Worldwide Clinical Trials

Guide

The Strategic Guide to Getting to "No" Faster in Early Drug Development:

Avoiding Hidden Costs & Pitfalls

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Early drug development is a pivotal stage where strategic choices drive progress or cause setbacks. This guide shows investigators with a novel drug or molecule how to plan Phase I clinical development efficiently, reach go/no-go decisions quickly, and avoid hidden costs and pitfalls. By setting clear regulatory strategies, understanding target markets and patient populations, and selecting the right clinical research partners, sponsors can design protocols to maximize value while minimizing risk and cost.

Understanding the Early Development Process & Essential Role for Phase I Clinical Development Planning

Phase I clinical trials serve as the foundation for all subsequent drug development efforts. Unlike later-phase studies that focus on efficacy, Phase I trials assess safety, tolerability, and pharmacokinetics (PK), establishing dosing parameters and safety profiles that will guide subsequent investigations. This fundamental role makes Phase I development paramount for the entire drug development lifecycle (Figure 1).

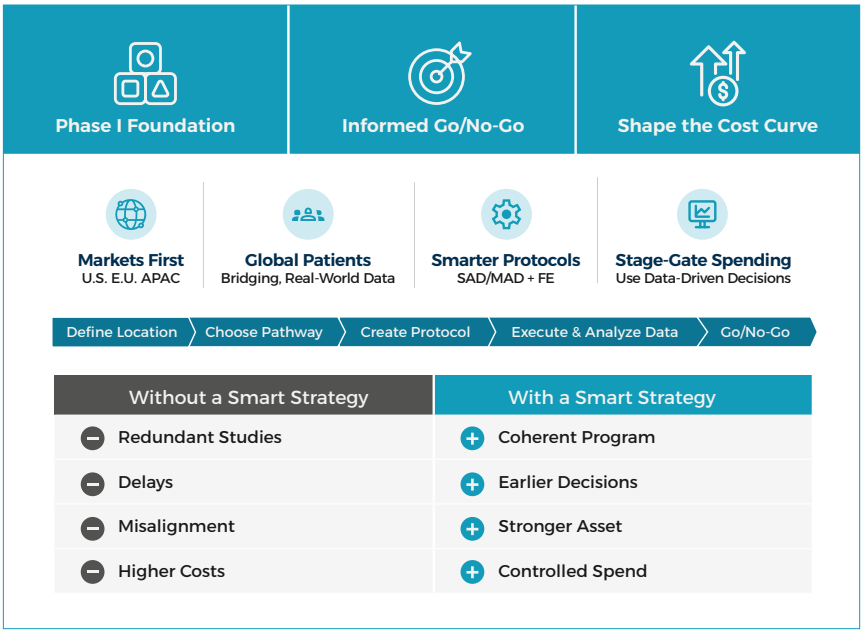

Figure 1. Success in early development begins with a robust regulatory strategy. Phase I strategy determines your cost, speed, and decision quality, and strategic early regulatory engagement positions your program for positive outcomes.

A robust, strategic framework determines the optimal path forward and enables studies to reach critical decision points by using predicted cost curves and resource allocation. The regulatory environment mandates structured progression. This begins with carefully designed study protocols, advances through healthy volunteer (HV) or patient populations as appropriate, and systematically gathers and analyzes data to determine whether the molecule merits continued investment.

The primary objective of this phase is clear: to reach an informed go/no-go decision as early as possible. This approach allows sponsors to make expedited decisions about moving forward with their current molecule or pivoting to alternative candidates or therapy targets before committing additional time and funding. Every regulatory environment requires this work, making it essential to ask the critical question early regarding where you want to go to reach your go/no-go decision, and how the anticipated cost curve influences that path.

