Decision-Making Criteria and Methods for Initiating Late-Stage Clinical Trials A Multi-Stakeholder Perspective

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Background

- Drug development involves multiple development phases
- Each phase serves as a critical step for Go/No-Go decisions
- Transition from Phase II to Phase III is particularly challenging
- Pharma has experienced rising costs and persistently high attrition rates

Multi-Stakeholder Context

Historically, Go/No-Go decisions have been sponsor-centric, relying on internal criteria like Phase II efficacy (p-values, effect sizes) and financial projections (e.g. net present value)

While the sponsor ultimately decides to proceed or terminate a program, they must anticipate the requirements of regulators, HTA bodies, payers, patients, ethics committees, etc., for a robust decision

These frameworks could potentially overlook external perspectives. Factors like regulatory acceptability, market access conditions, patient preferences, etc., may not be explicitly included

Multi-Stakeholder Perspectives

Stakeholders and their priorities

- Drug Manufacturers: R&D investment efficiency, alignment with portfolio strategy, competitive differentiation, time-to-market
- Regulators: Safety & efficacy meeting regulatory standards (risk/benefit)
- HTA: 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 integrity, trial justification
- Healthcare Professionals: Clinical utility, ease of use, alignment with treatment guidelines, likelihood of adoption in practice

Challenges

- Limited alignment between stakeholder priorities and decision criteria
- Potential conflicts in defining "success" across stakeholders

Probability of Success (PoS)

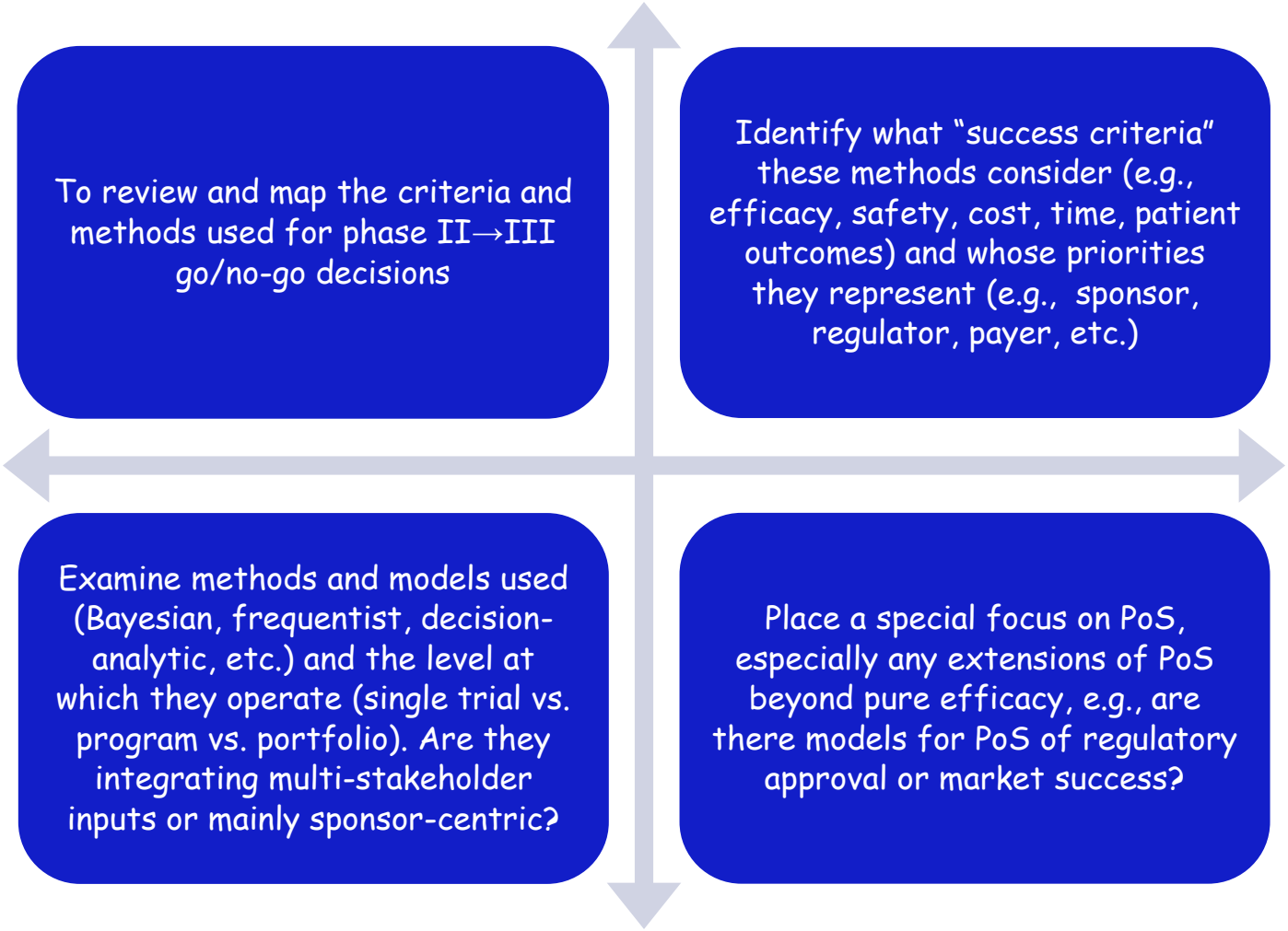
PoS (Traditional): The probability a drug will achieve statistically significant efficacy in Phase III (technical success). Historically, companies used PoS ~ chance of a positive Phase III trial result

