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Appendix and Supplemental material not intended for publication-Round 2

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Please make the uploaded Appendix publicly available to readers.

I thank the Editor and the anonymous Referee for their valuable comments, which have helped improve this paper. I also thank peers in the field for discussions that inspired the comparative focus of this work. The usual disclaimers apply.
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Appendix: Supplementary Material

Appendix A: Phase transition example (detailed calculations)

This section provides the detailed calculations underlying the phase convergence analysis in Section 3.1. The transition probabilities are taken from Hay et al. (2014, Figure 1): $p_{12} = 0.64$ (Phase 1 to Phase 2), $p_{23} = 0.32$ (Phase 2 to Phase 3), and $p_{3A} = 0.49$ (Phase 3 to Approval).[1]

The probabilities of advancing from Phase i to approval, p_{iA}, are:

$$p_{1A} = p_{12} \cdot p_{23} \cdot p_{3A} = 0.64 \cdot 0.32 \cdot 0.49 \approx 0.1, \tag{1}$$

$$p_{2A} = p_{23} \cdot p_{3A} = 0.32 \cdot 0.49 \approx 0.16, \tag{2}$$

$$p_{3A} = 0.49. \tag{3}$$

The corresponding numbers of trials are:

$$\tilde{N}_i = \frac{1}{p_{iA}}, \qquad \hat{N}_i = \frac{\ln(1-\alpha)}{\ln(1-p_{iA})}. \tag{4}$$

Table I presents the number of trials needed at each phase under both approaches.

Table I: Number of trials needed for “at least one success” and “one success in expectation”

Phase	**Phase i to Approval probabilities**	$\tilde{N}_i = \frac{1}{p_{iA}}$	$\hat{N}_i = \frac{\ln(1-\alpha)}{\ln(1-p_{iA})}$		
			$\alpha = 0.79$	$\alpha = 0.89$	$\alpha = 0.99$
$i = 1$	$p_{1A} \approx 0.1$	≈ 9.96	≈ 14.76	≈ 20.87	≈ 43.55
$i = 2$	$p_{2A} \approx 0.16$	≈ 6.38	≈ 9.15	≈ 12.94	≈ 27.00
$i = 3$	$p_{3A} = 0.49$	≈ 2.04	≈ 2.32	≈ 3.28	≈ 6.84

Figure A1 illustrates the ratio $\hat{N}_i/\tilde{N}_i$ across phases for different confidence levels, demonstrating the narrowing gap as programs advance.

[1] The model aggregates the final regulatory stages for analytical tractability. The probability p_{3A} from Phase 3 to approval is a composite metric that incorporates the success of Phase 3 trials, NDA submission, and regulatory review, consistent with the aggregated “Phase 3 to Approval” probabilities used in related studies like Wong et al. (2019).