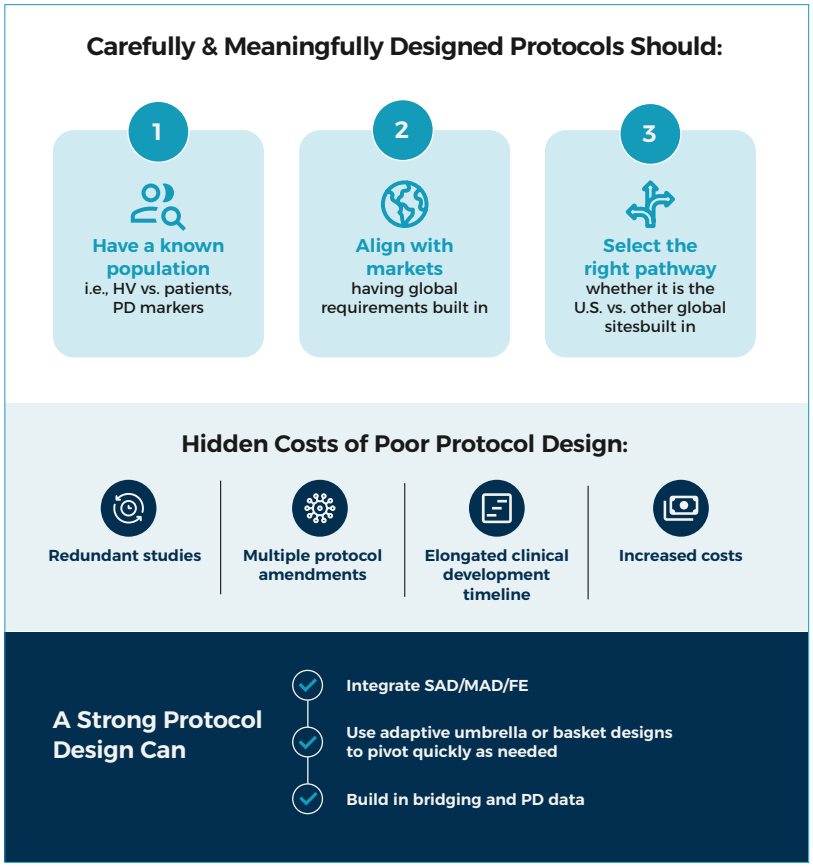

Figure 2. Strategic protocol design in early drug development ensures the trial is run properly the first time.

A strategic approach to protocol creation involves thoroughly understanding your patient population, identifying target markets for commercialization, and making informed decisions about regulatory pathways — whether opening an Investigational New Drug (IND) application in the U.S. or pursuing alternative routes such as Phase I clinical trials in Australia or New Zealand (**Figure 2**).
Each pathway carries distinct implications for timeline, cost, visibility, and downstream development, making it crucial to understand the consequences of each decision before committing resources.

Identifying Hidden Costs Resulting From Ineffective Strategy

As Phase I studies focus explicitly on safety and tolerability, HV populations provide predictable, clean data with well-controlled variables, and sponsors can accurately forecast both timeline and cost. This predictability stands in contrast to patient studies, where recruitment challenges, disease heterogeneity, concerns about polypharmacy, and ethical considerations introduce complexity and increased expense. The strategic decision is to establish the point at which patient involvement becomes truly essential rather than simply desirable. This is where expertise in complex trial designs can create an advantage, with pre-determined plans to move swiftly from HV to patient populations in adaptive Phase Ia/Ib studies.

Critical decisions emerge throughout the early development process that sponsors must address thoughtfully. Food effect (FE) studies present one such decision point: whether to incorporate these assessments into the Phase I protocol or conduct them as standalone trials. These choices carry significant implications for cost and timeline. Similarly, understanding your target population is paramount before finalizing development plans. Consider, for example, a therapy intended for idiopathic pulmonary fibrosis patients who have trouble with inhalation. Developing an aerosolized formulation without first confirming that the target population can effectively use it represents a substantial waste of resources and a preventable strategic failure.

Global market considerations introduce another layer of complexity that must be addressed during initial protocol design. Failing to incorporate international regulatory requirements, such as ethnic bridging studies for Asian markets or FE assessments required in specific regions, can set back development timelines by months or years. When these essential elements are overlooked, sponsors face the costly proposition of designing and executing additional standalone protocols, which significantly delays market entry and consumes resources that could have been preserved through thoughtful upfront planning.

Strategic Protocol Optimization

Strategic protocol optimization in early phase development is not about accelerating the process at any cost; it is about making the right decisions in Phase I that enable faster, more informed progression to Phase II and beyond (**Figure 3**).

Consider the strategic advantages of umbrella protocols that incorporate proof-of-concept (PoC) elements (i.e., Phase IIa) or adaptive designs that evolve based on accumulating data, rather than requiring entirely new protocols for each stage.

