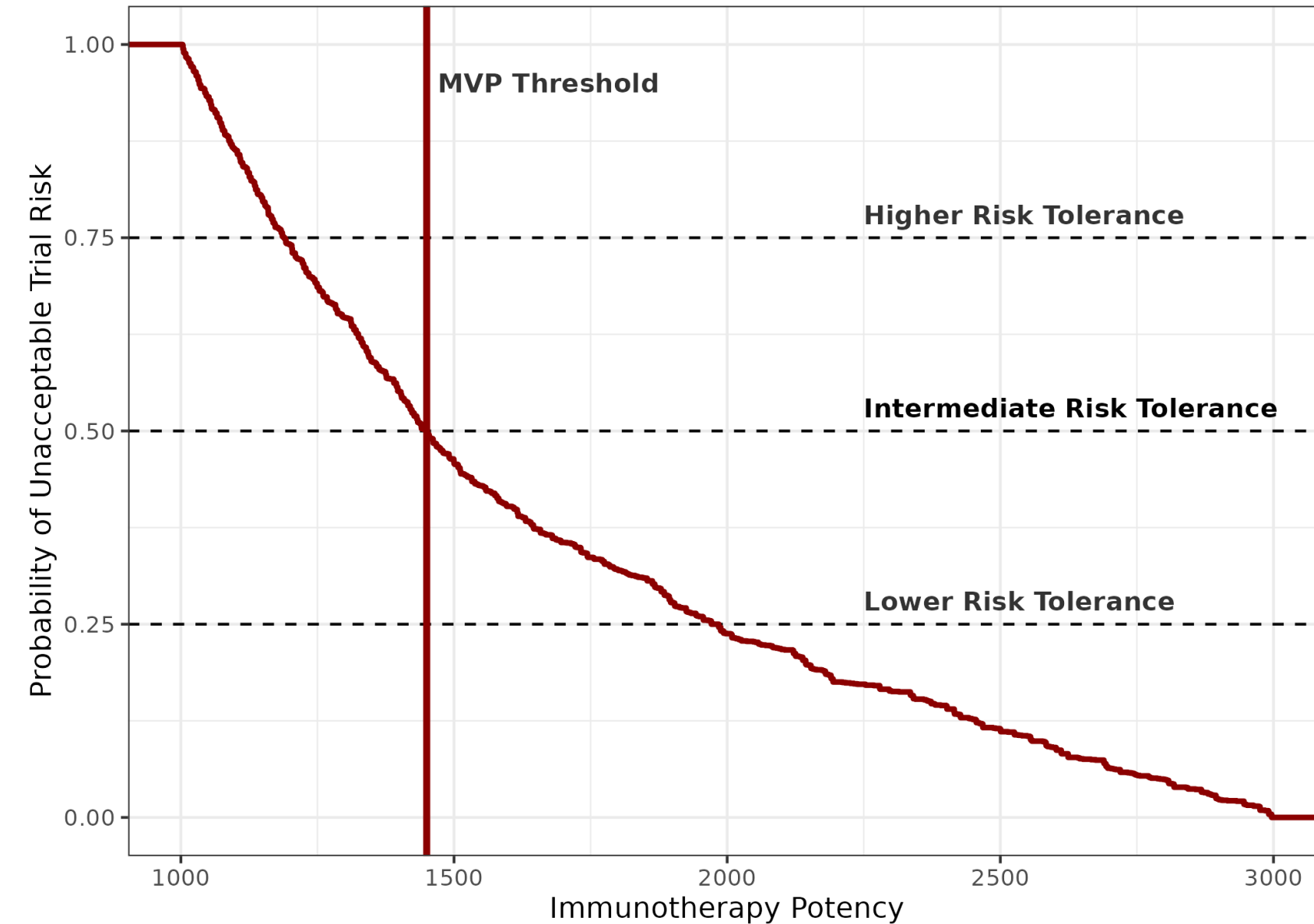