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 expectations)	Outperforming competitors in the market (commercial success)

PoS of what? "success" = multi-criteria. Success can mean different endpoints – regulatory approval, market uptake, etc. This broader view requires incorporating multiple criteria and stakeholder priorities

Objective of the Scoping Review



Search Strategy & Selection

Literature Search	Keywords	Excluded	Included
PubMed (2010 – Mar 2024) focusing on late-stage Go/No-Go decision methods	Covering "go/no-go decision", "Phase II-III transition", "Probability of Success", etc.	Papers focusing only on Phase III efficacy PoS (those are covered by a separate companion review)	Papers that propose or evaluate quantitative criteria or models to inform Phase III Go/No-Go – especially those going beyond pure efficacy or incorporating broader success factors

Data Extraction & Synthesis

Data Extraction

- Decision criteria considered (e.g., efficacy, effectiveness, safety, development cost, financial benefit, time, patient involvement, etc.)
- Stakeholder perspective (whose priorities? sponsor, regulator, payer, patient, etc.)
- Data input used (e.g., RCT results, expert elicitation, real-world data, etc.)
- Methods/models applied (Bayesian approaches, decision-analytic models, machine learning, etc.)
- Level of decision (trial(s), program, or portfolio level) and any trial design aspects

Grouped into five categories based on methodological focus

- PoS-based methods
- Trial design optimisation
- Utility-based approaches (combining multiple factors into one decision metric)
- Financial metrics (economic value and investment return focused)
- Other approaches (e.g. ML-based predictions or decision-process frameworks)

