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

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The decision-making process in drug development involves "go/no-go" decisions, particularly at the transition from early to late-stage trials. While the decisions are solely made by drug developers, they must take into account the perspectives of multiple stakeholders—such as regulatory agencies, HTA bodies, payers, patients, and ethics committees—to ensure well-informed and robust decision-making. These perspectives influence key considerations, including resource allocation, risk mitigation, regulatory compliance, etc. To support this process, quantitative methodologies, including Bayesian and hybrid frequentist-Bayesian approaches, have been introduced to improve decision-making. However, these methodologies often do not fully account for the diverse priorities and needs of all stakeholders. This scoping review examines criteria and methods used in decision-making at the phase II to III transition, with a focus on broadening the probability of success (PoS) concept beyond efficacy alone. Our review explores PoS for different success definitions, such as regulatory approval, market access, financial viability, and competitive performance. Key themes include decision criteria selection, trial design optimization, utility-based approaches, financial metrics, and multi-stakeholder considerations in decision-making. Our findings highlight both the limitations of current methodologies and potential paths forward, including the integration of real-world data (RWD) and advanced analytics. This work complements a companion manuscript by Cetinyurek-Yavuz *et al.* (2025) providing a detailed review of PoS methodologies focused solely on efficacy, specifically PoS for achieving statistical significance in phase III studies, including definitions, terminologies, and analytical approaches. Together, these studies provide a foundation for advancing late-stage trial decisions toward a more balanced, data-driven, and stakeholder-aligned approach.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Go/no-go decisions in drug development, particularly between phase II and phase III, often rely on quantitative methodologies centered on efficacy and financial metrics. These frameworks, though data-driven, frequently overlook the multi-stakeholder perspectives essential to comprehensive decision-making, such as those of regulatory agencies, HTA bodies, payers, and patients.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ This scoping review examines current methodologies in go/no-go decision-making within the literature, focusing on how these approaches incorporate diverse stakeholder perspectives. Special emphasis is placed on probability of success (PoS) extended beyond efficacy only and on those optimize decision criteria and trial design to improve the quality of decisions.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ The review underscores a gap in methodologies that fully integrate multi-stakeholder priorities into the go/no-go decision-making process. Although methods exist to quantify PoS and refine trial designs, limited data-driven approaches incorporate HTA, payer, and patient input. Furthermore, this review highlights the under utilisation of real-world data (RWD) in decision frameworks.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ By identifying areas for methodological expansion, this review advocates for more inclusive decision frameworks, potentially enhancing the alignment of clinical, commercial, and regulatory objectives. It suggests that developing multi-stakeholder models and even adopting RWD could support more comprehensive and adaptive decision-making in drug development.

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The development of new drugs is a complex process, generally involving a series of randomized controlled trials (RCTs), marked by increasing challenges, resources, and time-intensive tasks, with significant costs in later clinical phases.[1–3] The ongoing decline in productivity, coupled with increasing R&D spending, has been a long-standing concern for the pharmaceutical industry which has experienced rising costs and persistently high attrition rates in drug development, especially in recent years.[1,4–6] This underscores the potential for improving decision-making capabilities.

The decision-making process in drug development involves multiple critical steps, each carrying distinct risks that can impact the likelihood of global success. To enhance this process with a structured approach, the concept of Target Product Profile (TPP) was adapted from other industries by pharmaceutical developers in various forms in the 1980s/90s and its use has been promoted by the FDA through their draft guidance in 2007.[7] The TPP serves as a strategic document outlining the desired characteristics and objectives of a new drug. More precisely, it defines desired labeling goals for a drug, focusing on indications, target patient population, dosage, efficacy, safety, and other critical attributes. The TPP provides a roadmap to set R&D targets for drug funders and developers, and a communication tool with regulatory agencies to ensure that a clear understanding of the intended product profile exists from the earliest stages. This strategic focus ultimately helps streamline development, reduce costs, and improve the chances of regulatory approval.

Though not publicly disclosed by drug developers, each development stage has specific milestones that define "success" and guide the associated "Go/No-Go" decisions for advancing to the next stage. The definition of success at each stage is inherently informed by the content of the TPP. For instance, at the discovery stage, the success criteria might be the identification of promising drug candidates that align with the intended mechanism of action (MoA) and therapeutic goals outlined in the TPP, where the probability of success factors might be selectivity, potency, and early toxicity profiles. In first-in-human studies, the success criteria might be to establish a favorable safety profile and understanding of the drug's pharmacokinetic/pharmacodynamic (PK/PD) properties, where the probability of success factors might be acceptable levels of safety, as specified in the TPP, and predictable human PK/PD profiles.

A pivotal point in this process is the "Go/No-Go" decision between phase II and phase III, that is, where the early phases have been successful, and the decision to move forward with phase III development is being considered. At this stage, success is typically defined as demonstrating efficacy and safety in a larger, more diverse patient population, with primary endpoint(s) met, generally through success factors as achieving statistically significant results, while meeting safety requirements. However, this point in development also carries considerable risk, as advancing to late-stage trials requires substantial resources and exposes developers to potential failures that could result in significant time and financial losses. Consequently, considerations at this stage go beyond efficacy and safety concerns only. Other critical success criteria, though not exhaustive, and beyond achieving statistical significance in one or more phase III studies, include obtaining regulatory approval, securing market access and payer endorsement, ensuring financial success through profitability and return on investment, and outperforming competitors in the market. Although the decision to continue the development of a new drug into a phase III is mostly taken by sponsors, various other stakeholders, such as regulatory bodies, HTA agencies, payers, patient representatives, and ethics committees, consider different factors and priorities beyond efficacy and safety concerns, which must be anticipated at this pivotal decision-making timepoint. These factors include development cost, financial benefit, time, marketing authorization, and, pricing and reimbursement reflecting the distinct interests and roles of the stakeholders.