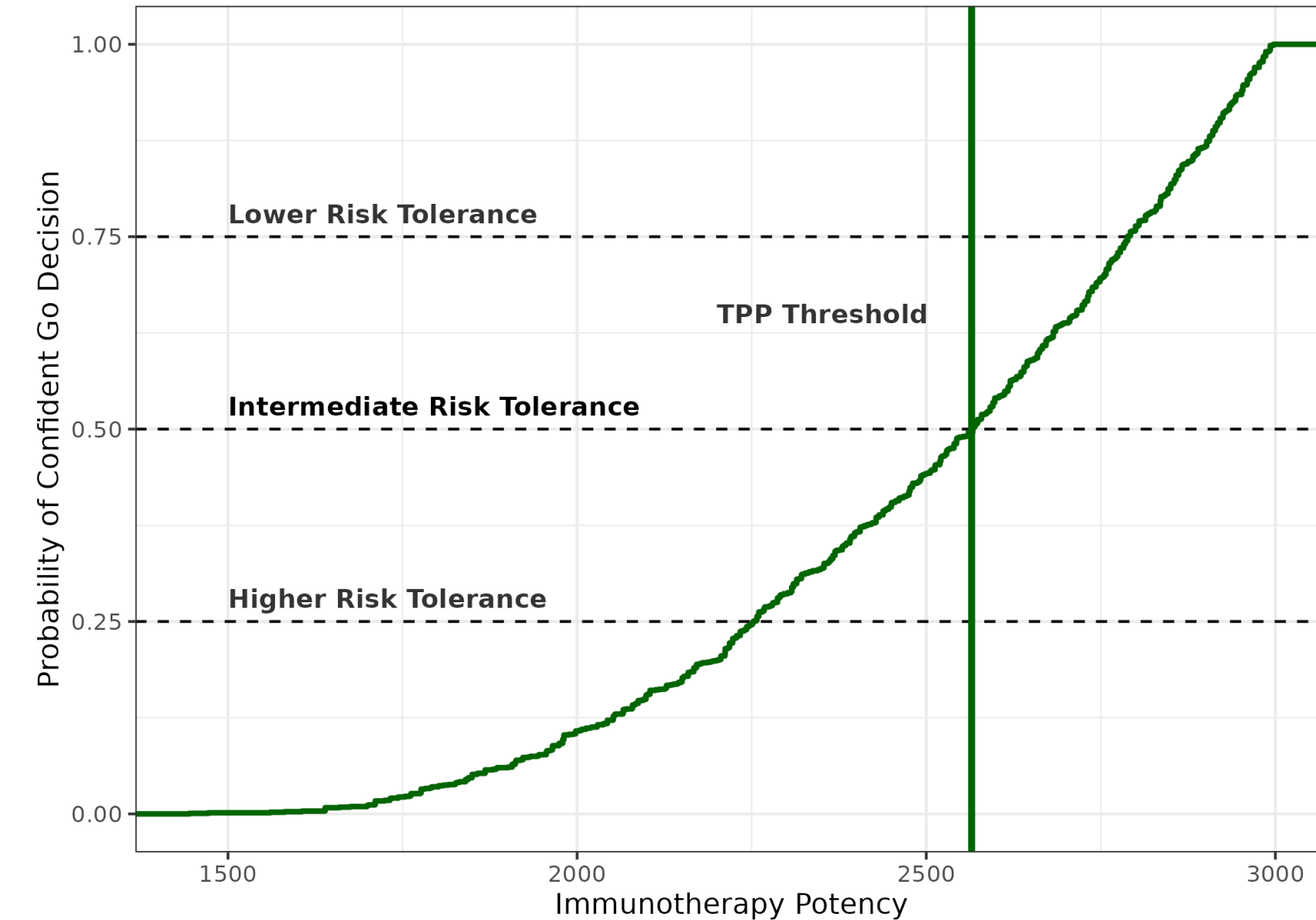