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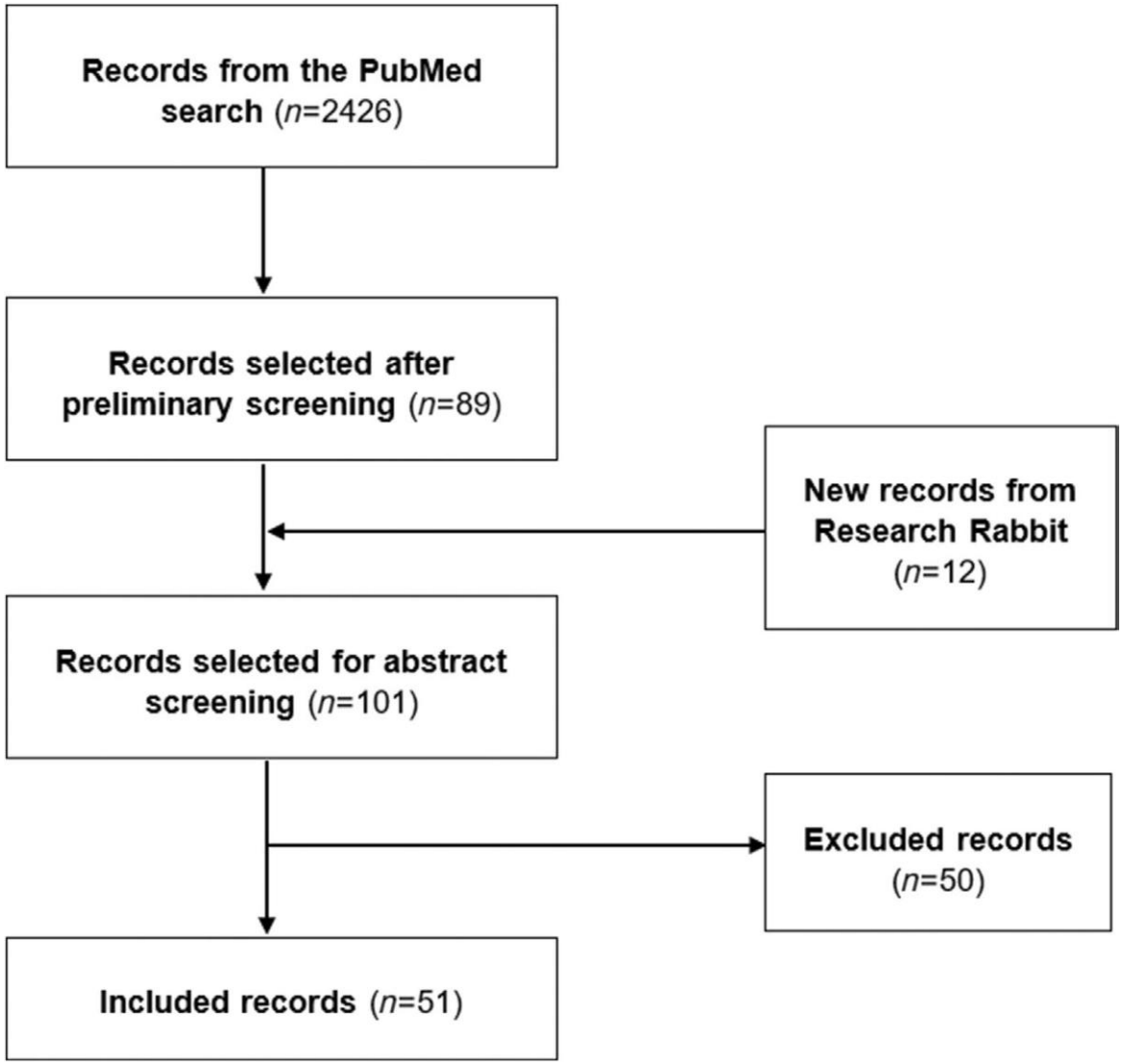
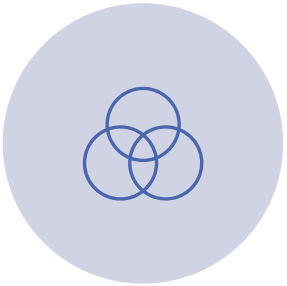
Study Selection