To meet the challenges of aligning these diverse perspectives, synthesizing information and quantifying uncertainties, evidence-based quantitative methodologies have been introduced to improve decision-making in drug development.[8] However, these methodologies often assess the evidence without fully considering the range of perspectives that are integral to a comprehensive drug development program. They typically focus on overall drug efficacy and financial considerations, without integrating other criteria, such as safety profiles, patient preferences, and market dynamics.

As a result, they may not consider the diverse needs and priorities of all stakeholders involved in the process. Typically, drug manufacturers prioritize clinical outcomes and de-risk investments while regulatory authorities ensure patient safety, efficacy, and adherence to ethical standards. Healthcare professionals evaluate the therapeutic benefits and side effects of treatments to determine their practicability. Patients, central to the process, focus on access to treatments, side-effect management, and overall quality of life improvements. Additionally, investors and sponsors analyze financial risks and potential returns. Critical roles are also played by HTA bodies, payers, and patient representatives, each evaluating the drug development process through their specific lens of responsibility and priority, ensuring a holistic approach to decision-making. Although different stakeholders may emphasize the same factor, the importance they assign to it may vary. Moreover, the same stakeholder may prioritize different factors depending on the research context. For instance, without overlooking efficacy, safety is of crucial importance in cancer care[9] where patients are used to face side effects of therapies while in rare disease management, the lack of effective treatments leads to a certain extent to be more flexible about safety.

With the aim to better understand how stakeholders' perspectives are incorporated into the decision-making process, this scoping review was undertaken to explore potential criteria and methodologies used in the decision-making process at the critical timepoint between phase II and phase III trials, when evaluating

whether to advance development to phase III. While some stakeholders, and consequently some criteria, are not yet directly involved at this stage, drug developers must also anticipate future requirements by considering other criteria that will play an important role in future interactions.

The probability of success (PoS) concept, a relatively recent and widely adopted quantitative approach, plays a central role in informing Go/No-Go decisions. For instance, PoS could be used to predict the probability that a clinical trial will meet its objectives, such as demonstrating drug efficacy and safety. The companion manuscript by Cetinyurek-Yavuz *et al*. (2025) provides an in-depth review of efficacy-only PoS methodologies, detailing definitions, terms, and analytical approaches. The current paper specifically examines the concept of PoS in conjunction with potentially other methodologies or that go beyond efficacy criteria alone as part of a multicriteria-based approach.

The remainder of this review is structured as follows: Section 2 outlines the methodology used to perform this scoping review. Section 3 presents a detailed overview of the review results, while Section 4 provides the authors' perspectives on these results, accompanied by key discussion points. Finally, Section 5 concludes with a brief summary.

METHODS

Search strategy

A scoping review was performed on PubMed to identify studies reporting criteria and methods applied to decision-making for initiating late-stage clinical trials from a multi-stakeholder perspective. References were identified using free-text search terms in titles and abstracts of articles and collected from selected databases for articles published between 1st Jan 2010 and 31st March 2024. Search terms were mainly related to drug development, go/no-go decision-making, decision criteria, methodologies, late-stage trial/phase II/III, reimbursement, payers/regulators/HTA perspective, and registry data. Exhaustive search terms are provided in Supplementary Materials S1.

Selection of studies

The initial selection underwent title and abstract screening by two independent researchers (JT and RP for the search conducted for the time period Jan 2010–May 2023, and then CJ and SZ for the time period June 2023–March 2024), through Covidence, a screening and data extraction tool for conducting systematic reviews. To ensure complementarity to the joint review (Cetinyurek-Yavuz *et al*. 2025), articles exclusively focusing on efficacy-based only PoS methodologies were excluded. Disagreements regarding article relevance were resolved through reviewer meetings. Selected articles from PubMed were cross-referenced using the online literature mapping tool Research Rabbit (https://researchrabbitapp.com) to avoid overlooking relevant studies potentially present in the reference list of included studies or absent from the PubMed database. Relevant articles that were absent from the PubMed database but available through Research Rabbit were included. Two independent researchers (CJ and CB) performed the data extraction followed by full-text screening. CJ reviewed all articles, while CB focused on extracting the information from the 25 most pertinent to the research question. Non-English publications and conference abstracts were omitted.

Data extraction and reporting

Data extractions were performed using a spreadsheet format, ensuring consistent extraction, and facilitating easy comparison across methods. Of paramount importance was the extraction related to go/no-go decision-making processes. Criteria such as efficacy, safety, cost, time, etc., were systematically extracted, along with the perspective and stakeholders considered for such decisions. Input data sources (RCT, expert elicitation, RWD, etc.) and output decision types, along with the methods/models applied for decisions, were also comprehensively recorded. Furthermore, information regarding the level of application of methods (trial/program/portfolio), trial design, and the use of Bayesian approaches and machine learning techniques were documented. Finally, a general summary of the articles with important conclusions provided closure to the structured extraction process. This systematic approach ensured comprehensiveness and consistency, with the aim to obtain reliable findings.

RESULTS

This scoping review yielded 2426 articles and the entire review process led to a final selection of 51 articles as per the PRISMA diagram in Figure 1.