Traditional early development separated HV and patient studies into discrete protocols, each with a narrow primary objective and limited flexibility to adapt once initiated. Over the past decade, this has shifted toward seamless, adaptive, and often biomarker-informed Phase I/II designs that combine multiple populations, endpoints, and decision rules within one master protocol. Modern early phase adaptive protocols typically include multiple cohorts (e.g., HV special populations, and early patient expansion) with prespecified rules for adding, pausing, or closing cohorts based on accumulating safety, PK, pharmacodynamic (PD), and early efficacy data.

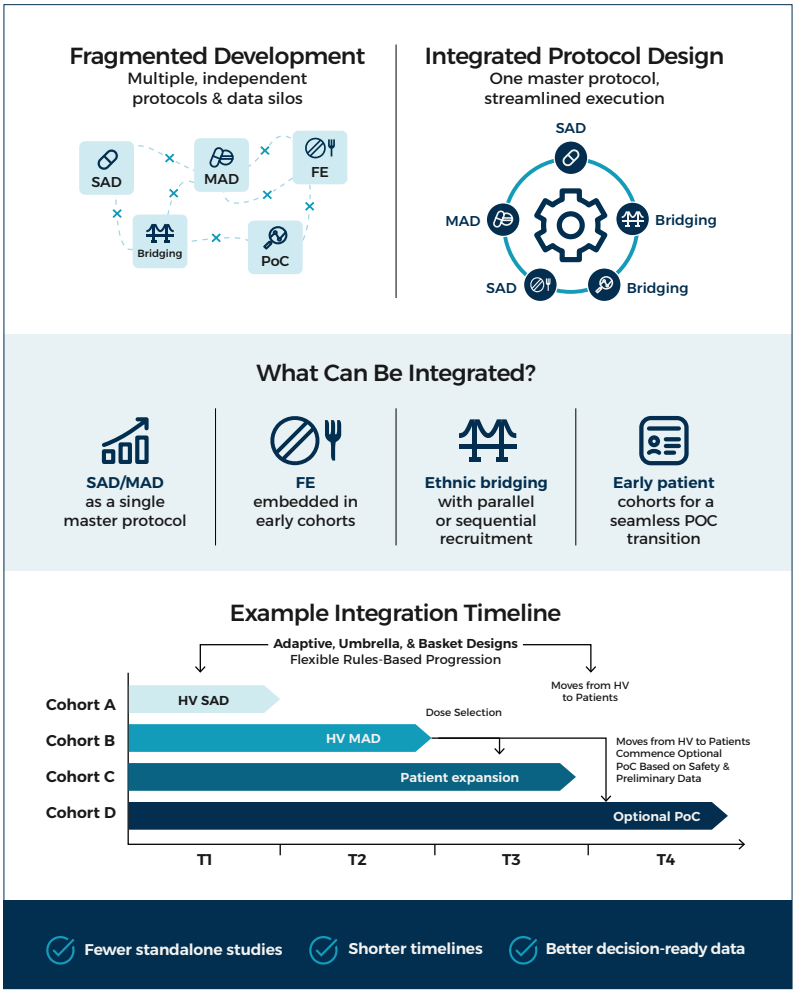

Figure 3. Rather than fragmenting development into multiple disconnected studies, innovative protocol designs can efficiently integrate essential elements.

The concept of basket trial designs represents another powerful optimization strategy. Rather than conducting separate studies for each indication, basket designs allow sponsors to evaluate multiple indications within a single protocol. Consider a cardiovascular therapy with potential applications across several related conditions. By conducting comprehensive HV assessments in favorable regulatory environments such as Australia or New Zealand, where protocols are approved based on design rather than a specific indication, sponsors can proceed to a Phase IIa basket design that includes small cohorts (e.g., 15 patients) from each target indication. This approach enables identification of frontrunner indications early in development, informing strategic decisions about resource allocation and targeted patient demographics.

It's critical to remember that Phase I studies do not aim to collect PD or efficacy data. However, strategic protocol design can incorporate patient cohorts within multiple ascending dose (MAD) studies, allowing evaluation of the drug's behavior in the actual target population while maintaining focus on safety and PK. The key question driving any decision to include patients early is: what information can we obtain from patient populations that cannot be

adequately assessed in HV? HV data provides essential foundational knowledge, but it cannot always predict how a drug will behave in diseased populations with altered physiology, concurrent medications, and comorbidities.

When patients are included in late-stage Phase I or early Phase II protocols, there's the added potential to observe efficacy signals. While not the primary objective, these preliminary indications of therapeutic benefit can prove invaluable when making investment decisions and planning subsequent development phases. The goal is to create an early phase population that best represents the intended Phase II and beyond study populations, ensuring that the data generated will translate meaningfully to later development stages.