Results: Overview



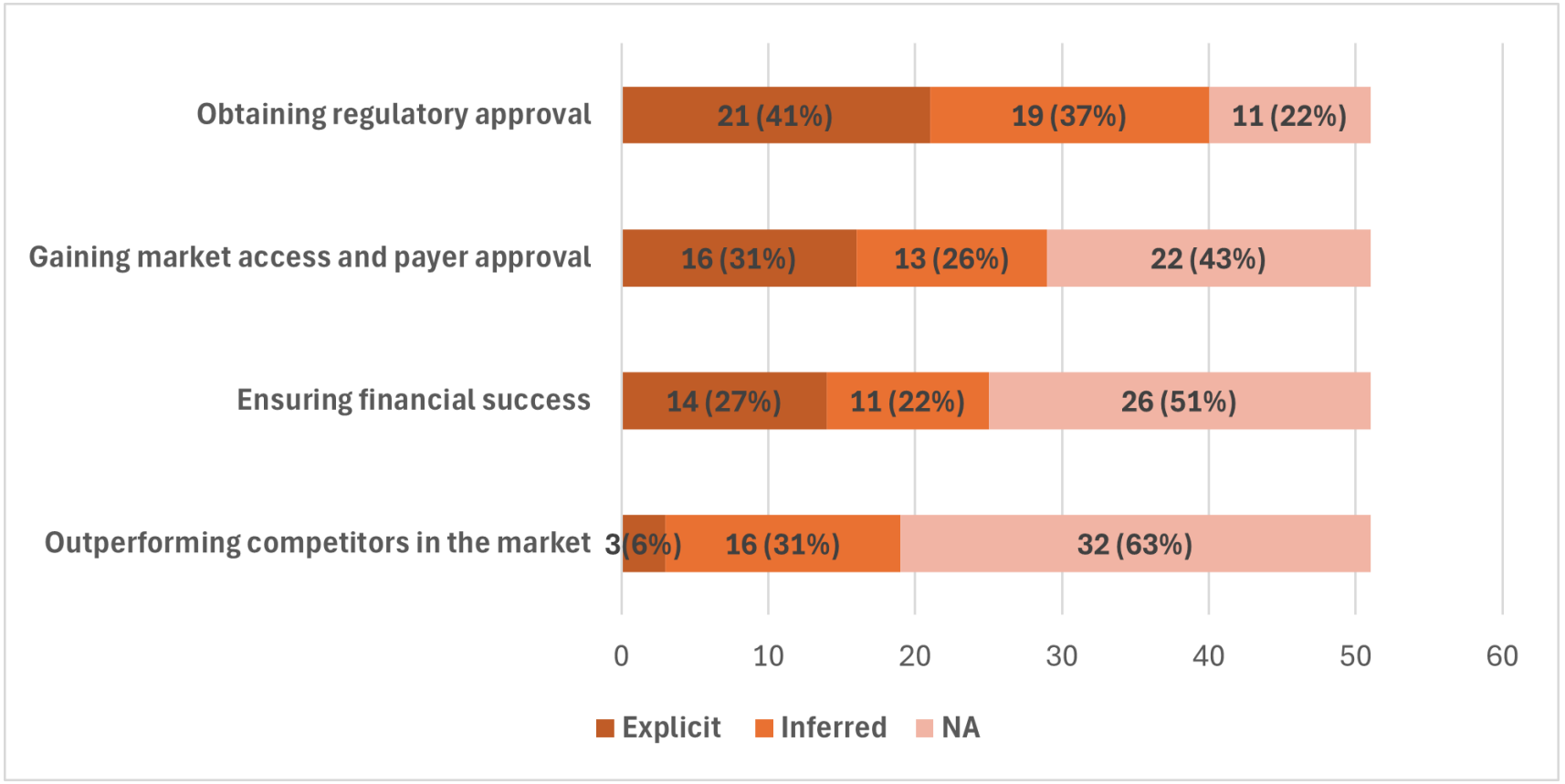
There is a wide variety of "success" criteria used for Go/No-Go decisions, reflecting different stakeholder perspectives, e.g., regulatory likelihood, market potential, patient-centric outcomes, in addition to scientific efficacy

PoS emerges as a central theme – all frameworks aim to estimate or maximize the probability of some form of "success" for the program moving forward. However, the definition of "success" varies across articles (beyond just statistical significance)

Most approaches still revolve around clinical efficacy as the key decision criterion (often using phase II results to predict phase III outcome). Yet, many papers attempt to broaden this by including other factors (for example, safety/tolerability, or economic factors) as part of the decision