Figure 5. Probability of confident Go decision versus immunotherapy potency. Horizontal dashed lines depict organizational risk tolerance thresholds. The Target Product Profile (TPP) threshold is identified at the intersection of the decision probability curve and organizational risk tolerance threshold ($F(X) = 0.50$).



Strategic Options to De-Risk the Trial

Figure 6. Accept the current risk level of the trial (Base Case). The base case serves as a benchmark for judging the efficacy and cost-effectiveness of risk mitigation strategies. If the strategic options are considered unviable, the trial may be conducted at-risk.

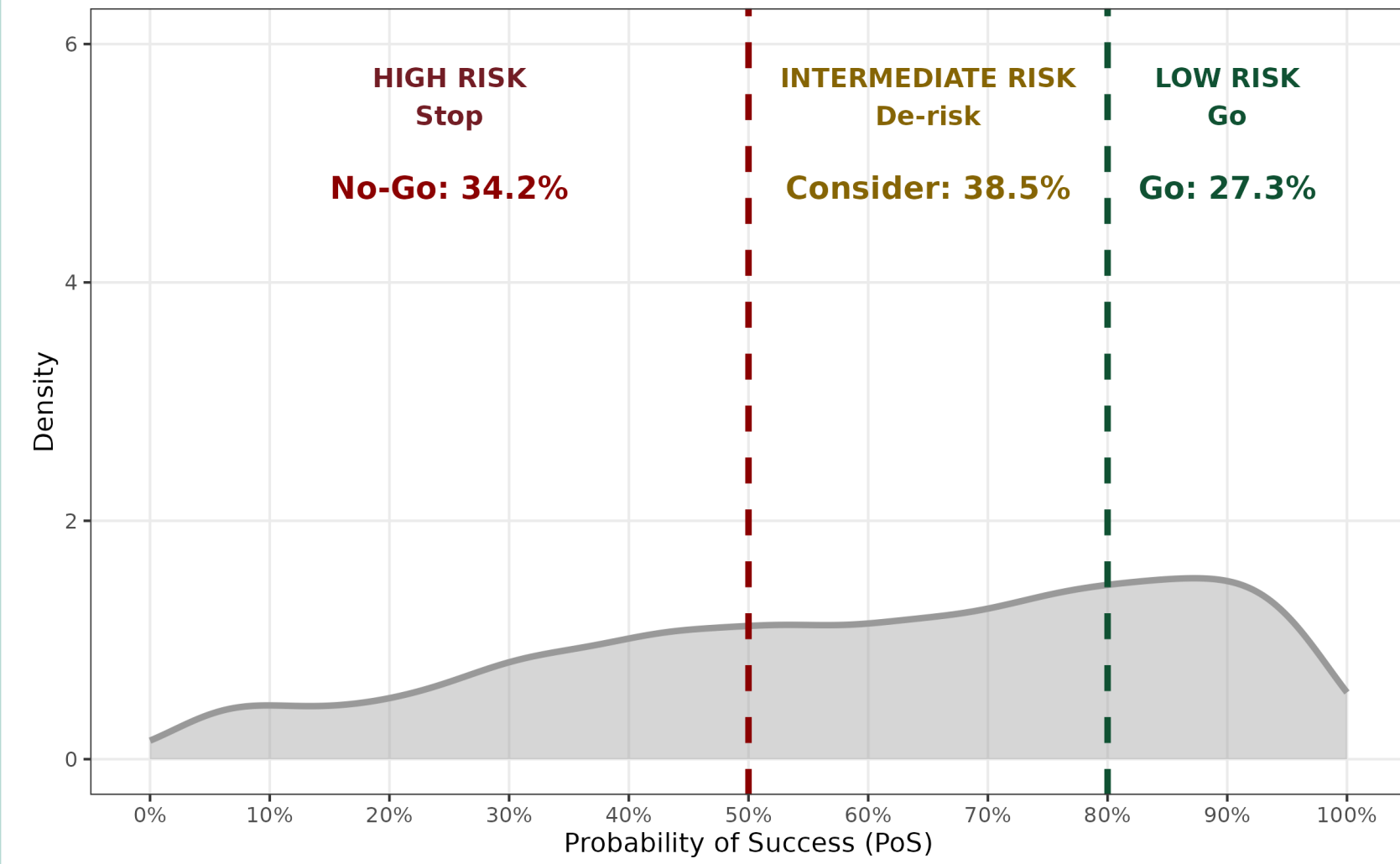


Figure 7. Develop T-cell killing rate assay to enrich trial population (Population Enrichment). Develop T-cell killing rate assay and modify Phase 3 inclusion criteria to enrich trial with subjects who have T-cell killing rate > MVP threshold.