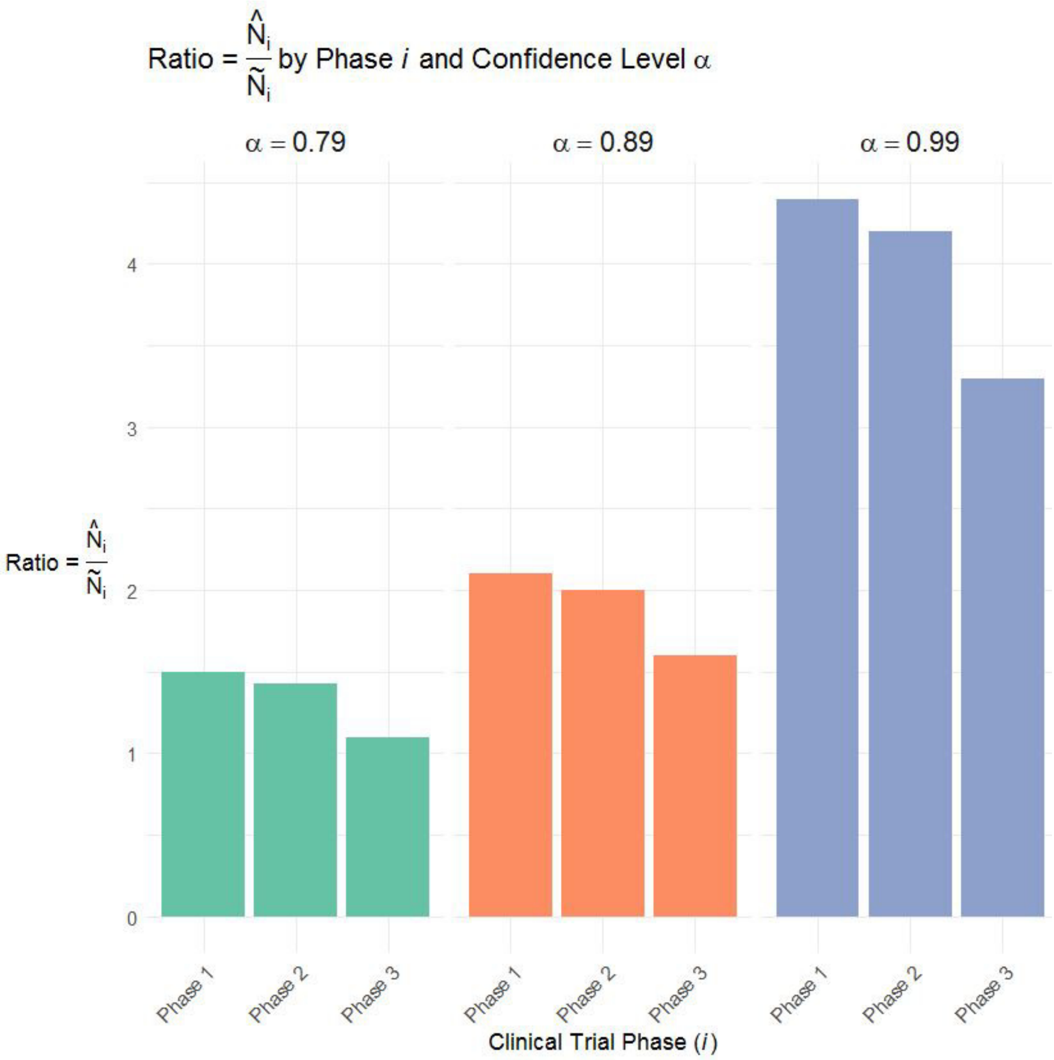

Figure A1: Ratio of the numbers of clinical trials by phase and confidence levels

Appendix B: Integer constraint analysis

This section examines how the continuous approximation used in the main text affects the results when the integer constraint on the number of trials is taken into account. Figures A2 and A3 replicate the analysis from Section 3 with the integer constraint imposed. While the continuous approximation yields smooth, monotonic functions, the integer-constrained versions exhibit stepwise, non-monotonic patterns. However, the general trends—decreasing for $\hat{N}/\tilde{N}$ and increasing for $\hat{N}/(\tilde{N}-1)$—remain unchanged, confirming that the continuous approximation does not alter the qualitative conclusions.