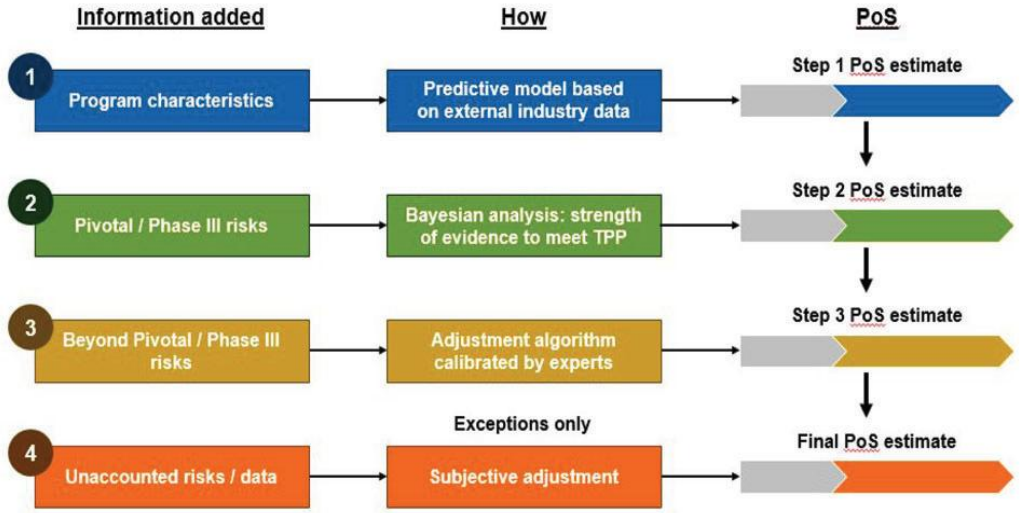
Terminology and frameworks are heterogeneous. Few standards exist on how to select and weigh decision criteria for phase III go/no-go. Each study often proposed its own bespoke model for specific contexts (oncology, portfolio management, etc.), highlighting a gap in generalisable guidance

PoS for Different "Success" Objectives



PoS-Based Methods

- These approaches calculate a quantitative PoS to decide whether to proceed to Phase III. They use Bayesian models to combine data and prior information to predict success probability
- For example, Hampson et al. (2022) introduced a Bayesian evidence synthesis model to estimate the overall PoS of a program succeeding, considering multiple factors simultaneously. Their model incorporated Phase II results + regulatory + market criteria simultaneously



- Such methods integrate multiple sources of uncertainty (e.g., variability in clinical data, prior knowledge of drug class, probabilities of regulatory approval) to output a single overall success probability. This gives decision-makers a structured, quantitative estimate of a program's overall probability of success (PoS) before initiating pivotal trials—beyond clinical efficacy alone

Trial Design Optimization

Why trial design matters

- Trial design choices (e.g., endpoints, sample size, interim analyses) directly influence the credibility and impact of Go/No-Go decisions
- Poorly optimized designs can negatively affect PoS estimates

What the review found

- Design choices should reflect what the trial is intended to decide, not just default statistical targets
- Introduce "consider" zones between binary Go/No-Go to handle uncertainty explicitly
- Align trial parameters with the Target Product Profile (TPP) and anticipated regulatory/HTA expectations
- Leverage RWD and prior knowledge where feasible to improve trial planning and endpoint selection

Bottom line

- Careful design helps avoid failure later by asking the right questions in the right way

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Utility-Based Approaches

These approaches recognise that a go/no-go decision involves trade-offs among multiple decision factors (e.g. success probability, costs, and timelines). They construct a utility function or score that aggregates all relevant criteria

Typically, they assign weights or utilities to each factor – for example ,weighting efficacy vs. safety vs. cost – reflecting the decision-maker's preferences. The go/no-go decision is then based on the overall utility (e.g., proceed if the combined score exceeds a threshold).

Kirchner et al. applied this idea to optimise phase II/III programs. Their method balances expected (fixed and variable) costs and potential gains to find the best sample size and go/no-go rule—maximising overall value to the sponsor

Utility-based methods aim to reflect the real-world complexity, and guide smarter choices by focusing on what brings the most overall value to the development program

