Decision-Making Criteria and Methods for Initiating Late-Stage Clinical Trials in Drug Development from a Multi-Stakeholder Perspective: A Scoping Review

Ce Jiang[1,‡], Céline Beji[2,‡], Sonia Zebachi[1,‡], Ghinwa Hayek[1,‡], Aysun Cetinyurek-Yavuz[3,‡], Muhammad Bergas N. Fayyad[3,‡], Laura Rodwell[3,‡], Kit C.B. Roes[3,‡], Billy Amzal[1,‡], Christoph Gerlinger[4], Raphaël Porcher[2,‡], Julien Tanniou[1,‡]

[1] Quinten Health, Paris, France, [2] Paris Cité University, Paris, France , [3] Radboud University Medical Center, Nijmegen, Netherlands, [4] Bayer AG, Statistics & Data Insights
[‡] More-EUROPA - More Effectively Using Registries to suppOrt PAtient-centered Regulatory and HTA decision-making – Project Consortium member

Introduction

- Drug development is a complex, high-risk, and costly process, particularly at the Phase II-III transition.
- "Go/No-Go" decisions at this stage are critical, relying on clinical efficacy and financial metrics.
- Success in late-stage development depends on a broader set of criteria, reflecting the interests of diverse stakeholders such as regulators, HTA bodies, payers, and patients.
- While quantitative methods like probability of success (PoS) are increasingly adopted in industry to inform these decisions, most focus narrowly on efficacy, overlooking the priorities of multiple stakeholders.
- **Objective: A scoping review to examine existing studies addressing go/no-go decision-making in drug development at the phase II–III transition from a multi-stakeholder perspective with expanded definitions of success, focusing on PoS beyond efficacy[1].**
- **This review complements a companion paper focused on efficacy-based PoS[2]. Both studies aim to provide a foundation for a more balanced, data-driven, and stakeholder-aligned approach for late-stage trial decision-making.**

Methods

- **Search Strategy**: English articles from PubMed (Jan 2010–Mar 2024) following the PRISMA-ScR framework, with terms related to drug development, decision-making, stakeholder involvement, and PoS.
- Data extraction focused on:
  - Definition of "success".
  - Stakeholders considered.
  - Decision criteria (e.g., efficacy, safety, development cost, etc.).
  - Methodological approach (e.g., Frequentist/Bayesian approach, RCT/RWD use, decision level: trial/program/portfolio).
- Two aspects were emphasized to support a comprehensive and stakeholder-aligned approach to decision-making in late-stage drug development:
  - **Multi-stakeholder perspectives in decision frameworks**: Capture drug developers, regulators, HTA bodies, payers, ethics committees, patients, and healthcare professionals' perspectives reflecting their distinct priorities (Table 1).
  - **Expanded definition of success**: Exploration of how the definition of success (beyond efficacy only) is expanded in practice given that traditional go/no-go decisions have typically focused on technical success.

Table 1 : Stakeholders and their key priorities

Stakeholder	Key Priorities
Sponsors	R&D efficiency, portfolio alignment, competitive differentiation, time-to-market
Regulators	Safety, efficacy, risk/benefit balance, regulatory standards
HTA Bodies	Clinical effectiveness in practice, cost-effectiveness (value for money)
Payers	Economic value, budget impact, pricing, reimbursement potential
Patients	Treatment outcomes (survival, quality of life), and accessibility
Ethics Committees	Patient protection, risk/benefit balance, informed consent, trial justification
Healthcare Professionals	Clinical utility, ease of use, guideline alignment, adoption likelihood