This review pinpointed several criteria during the go/no-go decision-making process reflecting a multi-stakeholder perspective. First, we identified each selected article's success criteria, data used, approaches, and methods. Because the methods and approaches developed to optimize the PoS during the decision-making process are inherently related to the priorities and concerns of stakeholders, assessing the amount of papers identified through this review dedicated to one of the following objectives: PoS for obtaining regulatory approval; PoS for gaining market access and payer approval; PoS for financial success; and PoS for outperforming competitors in the market; would allow us to pinpoint for which objective the literature is most extensive. Table 1 presents the distribution of articles based on their application of these different types of PoS. PoS for obtaining regulatory approval is the most commonly addressed, with 42% of articles applying it explicitly and an additional 36% inferred. PoS for gaining market access and payer approval is also frequently considered, with 32% explicitly and 26% inferred applications. Financial success PoS is explicitly applied in 26% of articles and inferred in 22%. In contrast, PoS for outperforming competitors in the market is the least addressed, with only 6% of articles applying it explicitly and 32% inferred.

The decision has been made to describe the identified articles according to their methodological aspects, namely PoS-based methods, trial design-related criteria & methods, utility-based approaches, financial metrics, and other methods. This will help to assess the prioritized approaches and tools used to make informed decisions at critical points in the drug development process, considering scientific, practical, and economic factors.

Probability of success (PoS) beyond efficacy only

Traditionally, research has relied on phase II data to decide whether to proceed to phase III trial(s) by testing hypotheses about a pre-defined and assumed fixed true treatment effect. However, since the true treatment effect is inherently unknown, and because phase II studies results may be overoptimistic, this approach can lead to unsuccessful phase III studies.[5,10–16] As a result, a go/no-go decision based solely on statistical power may not be as reliable as expected, since high power does not

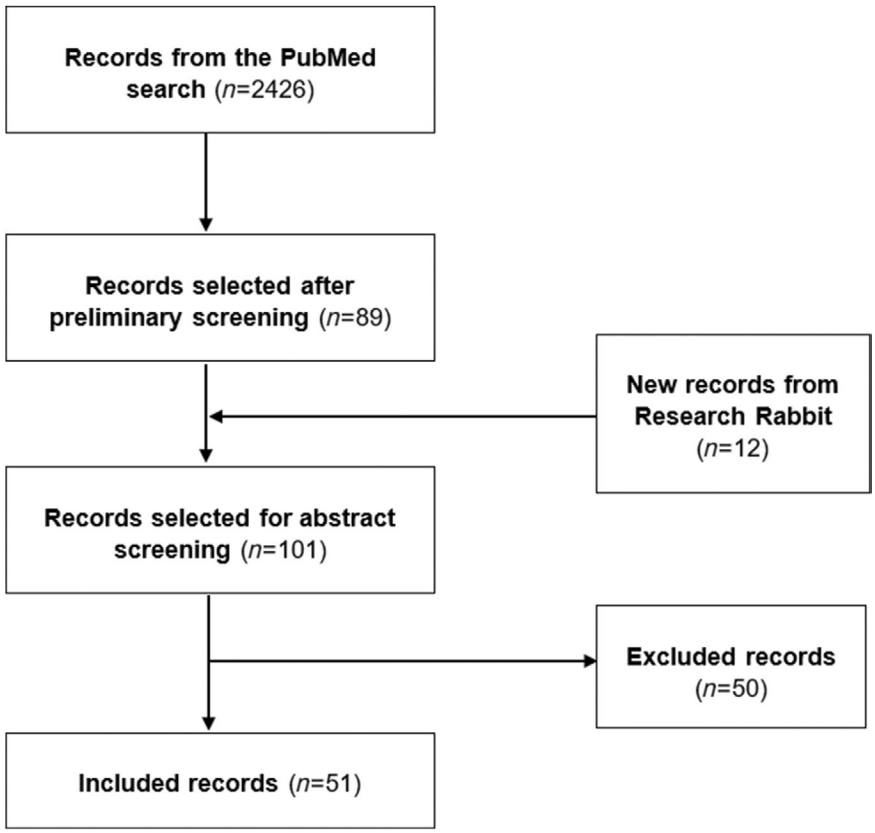

Figure 1 PRISMA flow diagram from identification, screening, to those included in the final review.

Table 1 Distribution of articles based on their application on different types of PoS

		PoS for obtaining regulatory approval	PoS for gaining market access and payer approval	PoS for financial success	PoS for outperforming competitors in the market
Explicit application	*N* (%)	21 (41%)	16 (31%)	14 (27%)	3 (6%)
Inferred application	*N* (%)	19 (37%)	13 (26%)	11 (22%)	16 (31%)
Not applicable	*N* (%)	11 (22%)	22 (43%)	26 (51%)	32 (63%)

N and % denote respectively the number and percentage of articles.

necessarily guarantee a high probability of success in later trial.[11] To address this issue, the PoS has emerged as a widely used quantitative approach. Of course, this methodology is rather general and can be adapted depending on the definition of the success of interest.[17] For instance, statistical power could be considered as the PoS for achieving statistical significance in a single-phase III study. But other types of PoS can also be relevant at the timepoint before starting phase III trials, such as PoS for achieving statistical significance across multiple phase III studies, PoS for obtaining regulatory approval (FDA/EMA), PoS for gaining market access and payer approval, PoS for financial success (profitability and return on investment), and PoS for outperforming competitors in the market. The companion manuscript by Cetinyurek-Yavuz *et al*. (2025) provides a detailed review of PoS methodologies focused solely on efficacy, specifically PoS for achieving statistical significance in one or multiple phase III studies, including definitions, terminologies, and analytical approaches. Some Bayesian-frequentist hybrid approaches estimate PoS using a prior distribution of the true treatment effect, so-called "design prior".[18–20] Various interchangeable definitions are found in the literature, such as assurance,[13] Bayesian Expected Power,[21] Bayesian Predictive Power,[22,23] average success probability,[24] average power[25,26] offer a comprehensive overview of these terms.