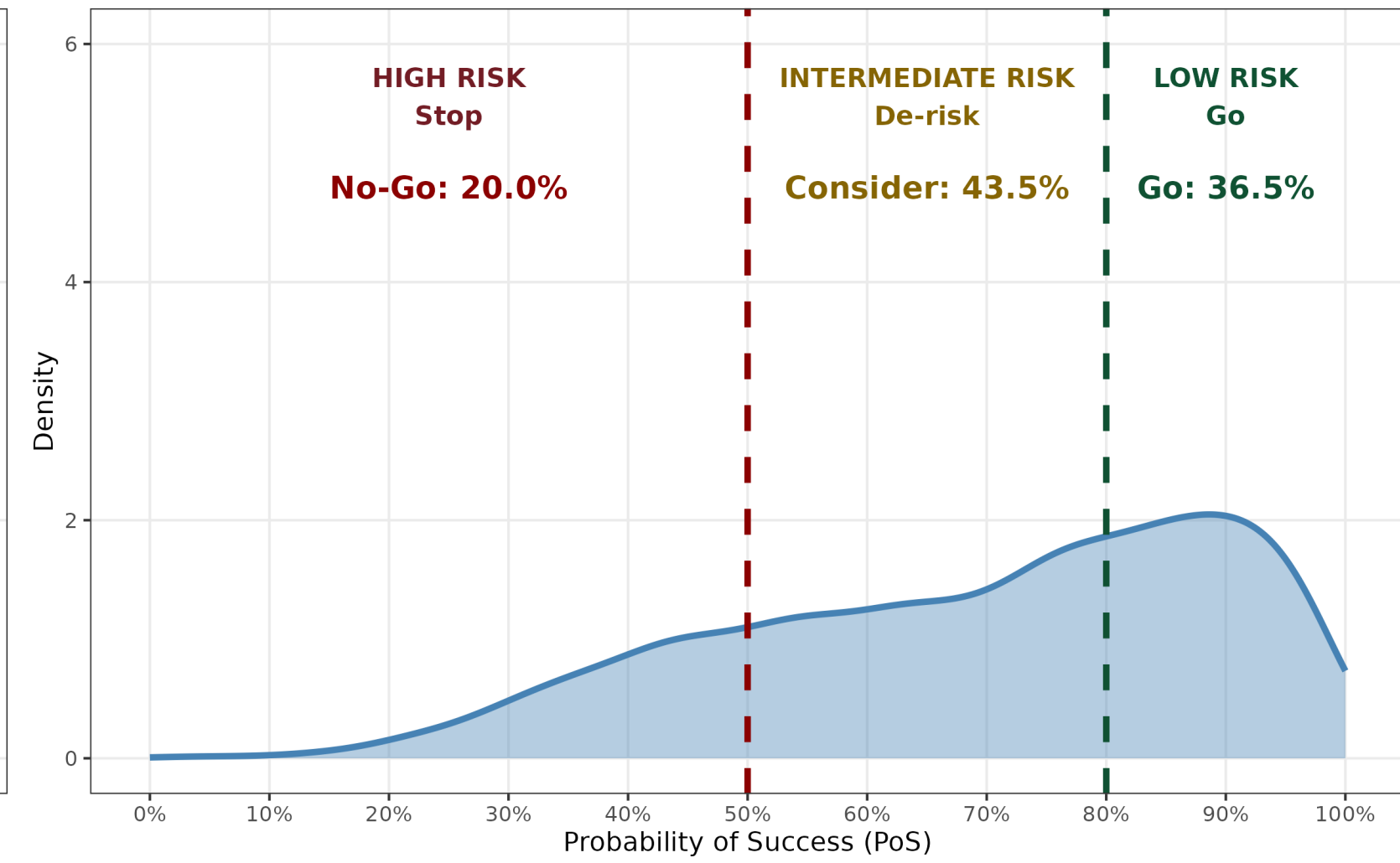


Figure 8. Improve the functional potency of the drug candidate (Potency Optimization). Functional potency may be improved with alternative dosing strategies (e.g., loading doses), combination therapy, alternative chemotherapy backbones, or asset engineering.