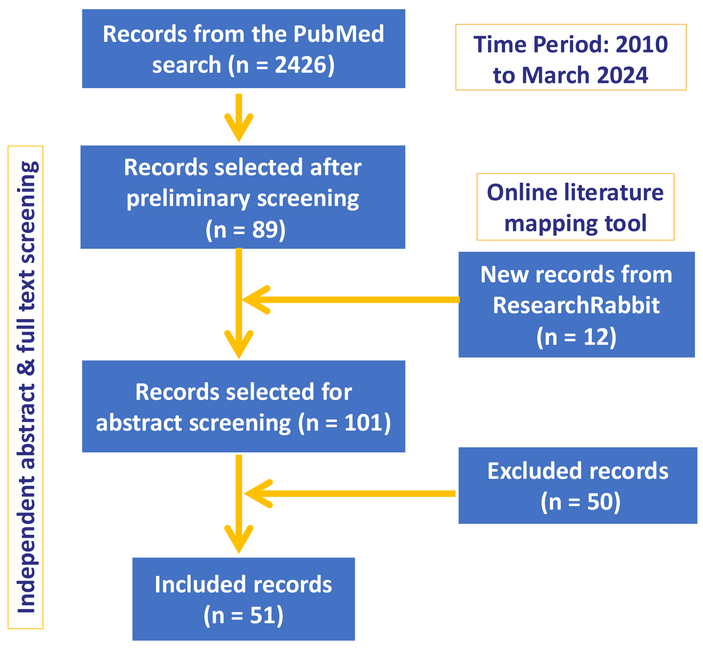


Figure 1: PRISMA diagram

Results

A final selection of 51 (Figure 1) articles on go/no-go decision-making frameworks was grouped into five categories. Terminology and frameworks are heterogeneous, with little consensus on criteria selection or weighting. Most studies propose bespoke models, highlighting a lack of generalisable guidance.

1. **Central theme: The use of PoS-based methods**
   - The definition of "success" varies and extends beyond statistical significance to include regulatory approval, HTA/payer access, and financial viability, aligning with a more integrated PoS concept (Figure 2).
   - Success objectives of included studies are summarised in Figure 3.
2. **Trial design optimisation**
   - Focus on optimising parameters (e.g., sample size, decision thresholds) to balance decision quality with development cost. Some include adaptive features (e.g., interim analyses) or use external data (RWD, expert input).
3. **Utility-based approaches**
   - Integrate development costs, expected benefit, and program risks (via PoS), allowing optimisation of trial design and decision rules and comparison of strategies.
4. **Financial metrics**
   - Focus on economic metrics like expected Net Present Value, Return On Investment, and benefit-cost ratio to support go/no-go and portfolio-level decisions under budget constraints.
   - These sponsor-driven approaches are often proprietary with limited transparency.
5. **Other approaches**
   - Emerging methods such as machine learning based predictions, patient preference studies, and multi-criteria decision analysis to inform benefit-risk or access decisions.
   - These approaches remain early-stage but reflect a growing interest in predictive, data-driven, and patient-oriented decision-making.