In this review, we specifically examine the use of PoS where success is defined beyond efficacy alone or in conjunction with other methodologies. First, the PoS can be used directly as a go/no-go decision criterion. Hampson *et al*.[19,27] recently introduced an innovative Bayesian approach to synthesize all evidence and numerous sources of uncertainties and risks in the assessment of PoS to guide the go/no-go decision. They adopted a comprehensive definition of success, incorporating successful outcomes of phase III trials, regulatory approval, and meeting market access requirements as outlined in the TPP document. Their assessment of PoS also integrated multiple stakeholders' perspectives into the estimation of PoS or various factors affecting it. For example, they used industry

benchmarks to estimate the probability of efficacy success in phase IIb/phase III trials and regulatory approval likelihoods. Linkages and uncertainties between phase II and phase III were addressed through expert elicitation, reflecting diverse stakeholders' viewpoints. They also examined risks arising from misalignments with regulatory expectations and the need of additional outcomes for reimbursement considerations. However, there remains a general lack of assessment of go/no-go decision criteria based on the estimates of PoS, for example, what is the threshold of PoS under which the drug development program should be continued/terminated.

Secondly, apart from being used as decision criteria, PoS can also be used to improve the go/no-go decision-making process in a more implicit way. One common application of PoS in this context is in optimizing trial design to facilitate the go/no-go decision-making. Kirchner *et al.*[11] incorporated the PoS into a utility function, which represents the preferences of decision-makers related to the chosen combination of criteria, considering time-to-event endpoints typically met in an oncology setting. By optimizing the utility function, the optimal go/no-go decision criteria can be determined. This optimization also facilitates the simultaneous determination of optimal phase II sample sizes, reflecting their interdependence with the go/no-go decision criteria. Incorporating PoS into the utility function allows decision-makers to account for the risks and uncertainties associated with the development program when designing trials and setting decision criteria. Building on this, Preussler *et al.*[28,29] and Erdmann *et al.*[30] extended this method to scenarios involving several phase III trials and multi-arm phase II/III programs, acknowledging the common overestimation of phase II results. While these studies utilize PoS in shaping the utility function, their focus is more on trial design and will be elaborated in the subsection on utility-based approaches.

In addition to the two main uses of PoS for go/no-go decision-making mentioned above, PoS is also widely used to compute key metrics for project evaluation on program and portfolio level.[6,19,31] The decision-making framework at program and especially portfolio level can be complex, as it involves multiple factors influencing the drug development process. The literature highlights the challenge of quantitatively assessing the relationship between the go/no-go decision between phases II and III and other decisions, such as regulatory approval and reimbursement. Understanding how these decisions impact and influence each other remains a difficult yet critical aspect of the drug development landscape. Several authors[1,27,32] have developed methodologies for this purpose, though these often lack detailed guidance and clear instructions. This scarcity of information may be intentional, as these methodologies are typically created by professionals within the pharmaceutical industry, where strategic considerations and business confidentiality are prioritized.

Trial design-related criteria and methods

The above-mentioned PoS methodologies can provide insight on how to appropriately assess available evidence to guide and support the go/no-go decision-making. Apart from this, multiple researchers have equally investigated the impact of trial design on the go/no-go decision-making. They proposed methodologies to determine optimal decision criteria, sample size/resource allocation, and appropriate study design to enhance the performance of phase II/III programs and ultimately support robust go/no-go decisions. While this review focuses on the period after phase II, it is important to note that in certain cases, phases II and III can be interlinked, such as in seamless designs where planning decisions for phase III rely on resource allocation and outcomes from phase II.

Decision criteria in trials. Wiklund[1,33] and Miller and Burman[34] pointed out that the go/no-go decisions have often been made based on evidence and knowledge available at the decision points, often without significant prior planning. Therefore, it is crucial to choose appropriately the decision criteria and optimize it, based on the perspective of decision makers and the specific context, at the trial-design stage in order to facilitate the decision-making when the time comes. Most of the selected publications through this review generally adopt the treatment effect (efficacy) as the main criterion for the go/no-go decision in the oncology setting. However, none of them offered comprehensive guidance on how to select the appropriate decision criteria in a general context. The proposed methodologies focus rather on the choice and optimization of decision criteria in different specific circumstances.

For situations where go/no-go decisions rely on limited data from early efficacy endpoint and cost-effectiveness is of major concern, Chen *et al.*[35] developed a framework for proof-of-concept phase II trials that determine optimal go/no-go decision criteria for progressing to phase III. The framework also incorporates strategies for allocating resources efficiently when conducting multiple proof-of-concept trials within a portfolio under fixed resource constraints, ensuring that decision-making and resource allocation are aligned with the goals of the overall development program. The authors considered relative effect size to assess early efficacy endpoints in relation to clinical outcomes and integrated benefit and cost as additional key factors into a single Benefit–Cost Ratio (BCR) for decision-making.

Subsequently, Chen *et al.*[36] introduced a new decision rule for single-arm phase II trials with binary endpoints, incorporating a "testing confidence value" that reflect the uncertainty of the true efficacy, blending Bayesian concepts with frequentist methods. This approach can be considered as a specific case of the broader phase II go/no-go decision framework, tailored to the unique characteristics of single-arm trials with binary outcomes. The authors demonstrated through a simulation study that their new rule significantly lowers the risk of incorrect go decisions in phase II single-arm trials, compared to traditional and Bayesian methods.