Know Your Market & Goals

Strategic market planning should drive Phase I protocol design, not follow it. Every investigator should consider the markets they intend to enter with their therapeutic, and what it means for their Phase I development strategy. This market-first thinking requires sponsors to work backward from commercial objectives to determine what must be accomplished in Phase I to avoid foreclosing future opportunities.

Geographic market considerations carry specific regulatory requirements that must be anticipated. If China is a target market, Chinese participants must be included in PK assessments, as the China National Medical Products Administration does not permit market applications based solely on non-Chinese data. This necessity for ethnic bridging studies requires careful planning. Bridging protocols typically involve three cohorts of single-dose PK studies demonstrating that pharmacokinetic parameters in Caucasian populations align with those observed in Chinese populations. Similar requirements apply to Japan, though with the flexibility that Japanese participants can be enrolled anywhere in the world, provided they have four Japanese grandparents. Increasingly, sponsors are also conducting Caucasian bridging studies for drugs originating in Asia that seek Western market approval.

The strategic advantage of incorporating bridging studies into the original protocol provides significant time savings. Designing these elements into the initial Phase I study proves substantially less expensive than creating dedicated bridging studies later in development. Beyond cost savings, early integration prevents delays in Asian market entry, a particularly critical consideration, for example, if your target disease population is concentrated in Asian countries. Despite these clear benefits, few sponsors proactively address these global regulatory requirements during initial protocol development. Many sponsors are eager to get into the clinic, overlooking these strategic considerations that later prove costly to address.

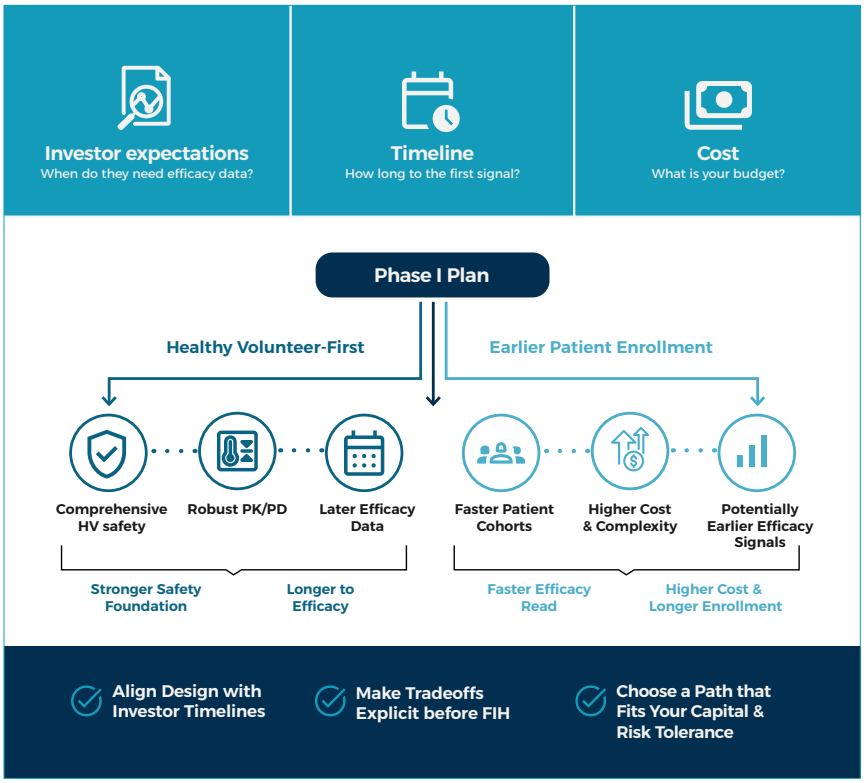

Figure 4. Balancing safety foundations and time-to-efficacy data requires key strategic questions that link investors, timelines, and trial design.

The regulatory strategy process follows a logical sequence: identifying target markets, aligning protocol design with each market's regulatory expectations, and finalizing trial design details only then. FE studies represent another regulatory requirement that demands early consideration, whether incorporated into the Phase I protocol or conducted as a separate investigation.