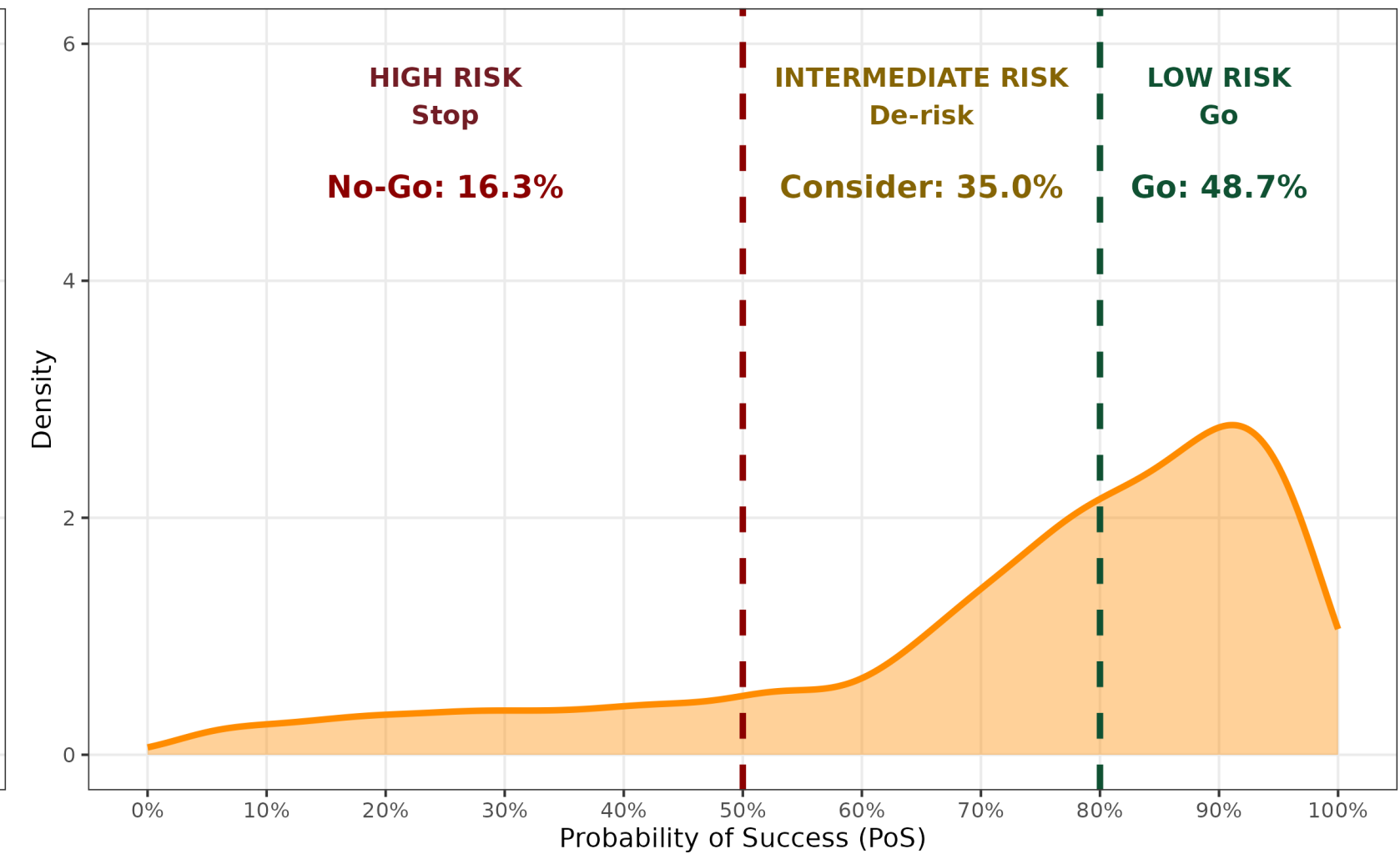


Figure 9. Population enrichment & potency optimization (Optimize Both). For the risk-averse organization, minimizing trial risk may be preferred. Optimizing both the trial population and functional potency is expected to maximize the probability of success.



Conclusions

Use of quantitative modeling and QDFs to inform major decisions is needed to improve R&D productivity. Broad adoption of MIDD models within QDFs could shift MIDD from a supportive role to a key contributor to strategic decision-making.

References

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- [2] 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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- [4] Saltelli, A., Ratto, M., Andres, T., et al. *Global Sensitivity Analysis: The Primer* (John Wiley & Sons, Chichester, UK, 2008.)

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