Traditional binary criteria decision-making systems (go/no-go) stress much on the statistical significance and have shown a lack of flexibility in real practice. To overcome this situation, various triple decision criteria models (also often referred to as triple outcome decision-making models) have been proposed considering in addition a "gray" zone reflecting the dilemma between the no-go and go decisions. Zang and Liu[37] gave a general overview of the evaluation of the triple decision criteria framework during the last decades. Moreover, Frewer *et al.*[38] introduced a triple-outcome decision structure, including a 'consider' option alongside 'go' and

'stop,' which can be adapted for interim analyses and safety endpoints. It employs a likelihood-based approach with the potential for Bayesian adaptation to incorporate financial metrics. Zang and Liu[37] developed general triple outcome decision methods for basket single-arm phase II trial designs for which the Bayesian methods to borrow information are still based on the binary decision-making framework. The new framework aimed at providing a solution by shrinking the dilemma zone, which facilitates the decision-making. If improvements on Bayesian information borrowing models are available, it remains possible to incorporate them easily into the proposed framework and further reinforce the decision-making process.

Similarly, Yin[39] designed a "backward" Bayesian method for setting go/no-go criteria based on efficacy or safety, using an exponential model that can be extended to other nonlinear models. These early indicators seem particularly useful, especially when seeking to perform a quick assessment of the drug's therapeutic effect.

Teng *et al*.[40] and Götte *et al*.[18] focused on the use of efficacy-based PoS to determine optimal go/no-go decision criteria. Teng *et al*.[40] developed a methodology to determine the optimal decision criterion on the efficacy under pre-fixed thresholds on the probabilities of correct go and no-go decisions and the PoS of phase II/III program, although for time-to-event outcomes the methodology's reliability may be affected when the proportional-hazards assumption is not met. Götte *et al*.[18] proposed a "phase II+" design and used directly efficacy-based PoS using all possible available information from different endpoints (response and overall survival) as a decision criterion for interim decisions with further phase II data after a "go" decision, aiming to optimize decision criteria and decision timing which balance decision quality with program duration.

From a more general perspective, Wiklund.[1,31] proposed a comprehensive modeling framework that integrates a holistic view of drug development programs, using simulation algorithms to derive optimal go/no-go criteria based on clinical effects linked to cost, time, and sales revenue. This model considers additional decision criteria to the statistical significance of efficacy endpoints such as clinical relevance, safety, and overall benefit–risk, aiming to enhance go/no-go decisions within the development cycle.

Most existing methodologies for setting decision criteria rely on data-based approaches. Gould *et al*.[41] suggested incorporating a simple analytic hierarchy process to integrate clinical and regulatory expertise into these data-based decisions, although the effectiveness of this method is limited by the precision of the assumed data distributions and the completeness of the decision criteria. Furthermore, expert elicitation is employed to enrich decision-making with clinical and regulatory insights at both trial and program levels, highlighting stakeholders' involvement in shaping these criteria.[41]

Sample size and resource allocation. In contrast to decision criteria, which involve clear-cut rules or thresholds, sample size and resource allocation are more indirectly linked to decision-making, through the development cost factor. Indeed, several publications[1,11] pointed out that the sample size is also related to the cost of trials/programs and trial duration which are also crucial factors considered by decision-makers. For example, Götte *et al*.[42] developed a framework for sample size planning for phase II trials based on the PoS of phase III which is crucial for go/no-go decision-making in a time-to-event setting. The authors developed this approach by using efficacy-based PoS and mentioned the possibility to integrate regulatory approval and consideration of competitors into the definition of success in the future research. In our scope, this study can provide insights on the relationship between phase II sample size and the go/no-go decision criteria. Moreover, Antonijevic *et al*.[43] initiated a study on the impact of phase II sample size on the PoS of phase III trials, focusing on the effectiveness of different treatment-dose selection strategies. This concept was further developed by Chen *et al*.,[35] who optimized resource allocation strategies specifically for managing sample sizes across multiple proof-of-concept trials, effectively integrating these strategies into portfolio management, for which the go/no-go decisions are made not for one single trial but multiple trials or even multiple development programs.

A common way to determine the optimal sample size for phases II and III is to maximize the expected utility when using a utility-based approach.[11,28–30] This approach is complemented by the work of Teng *et al*.,[40] who used efficacy-based PoS to define minimum sample sizes necessary to meet desired study power based on go/no-go decision criteria and timing. Moreover, Huang *et al*.[12] applied PoS to set quantitative criteria for evaluating the adequacy of sample size in proof-of-concept studies, aimed at ensuring sufficient data for robust phase III go/no-go decisions. Another method[44] sought to determine the optimal sample size and design using the expected net present value (eNPV) specifically for a biomarker-driven phase III study.

From a statistical perspective, unconditional probabilities of go/no-go decision-making and the unconditional PoS of phase III are both influenced by the number of events observed in phase II, particularly in the case of binary or survival endpoints.[42] Increasing the sample size of a phase II trial leads to a greater increase in the PoS of a phase III trial than increasing the phase III trial sample size by an equal amount.[12] Sample size considerations can therefore influence the choice of the trial design. In the case where the phase III sample size is smaller and historical control data has low uncertainty, single-arm trials might be favored by some researchers for oncology proof-of-concept phase II trials, although this approach is subject to ongoing debate and consideration of other factors.[45]

Methodological and structural trial designs. The choice of trial design is crucial for optimizing go/no-go decisions, which is a widely discussed topic in the literature. Trial designs influence the way data is collected, analyzed, and interpreted at different stages of clinical trials, directly impacting decision-making between phase II and phase III.

One key advantage of phase II designs is their flexibility, allowing the incorporation of interim analyses to support timely and efficient go/no-go decisions at the end of phase II trials. Frewer *et al*.[38] explored both adaptive and non-adaptive designs, examining the benefits and risks of incorporating such analyses. Building on this, Teng *et al*.[40] and Götte *et al*.[18] introduced more advanced approaches that allow continuous evaluation of PoS through the

"phase II+" design. Instead of stopping a trial immediately after a go decision, the "phase II+" design extends data collection, refining ongoing decisions and ensuring a more robust transition to phase III.