Resource allocation becomes a central consideration in these strategic decisions. This includes the amount of available capital and how far it can take the study. One must also decide whether all elements should be incorporated into a comprehensive protocol from the

outset, or whether development should be stage-gated with sequential protocol amendments. For biotechnology companies, particularly, stage-gating represents a prudent approach. It is wise to begin with a single ascending dose (SAD) protocol, then add MAD elements, followed by subsequent amendments for PoC cohorts or basket-trial expansions. Each stage represents an incremental cost increase, but sponsors pay only for work actually conducted rather than committing resources upfront for protocol elements that might never be implemented.

Opening an IND in the U.S. carries implications beyond regulatory compliance; it represents a public disclosure of corporate strategy and development plans. For small biotechnology companies accustomed to operating in "stealth mode," this transparency can feel uncomfortable. Opening an IND requires disclosure of corporate structure, board composition, C-suite leadership, and development intentions. This visibility, while serving important public health functions, may not align with every sponsor's strategic preferences for confidentiality during early development phases. Alternative pathways, such as conducting initial studies in Australia or New Zealand, allow sponsors to gather essential safety and PK data while maintaining greater discretion about development plans and corporate activities.

Recognizing Your Patient Population Is Integral

Deep understanding of your target patient population should inform every aspect of early development planning. This knowledge extends beyond basic disease pathophysiology to encompass the practical realities of how patients will use your therapeutic. Factor in what indications this molecule might best address. This includes determining whether different indications suggest distinct PD markers that need to be assessed, and whether different patient populations require distinct monitoring strategies or safety assessments. These considerations must be incorporated before finalizing the protocol design, as retrofitting them later proves far more expensive and time-consuming than incorporating them from the outset (**Figure 5**).

Intermediate data selection exemplifies the importance of population-specific planning. Studies in substance abuse or psychiatric indications, for example, might include electroencephalography (EEG) assessments to evaluate central nervous system effects if including a patient population toward the end of the Phase I studies. This provides an internal comparison between HV and patient populations. Metabolic disorder studies might emphasize continuous glucose monitoring or detailed lipid profiling. Cardiovascular investigations might require extensive cardiac imaging or hemodynamic monitoring.

Indication-Specific Considerations

Different therapeutic areas present unique challenges and requirements for early phase development, demanding tailored approaches that reflect the specific characteristics of each indication (**Figure 5**).

Oncology investigations represent one of the most distinctive paradigms in Phase I development. Most cancer therapies cannot be safely evaluated in HV populations due to their mechanisms of action and anticipated toxicities. Therefore, oncology Phase I studies typically enroll patients with advanced-stage disease who have exhausted

Figure 5. Design assessments around the patients and based on your therapeutic area's unique factors. The right measures should be built into the protocol, not fixed after the fact.

standard treatment options. Rather than the traditional focus on safety, tolerability, and PK observed in HV studies, oncology Phase I trials concentrate on identifying the maximum tolerated dose or recommended Phase II dose while carefully monitoring for dose-limiting toxicities. This patient-first approach is a necessity driven by the therapeutic area's unique characteristics.

Investigations of cardiovascular and metabolic disorders present different challenges. For conditions such as metabolic dysfunction-associated steatohepatitis or obesity, drug-drug interaction assessments become vital. Patients with these conditions frequently take multiple concurrent medications, antihypertensives, lipid-lowering agents, and diabetes medications that could interact with the investigational therapy. These studies, therefore, require careful attention to potential interactions, comprehensive metabolic monitoring, and detailed hepatic function assessment. Your protocol design must account for the complexity of managing patients with multiple comorbidities and concurrent therapies rather than the relatively straightforward assessments possible in HV.

Central nervous system indications introduce yet another set of considerations. For therapies targeting Alzheimer's disease or other neurodegenerative conditions, a critical question must be addressed early regarding whether the molecule can cross the blood-brain barrier and achieve therapeutically relevant concentrations in the central nervous system. These mechanistic questions often cannot be answered definitively through in vitro or animal studies alone. Phase I protocols for CNS therapeutics frequently incorporate multiple cohorts. These begin with HV for initial safety and PK assessment, progressing to healthy elderly volunteers to evaluate age-related effects on PK and safety, and finally enrolling patients with mild cognitive impairment to confirm target engagement and begin characterizing therapeutic potential. This staged approach balances safety considerations with the need to evaluate the drug in populations that meaningfully represent the clinical target.