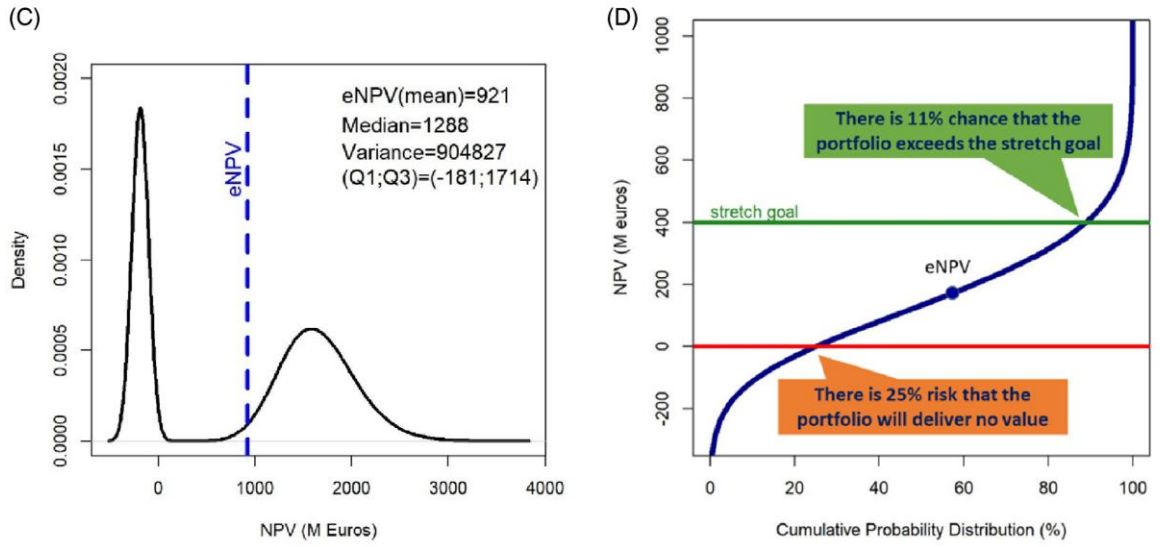
Financial Metrics

Different metrics might be of interest: Net Present Value (NPV), expected Net Present Value (eNPV), Return on Investment (ROI), and Cost-Benefit Ratio (BCR)

Hampson et al. recognised eNPV not only as a metric but as a pivotal decision-making tool that can directly impact trial design through optimizing sample sizes and decision criteria

Several authors have explored how to optimize phase III trial designs to maximize eNPV under budget constraints, reflecting a financially driven decision criteria at the portfolio level. Such models are likely used internally in industry (e.g., portfolio optimization tools), and rarely published

These models tend to focus heavily on the sponsor's perspective (i.e., financial returns). While they may indirectly reflect other stakeholder considerations (e.g., via cost-effectiveness), they often assume the company's definition of success: being profitable and staying within budget



Other Methods

A minority of studies explored emerging approaches

- Machine Learning and RWD: e.g., proposals to use ML on historical trial data to predict success of new trials. These are still conceptual and not widely adopted yet, but highlight interest in data-driven prediction beyond traditional biostatistics
- Decision quality frameworks (rather than just models): Some conceptual works (like Donelan et al. referenced in discussion) emphasised improving organisational decision-making processes (structure, bias, culture). While these are more qualitative, they underscore that sometimes the process of making the decision needs improvement (e.g., checklists to avoid bias), not just numbers.

Upcoming trends

- These approaches are relatively rare in literature compared to the other categories, but they hint at emerging trends: leveraging big data (ML), use of RWD and recognizing human/organisational factors in decision-making

Conclusion

Most (published) frameworks for phase II→III transition are developed from the sponsor's perspective, focusing on statistical and financial metrics

The limited inclusion of HTA/payer and patient perspectives may not align with real-world success factors

Despite discussion on RWD to refine success probabilities (e.g., understanding unmet need or comparator performance), most decision models rely primarily on clinical trial data and simulations

Inconsistent terminology (e.g., go/no-go criteria, PoS definitions, etc.) across studies makes it hard to compare or establish best practices

Recommendations

Broaden criteria early

Multi-stakeholder perspectives could be incorporated earlier in development to better align Phase III trials with real-world success

Leverage diverse data

Use Real-World Data (RWD) and other external data to improve PoS estimates (epidemiological data could inform market size and unmet need; competitor trial data can inform probability of being best-in-class, etc.)

Advanced analytics (AI/ML) can improve prediction beyond traditional methods

Improve decision-making

Adopt structured frameworks, checklists, and bias-awareness, e.g. training decision boards, instilling a culture that values cross-functional input, and using tools to mitigate cognitive biases during go/no-go meetings

Treat decisions as iterative, not one-off (dynamic approach)

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