Further enhancing interim decision-making, Zocholl *et al.*[46] proposed trial designs that integrate short-term endpoints with conditional power or Bayesian predictive probabilities to guide interim decisions in trials with binary endpoints. This approach is particularly beneficial in scenarios of slow patient recruitment, allowing trials to be halted for futility without depending solely on early endpoint assumptions. Additionally, addressing the unique challenges in immunotherapy, Xie and Lu[47] introduced a change-point approach to better manage delayed treatment effects, aiming to preserve the integrity of go/no-go decisions.

Moreover, Preussler *et al.*[28] expanded on the examination of multiple phase III trials to emphasize the regulatory authorities' perspective, noting that approval processes often depend on demonstrating statistical significance across several trials. This research complements their subsequent investigation into multi-arm phase II/III designs, which are particularly effective in optimizing dose and treatment selection strategies to enhance PoS.[29] Antonijevic *et al.*[43] further showed that adaptive dose-finding designs in phase II can be beneficial for identifying optimal dosages and informing go/no-go decisions regarding the progression of treatments to phase III. However, the success of adaptive designs depends on the specific context and goals of each trial, necessitating careful consideration before implementation.

Takazawa and Morita[44] explored a range of phase III trial designs—including traditional, enriched, stratified, and adaptive enrichment designs—employing eNPV as a criterion to determine the most effective design for biomarker-driven trials. Their use of numerical simulations to evaluate these designs reflects a methodological advancement, aligning with other efforts to refine the trial design and decision-making processes from both clinical and regulatory perspectives. This research highlights the growing importance of incorporating biomarkers and adaptive strategies to ensure optimal trial outcomes and informed go/no-go decisions.

In certain cases, such as oncology trials where resources are limited, and patient populations are small, single-arm designs are frequently used. Zang and Liu[37] underscore the prevalence of small, single-arm Proof of Concept trials in contemporary practice, highlighting their essential role in determining the feasibility of progressing to more extensive late-stage trials. However, it is important to note that from a methodological perspective, single-arm trials might not be recommended under conditions of high historical data uncertainty or when phase III involves small sample sizes.[36] These findings emphasize the necessity of refining the go/no-go decision-making process in the context of single-arm trial designs while carefully considering the methodological limitations and the appropriateness of their use.[42]

Beyond traditional trial designs, the growing incorporation of real-world data (RWD) is reshaping clinical trial methodology. Dagenais *et al.*[48] summarized how RWD has shortened trial durations and reduced costs, offering pharmaceutical companies crucial insights to enhance decision-making. Their work highlights that RWD can inform various decision criteria by providing additional evidence on efficacy, safety, patient outcomes, etc. According to their findings, much of the recent literature has focused on using RWE for regulatory purposes, offering detailed guidance on how pharmaceutical companies can leverage these data to enhance both internal decision-making and trial design. By incorporating RWD, companies could refine criteria such as patient selection, endpoint determination, and overall benefit–risk assessment, thereby making more informed go/no-go decisions.

Finally, Jackson *et al.*[49] highlighted the importance of incorporating patient perspectives into trial design through patient preference studies. However, there is still a lack of general methodologies on this purpose as most of the results identified in the literature on trial design are based on the perspective of drug manufacturers and/or regulators.

Utility-based approach

Kirchner *et al.*[11] pioneered a utility-based approach for clinical trial planning in a time-to-event setting, optimizing go/no-go decisions and phase II sample sizes through a utility function. This function, designed from the drug developer's perspective, incorporates fixed and variable costs, potential post-launch gains, and development risks measured by the PoS. By accounting for these factors, the utility function provides a sophisticated tool for evaluating different trial and program designs. However, a significant challenge in applying this model lies in accurately setting the parameters of the utility function, as costs and benefits vary widely across different therapeutic areas. While the approach was initially applied in oncology, it has potential for expansion into more complex settings, such as those involving interim analyses or multi-arm trials.

Building on this, Preussler *et al.*[28,29] and Erdmann *et al.*[30] extended this framework to phase II/III trials, including those with multiple phase III components, focusing on the regulatory requirements for statistical significance for drug approval. They explored different strategies for managing multiple phase III trials, fitting the utility function to compare different program planning strategies, such as choosing between one large phase III trial and two smaller phase III trials. In addition, they addressed the limitations of the previous framework by incorporating dose selection strategies and multi-arm trial designs,[29] improving the speed and efficiency of information acquisition while navigating more complex decision-making scenarios.

Within the context of utility-based approaches, determining the optimal design for a clinical trial involves maximizing the expected value of the utility function, which encompasses factors such as expected costs, revenues, and probability of success. The approach introduced by Kirchner *et al.*[11] is similar to the eNPV calculations typically used by drug developers, but it can be adapted to the perspectives of various stakeholders, allowing for a more comprehensive approach to decision-making in clinical trials.

Building on this utility-based model, Miller and Burman[34] incorporated the regulator's perspective into the decision-making process. They developed theoretical models aimed at optimizing decision-making by balancing the needs of both drug developers and regulators. Their work focused on refining utility functions

to align the commercial gains for developers with societal benefits, considering how regulatory decisions might influence commercial strategies based on factors such as population size and disease prevalence. Their analysis suggests that regulatory criteria should be adjusted according to disease rarity to optimize outcomes for all stakeholder groups. This approach highlights the adaptability of the utility function to meet the diverse needs of stakeholders and emphasizes the dynamic interaction between drug developers and regulatory authorities in shaping clinical trial strategies.

Recent work by Wiklund[33] highlights that rigid decision criteria may inadvertently hinder productivity in drug development, reinforcing the need for utility-based approaches that balance statistical rigor with broader success factors, such as resource optimization and stakeholder priorities.