Evaluating a Successful Partnership

Selecting the right clinical research organization (CRO) partner represents one of the most consequential decisions investigators make in early development. This partnership extends far beyond a simple vendor relationship; it should represent a true collaboration where the CRO actively contributes to strategic thinking and protocol optimization. The most valuable partners do not simply execute protocols; instead, they engage in thoughtful discussion about strategic considerations, financial implications, market requirements, regulatory implications, and design opportunities that sponsors might not have considered (**Figure 6**).

Figure 6. An upstanding CRO that serves as a true differentiator in delivery will collaborate genuinely on protocol design, asking probing questions about market strategy, regulatory plans, and commercial objectives.

Meaningful partnership begins with communication and strategic alignment. Look for CROs that sit down to discuss all relevant factors comprehensively rather than rushing to generate quotes for the proposed study as written. Some organizations will happily execute any protocol, regardless of the sponsors present, viewing each study primarily as a revenue opportunity. While these organizations may be competent in study execution, they fail to add strategic value where sponsors most need it, which is during protocol development, when thoughtful design can prevent costly mistakes and missed opportunities.

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A true partnership approach yields optimal study designs that balance scientific rigor, regulatory requirements, resource constraints, and strategic goals. For the majority of small to mid-sized pharmaceutical and biotechnology sponsors who plan to out-license their molecules after Phase IIa or early Phase IIb, this strategic partnership becomes even more critical. These companies need to maximize the value proposition they can present to potential acquirers or partners, which requires data packages designed with commercial objectives in mind from the earliest stages.

Experience provides important indicators of partnership quality. For instance, reputable early phase CROs will rarely, if ever, recommend conducting Phase Ia (SAD) and Phase Ib (MAD) as completely separate studies. These study phases can and should be integrated into unified protocols with stage-gate amendments as appropriate. The exception would be situations where regulatory authorities express specific safety concerns that necessitate completion of SAD before initiating MAD, but this should be a carefully considered response to regulatory feedback rather than standard practice. A partner who reflexively recommends separate studies for each traditional development phase should raise concerns about whether they prioritize optimal study design or simply maximizing billable work.

Ultimately, the right CRO partner understands that their success is inextricably linked to yours. They recognize that delivering high-quality data on time and on budget represents only the baseline expectation. True partnership means contributing strategic insights, anticipating potential challenges, identifying opportunities to optimize protocols, and serving as an extension of your development team rather than an external vendor. This level of engagement transforms the CRO relationship from transactional to strategic, yielding dividends throughout development and beyond.

Conclusion

The path to successful drug development begins with strategic thinking in Phase I. Getting to "no" faster is not about rushing through development or cutting corners. Instead, it is about making informed decisions earlier in the process, when course corrections cost less and take a shorter time. By establishing comprehensive regulatory strategies from the outset, understanding target markets and their specific requirements, deeply knowing patient populations and their unique needs, and partnering with CROs that bring strategic value rather than simply executing protocols, sponsors can navigate early development more efficiently and effectively.

Every decision made during Phase I protocol design carries downstream implications (**Figure 7**). Incorporating ethnic bridging studies, FE assessments, and appropriate patient cohorts at the right time prevents costly standalone studies later. Choosing between immediate IND filing versus international FIH studies affects both visibility and the regulatory pathway. Selecting between HV-first approaches and earlier patient enrollment influences both the cost curves and the timeline to efficacy data. None of these decisions has a universally correct answer; the right choice depends on each sponsor's specific circumstances, resources, strategic objectives, and target indications.

Figure 7. Success requires asking difficult questions early, seeking expert guidance from experienced partners, and designing protocols that reflect strategic thinking rather than simply checking regulatory boxes.

What remains constant across all scenarios is the value of thoughtful planning. The hidden costs of ineffective strategy, redundant studies, delayed market entry, foreclosed regulatory pathways, and inappropriate patient selection dwarf the investment required for comprehensive protocol optimization during development planning. Small and mid-sized pharmaceutical and biotechnology companies, often operating with limited resources and compressed timelines, cannot afford these preventable setbacks.

The goal of early phase development is to establish robust foundations for later development while preserving strategic flexibility and managing resources effectively. Whether your molecule ultimately succeeds or fails, you want that determination made based on solid data collected efficiently, not obscured by preventable design flaws or delayed by oversight of critical regulatory requirements. Getting to "no" faster, when appropriate, frees resources to pursue more promising candidates. Getting to "yes", a clear go-ahead to Phase II, positions your program optimally for success in later development and ultimately for the patients who need new therapeutic options.

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