Figure2 : Probability of Success with expanded definition of success

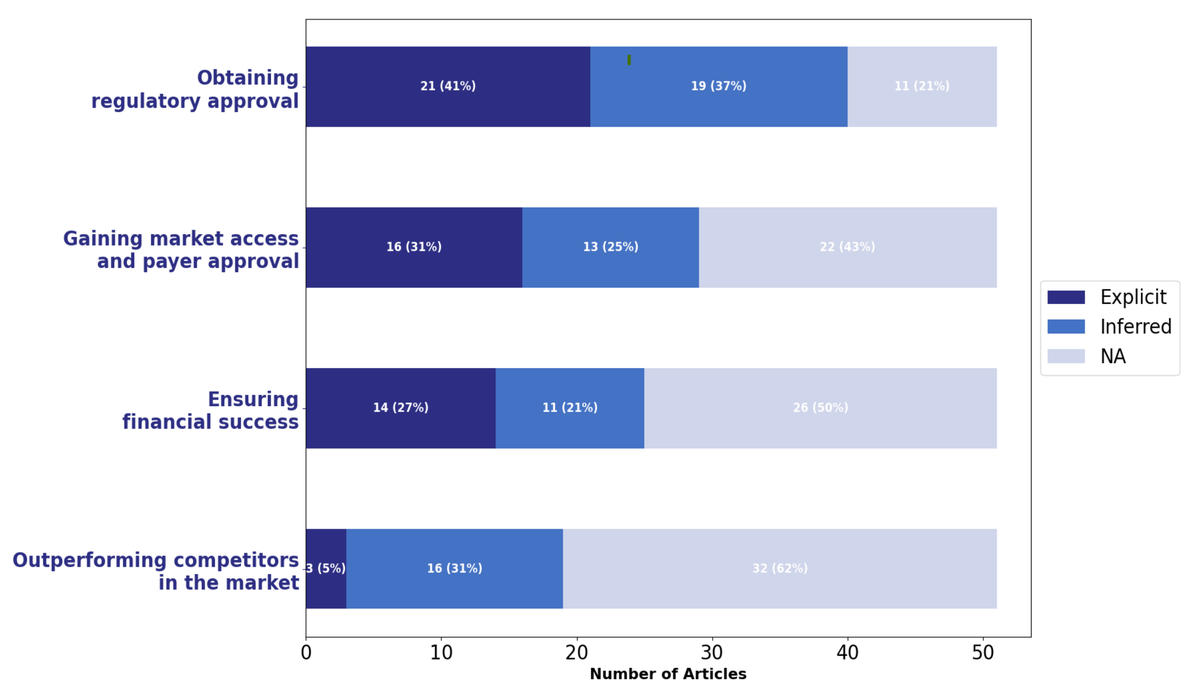
PoS (Traditional): The probability a drug will achieve a statistically significant efficacy in Phase III (technical success).
If we focus only on efficacy and let **Θ** be the true unknown treatment effect:
Power = P(Successful trial |**Θ** = Θ) -> PoS = ∫P(Successful trial|Θ) x Prior(Θ|data) d**Θ**

Definition of "success" could be broadened

Achieving Phase III efficacy and safety goals (technical success)	Obtaining regulatory approval (regulatory success)	Gaining market access and reimbursement (HTA/payer success)	Achieving financial success (meeting ROI or profit expectation)	Outperforming competitors in the market (commercial success)

PoS of what? "success" = multi-criteria.
PoS calculation with hybrid approaches (frequentist + Bayesian) and/or Bayesian approaches

Figure3 : Types of Probability of Success considered in the Literature



Conclusion

- Most published frameworks for Phase II-III transition are developed from the sponsor's perspective, focusing on statistical and financial metrics. However, the limited inclusion of HTA/payer and patient perspectives may not align with real-world success factors.
- Despite discussions on real-world data to refine success probabilities, most decision models rely primarily on clinical trial data and simulations.
- To strengthen Phase II–III go/no-go decision-making, it is essential to broaden success criteria early by incorporating a multistakeholder perspective, make use of diverse data sources, apply structured decision-making frameworks and treat decisions iteratively with a dynamic approach.

References: 1.Jiang, C., Beji, C., Zebachi, S., Hayek, G.Y., Cetinyurek-Yavuz, A., Fayyad, M.B.N., Rodwell, L., Roes, K.C.B., Amzal, B., Gerlinger, C., Porcher, R. and Tanniou, J. (2025), Decision-Making Criteria and Methods for Initiating Late-Stage Clinical Trials in Drug Development From a Multi-Stakeholder Perspective: A Scoping Review. Clin Pharmacol Ther, 117: 978-988. https://doi.org/10.1002/cpt.3566
2.Cetinyurek Yavuz, A., Fayyad, M.B.N., Jiang, C., Brion Bouvier, F., Beji, C., Zebachi, S., Hayek, G.Y., Amzal, B., Porcher, R., Tanniou, J., Roes, K. and Rodwell, L. (2025), On the Concepts, Methods, and Use of "Probability of Success" for Drug Development Decision-Making: A Scoping Review. Clin Pharmacol Ther, 117: 967-977. https://doi.org/10.1002/cpt.3571

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more-europa@umcg.nl
Website
LinkedIn