Financial metrics for program-level decisions

Financial considerations play a critical role in shaping strategic decisions. Key financial metrics like Net Present Value (NPV), expected Net Present Value (eNPV), Return on Investment (ROI), and Cost–Benefit Ratio (BCR) are essential for assessing the viability of trials and making informed decisions.[1,6,19,45,50–52] Antonijevic *et al*.[43] and Takazawa and Morita[44] have demonstrated the application of eNPV and ROI in refining dose selection strategies and optimizing the design of phase III trials for biomarker-based studies. Building on this financial foundation, Hampson *et al*.[19] recognized 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. Kirchner *et al*.[11] further advanced these concepts by integrating cost considerations into a utility function, effectively balancing cost-efficiency with potential profitability, thus ensuring that financial objectives align with the clinical outcomes sought by drug developers. Wiklund[1] introduced a discrete cash flow model to calculate financial metrics such as NPV and eNPV, emphasizing the need for detailed modeling of cost allocations and sales revenues. These financial metrics are pivotal for evaluating the broader aspects of development programs, especially when sales predictions are uncertain in the early development stages. More recently, several authors have explored how to optimize phase III trial designs to maximize eNPV under budget constraints, reflecting a shift toward more financially driven decision criteria at the portfolio level, as noted by the European EFSPI/PSI special interest group.[6] This group highlighted that go/no-go decisions at the portfolio level often rely on different criteria than those at the trial or program level, primarily financial metrics. Chen *et al*.[35] utilized Benefit–Cost Ratio (BCR) analysis to select the most effective early endpoints for proof-of-concept phase II trials, integrating both cost and benefit considerations, alongside the relative effect size, to enhance decision-making efficacy for go/no-go decisions. This approach highlights the potential for considering both financial aspects and scientific and clinical outcomes in early trial phases, ensuring that the design and conduct of trials address both economic and scientific questions critical to the research process.

This financial framework is further developed by Miller and Burman,[34] who have adapted these financial principles to include the perspectives of drug developers and regulators. They have developed a utility function that not only considers financial gains but also incorporates safety penalties and the need for regulatory approval, ensuring that trials designed meet both market access requirements and societal benefits. This approach suggests the potential benefit of aligning regulatory requirements with financial objectives to optimize clinical trial outcomes, though this alignment may not be applicable in all contexts.

As regards portfolio management, the challenges of using average costs combined with PoS to compare projects highlight the complexities of financial decision-making where distinguishing the most promising projects can be challenging. Gerlinger *et al*.[53] developed a framework using RWD and Therapeutic Product Profiles to predict the economic benefits of new drugs, facilitating early portfolio decisions. Similarly, Jekunen[54] provided a broad overview of financial considerations in portfolio decision-making, emphasizing the importance of timely decision-making and the use of advanced analytical tools. Following this trajectory, Wiklund[1] advocated for the integration of statistical analysis into portfolio decision-making processes, suggesting that a more quantitative approach could enhance the precision and objectivity of decisions, thereby improving the overall strategic management of drug development portfolios.

Other methods

The set of papers included in this review revealed several methods that are more indirectly related to the go/no-go decision-making and more varied in terms of techniques used. They comprised model-based meta-analyses where case examples of their applications for quantitative go/no-go decision-making are described by Mold *et al*.[55] or the Approved New Drug Index (ANDI) algorithm[43] combining machine learning techniques and statistical inference methods. The outcome of the ANDI algorithm is the ANDI scoring metric as a drug developers-oriented tool to predict regulatory marketing approval along with traditional metrics as PoS to improve drug portfolio decision-making for new cancer drugs after phase II testing. Related to this, lessons from publications reporting experience related to approved drugs as well as those that failed at or before the regulatory decision may form a basis of novel tools to inform portfolio decision-making.[56]

It has been acknowledged that patients' perspectives, especially their preferences, are a missing component in the decision-making process in the drug life cycle.[49,57] Jackson *et al*.[49] presented case studies where stated-preference methods are applied throughout the product life cycle. These studies are hypothetical scenario-based surveys used to understand patient preferences to show how such studies can help decision making by, for instance, guiding regulators with benefit–risk decision-making and informing reimbursement decisions. Additionally, Overbeeke *et al*.[57] evaluated through two literature reviews and semi-structured interviews how patient preference studies should be designed and conducted to incorporate different stakeholders' perspectives - such as the value and position of patient preferences - in industry, regulatory and HTA decision-making processes. Regarding the HTA/payers' perspective, drug developers have the possibility to perform a multicriteria analysis to predict reimbursement decision for a new drug given drug and environmental attributes.[56]

DISCUSSION

This scoping review aimed to provide an overview of existing methodologies, as well as potential areas for further development, to include perspectives from all involved stakeholders in go/no-go decision making related to late-stage clinical trials and subsequent approval decisions. It is essential to underline that the different approaches examined in this review serve as methods to enhance the quality of information accessible to decision-makers, thereby improving the decision-making process. While the tools themselves do not make the decisions, their influence can sometimes be indirectly inferred. All identified methodologies through this study were mainly developed considering data from either RCTs or single-arm trials. These methodologies were built upon one of the following conceptual frameworks: (1) methods quantifying the strength of evidence and the degree of uncertainties to support decision-making, (2) approaches improving the trial design and the choice of optimal decision criteria to facilitate decision-making. Of note, this review highlighted that RWD were almost never used in the decision-making process; only three[48,53,58] of the selected articles mention the use of RWD. Reliability and limited access to these data might constitute some barriers to explaining this trend.