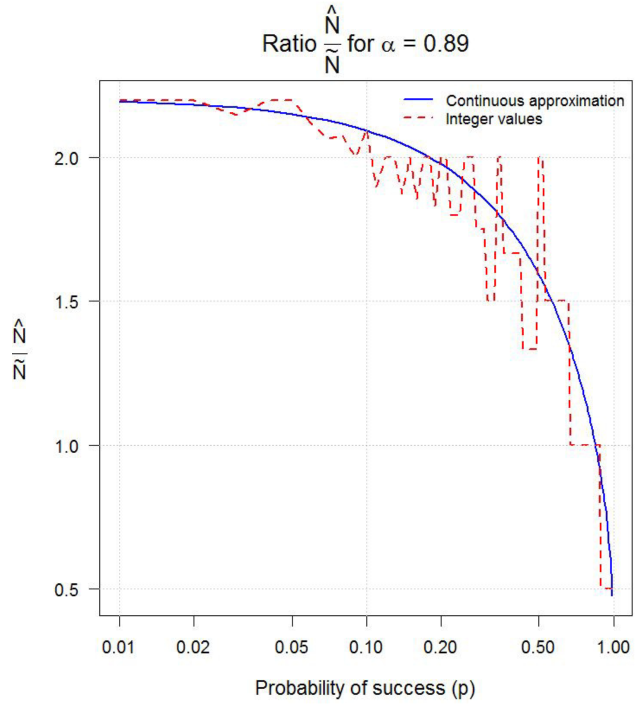

Figure B1: Ratio of the numbers of clinical trials with integer constraint ($\alpha = 0.89$)

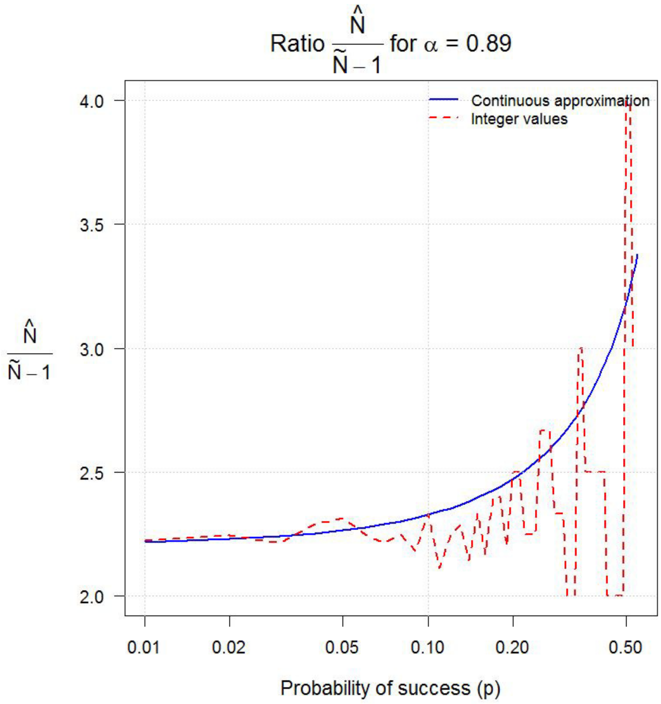

Figure B2: Ratio $\hat{N}/(\tilde{N}-1)$ with integer constraint ($\alpha = 0.89$)

Appendix C: Portfolio deficit analysis by phase

Figure A4 illustrates the ratio $\frac{\hat{N}_i}{\tilde{N}_i - 1}$ for the $y = -1$ case (portfolio short by one program) across different phases, using the same transition probabilities as in Section A. This figure complements Figure 2 in the main text by showing how the widening gap manifests at each specific phase for different confidence levels.

For Phase 1, the ratio $\frac{\hat{N}_1}{\tilde{N}_1-1} = \frac{\ln(1-\alpha)}{(\frac{1}{p_{1A}}-1)\ln(1-p_{1A})}$ is calculated rather than $\frac{\hat{N}_1}{\tilde{N}_1} = \frac{\ln(1-\alpha)}{\frac{1}{p_{1A}}\ln(1-p_{1A})}$. The latter expression would imply that the number of programs at Phase 1 corresponds to the one that leads to exactly one approval on average. From Table I, the ratio $\frac{\hat{N}_i}{\tilde{N}_i}$ ranges from approximately 1.48 (for $\alpha = 0.79$) to 4.37 (for $\alpha = 0.99$).