PoS is a flexible approach that can be applied to different types of success in drug development. At the key decision point between phase II and phase II trials, sponsors may consider several PoS measures. These include PoS for achieving statistical significance in one or more phase III studies, PoS for obtaining regulatory approval (FDA/EMA), PoS for gaining market access and payer approval, PoS for financial success (profitability and return on investment), and PoS for outperforming competitors in the market. As already mentioned, the companion manuscript by Cetinyurek-Yavuz *et al.* (2025) reviews PoS methods focused on achieving statistical significance, while this review focuses on the other types of PoS beyond efficacy.

As expected, it appeared that the efficacy and/or safety of the product, along with financial considerations representing the main interests of drug developers, were often the primary factors driving the decision-making process. Even in existing frameworks using PoS with consideration of multi-stakeholders' perspectives, factors other than efficacy and safety such as regulatory decisions or remaining uncertainties/risks often lacked statistical details or were elicitation-based.[19,27,34] Additionally, while the literature points to a general lack of inclusion of HTA, payer, and patient perspectives, several authors[27–30,34] did integrate the perspective of regulators by requiring sometimes experts and senior decision makers to adjust the estimate of PoS at final stages or provide insights on prior information of quantities of interest.

The lack of consideration of HTA, payers, and patients' perspectives in decision-making process, as observed in PoS-related and other quantitative methods[27,34], may be due to the fact that integrating these stakeholders' input is challenging at the phase II go/no-go decision point, as reimbursement rules and patient acceptance often depend on experiences not available until later stages. However, a trend in the increasing consideration of these stakeholders' perspective was observed in the literature.[49,59] Proposed approaches could allow decision-makers to adjust their decision criteria or design strategies according to different regulatory decision rules when planning for drug approval request.[34] Another illustrative example is the work of Thorlund *et al.*,[58] which provided a comprehensive overview of the methodologies employed in the use of limited evidence for HTA submissions for surrogate outcomes in oncology. It also outlined the gaps between regulators and HTA and addressed the voice of the patient.

Additionally, this review revealed that most of the methods built to improve the trial design were essentially data-driven strategies. Although most methods were developed for oncology trials with a time-to-event outcome, they can be extended to cover general settings.[11,12,18,28–30,36,40] Moreover, numerous authors adopted a function presenting the utilities or quantities of interest by seeking which broader decision criteria and trial planning (sample size or design strategies) could be optimized. This strategy is similar to approaches with the financial metric eNPV but presents the possibility to tailor the utility function to optimize in adequation with several stakeholders' perspectives simultaneously.[11]

Building on the identified need to broaden decision frameworks, the consideration of a multi-stakeholder perspective and the exploration of the use of RWD to support validation can be used as inspiration for future research in other therapeutic domains and more general settings. Beyond leveraging RWE to support decision-making process, innovative approaches such as machine learning techniques[60–62] have also been proposed to enhance decision-making frameworks.

Donelan *et al.*[63] underscore the complexity of decision-making in drug development, identifying four critical domains—structure, bias, culture, and impact—that influence decision quality. Their findings highlight the importance of structured frameworks and the integration of qualitative factors such as organizational culture and subjective biases. Incorporating these dimensions into current decision-making methodologies could enhance transparency and stakeholder alignment, addressing some of the gaps identified in this review.

Finally, this study has several limitations. First, the focus was only given to the go/no-go decision on whether to proceed with late-stage trials (phase III). Thus, some publications may have been missed on methodologies of general decision-making in drug development that could be adapted in our scope. Second, essential and emerging decision-making methodologies, particularly proprietary financial models and other approaches specific to drug developers may be sensitive or confidential and therefore not publicly disclosed. This proprietary nature means that what appears in the literature likely represents only a subset of the approaches used in practice, and some strategies may remain underrepresented. Third, terminology in this broad field is not standardized, for example, "go-no go," and identifying all potentially relevant articles remains challenging. Additionally, this review focused on quantitative methods that inform decision-making, and as such, do not provide a direct assessment of all factors that ultimately determine decisions. However, this focus on quantitative methods is deemed important as it can improve the quality and level of objectivity in the decision-making process.

CONCLUSION

This study synthesizes the existing body of literature on the criteria and methodologies utilized in decision-making processes for advancing to late-stage clinical trials, from a multi-stakeholder perspective. Thus far, the concept of PoS has emerged as the most widely employed approach for effectively synthesizing evidence and managing uncertainties to inform robust decision-making. Researchers have also explored optimal trial planning strategies and decision criteria to facilitate this process. Primarily developed from a drug developers' perspective, the decision-making frameworks are usually financially driven and focused on success in confirming efficacy, and a notable gap persists in integrating perspectives from other stakeholders such as HTA bodies, payers, and patients. Addressing these gaps presents a critical pathway for future research, requiring a more inclusive approach to decision-making that considers the diverse interests and priorities of all stakeholders. Additionally, there is a growing trend toward leveraging real-world data to inform decision-making processes and artificial intelligence techniques are rapidly advancing, which hold promise for future application to provide insights for decision-making. By highlighting key issues in the evolving landscape of drug development, these findings may contribute to the ongoing discourse on pharmaceutical development and promote more informed and inclusive decision-making practices to bring safe and effective treatments to market.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICT OF INTEREST

All authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

C.J., C.B., S.Z., G.H., A.C.Y., B.F., L.R. K.C.B.R., B.A., C.G., R.P., and J.T. wrote the manuscript; C.J., R.P., and J.T. designed the research; C.J., C.B., S.Z., R.P., and J.T. performed the research; C.J., C.B., R.P., and J.T. analyzed the data.

DISCLAIMER

The authors' perspective is solely conveyed in any dissemination of results and should not be interpreted or cited as representing their respective affiliations.

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