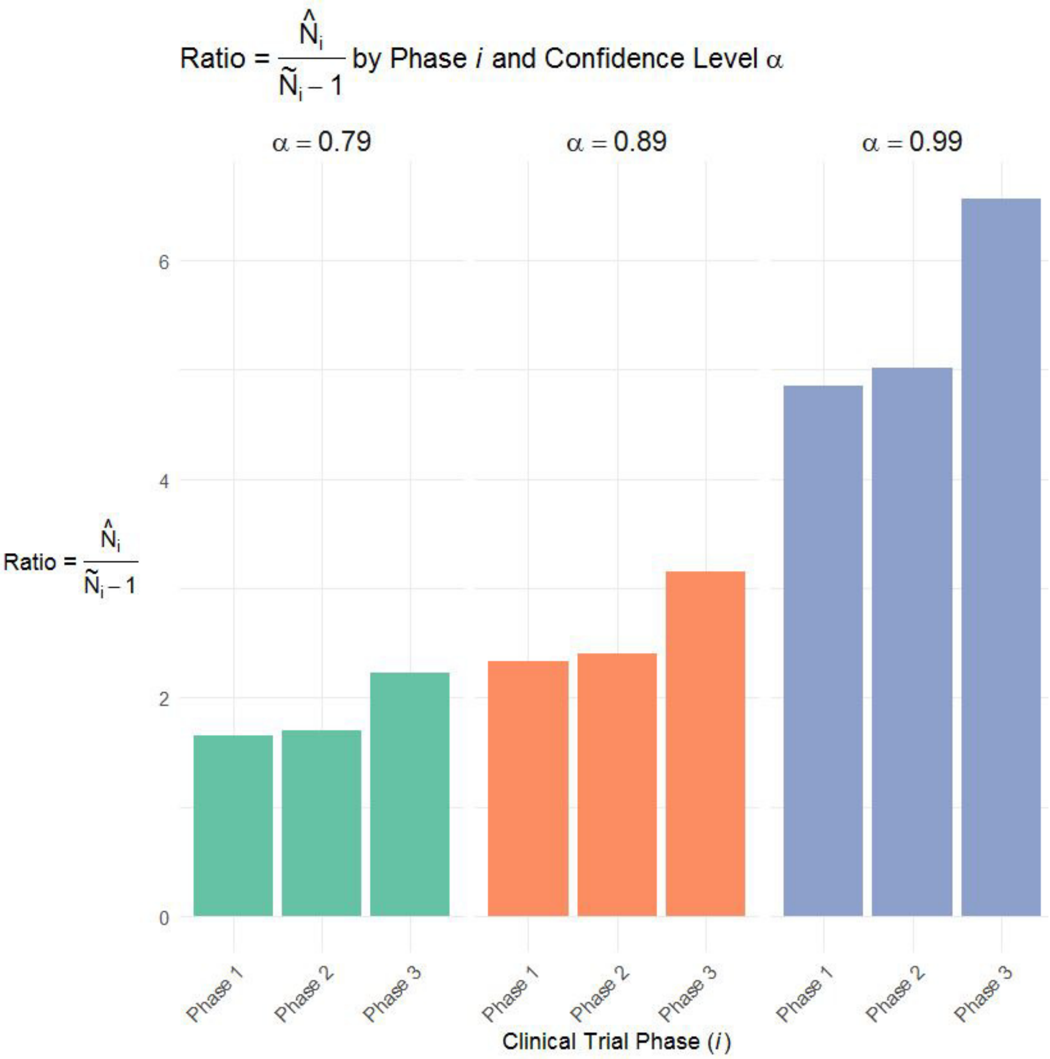

Figure C1: Ratio $\hat{N}_i/(\tilde{N}_i - 1)$ by phase for $y = -1$

Note: For $y = -1$, the ratio is $\frac{\hat{N}_i}{\tilde{N}_i-1} = \frac{\ln(1-\alpha)}{\left(\frac{1}{p_{iA}}-1\right)\ln(1-p_{iA})}$, where p_{iA} is the probability that a program entering Phase i will be approved. Phase-to-phase transition probabilities are $p_{12} = 0.64$, $p_{23} = 0.32$, and $p_{3A} = 0.49$, as used in Figure A1. For Phase 1, the ratio $\frac{\hat{N}_1}{\tilde{N}_1-1}$ is calculated rather than $\frac{\hat{N}_1}{\tilde{N}_1}$. The latter expression would imply that the number of programs at Phase 1 corresponds exactly to the one that leads to one approval on average. From Table I and Figure A1, the ratio $\frac{\hat{N}_i}{\tilde{N}_i}$ ranges from approximately 1.48 (for $\alpha = 0.79$) to 4.37 (for $\alpha = 0.99$).

Appendix D: Compounding portfolio risk analysis

This section provides the detailed probability calculations for the error compounding analysis summarized in Section 3. The number of programs entering Phase $i = 2, 3,$

denoted X_i, follows a Binomial distribution:

$$X_i \sim \mathrm{Bin}\Big(n,\, p = p_{1i}\Big), \tag{5}$$

where p_{1i} is the transition probability from Phase 1 to Phase i, and n is the initial Phase 1 portfolio size determined by the strategic target (expected-value or confidence-level). The probability that X_i falls below a required threshold k is:

$$P(X_i < k) = \sum_{x=0}^{\lfloor k \rfloor} \binom{n}{x} p_{1i}^x (1 - p_{1i})^{n-x}. \tag{6}$$

For the expected-value target, $n = \tilde{N}_1 = \lceil 1/p_{1A} \rceil$, where $p_{1A} = p_{12} \cdot p_{23} \cdot p_{3A} = 0.64 \cdot 0.32 \cdot 0.49 \approx 0.1$. Thus, $\tilde{N}_1 = \lceil 10 \rceil = 10$.

For the confidence-level target with $\alpha = 0.89$, $\hat{N}_1 = \lceil \ln(1-0.89)/\ln(1-0.1) \rceil = \lceil \ln(0.11)/\ln(0.9) \rceil = \lceil (-2.207)/(-0.105) \rceil = \lceil 21.02 \rceil = 21$.

The required thresholds for Phase i are:

- For the expected-value target: $\tilde{N}_2 = 1/p_{2A} = 1/0.16 = 6.25$, $\tilde{N}_3 = 1/p_{3A} = 1/0.49 \approx 2.04$
- For the confidence-level target: $\hat{N}_2 = \ln(1-0.89)/\ln(1-0.16) = \ln(0.11)/\ln(0.84) \approx (-2.207)/(-0.174) \approx 12.68$, $\hat{N}_3 = \ln(1-0.89)/\ln(1-0.49) = \ln(0.11)/\ln(0.51) \approx (-2.207)/(-0.673) \approx 3.28$

Table II presents the full set of probabilities.

Table II: Complete deficit probability calculations

Phase	p_{1i}	p_{iA}	$P(X_i < \tilde{N}_i \mid \tilde{N}_1 = 10)$	$P(X_i < \hat{N}_i \mid \hat{N}_1 = 21)$		
				$\alpha = 0.79$	$\alpha = 0.89$	$\alpha = 0.99$
$i = 2$	0.64	0.16	0.513	0.468	0.329	0.412
$i = 3$	0.20	0.49	0.678	0.398	0.370	0.195

These calculations confirm that the expected-value target carries a substantial risk of downstream shortfall, often exceeding 50%, while the confidence-level target is more robust.

References

[1] Hay, M., Thomas, D. W., Craighead, J. L., Economides, C., & Rosenthal, J. (2014). Clinical development success rates for investigational drugs. *Nature biotechnology*, 32(1), 40-51.

[2] Wong, C. H., Siah, K. W., & Lo, A. W. (2019). Estimation of clinical trial success rates and related parameters. *Biostatistics*, 20(2), 273-286.