Worldwide Clinical Trials

Strategic Partnerships in Clinical Development

Enhancing Value in High-Performing Research and Development Teams

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Abstract

At the interface between drug discovery and clinical development, there is an opportunity for strategic partnership. Strategic partnerships are characterized by highly advanced therapeutics and increasingly segmented patient populations. Below, the necessity of multidisciplinary collaboration, from drug discovery to commercialization, is highlighted. Milestone-based development programs are presented as an approach to maximize success rates, highlighting the role of Clinical Research Organizations (CROs) in providing specialized services that align with sponsors' goals at various touch points within a clinical development program. Regulatory strategies, innovative early phase clinical programs, and the importance of a global operational footprint are emphasized. A well-structured, efficiently integrated governance framework is characteristic of a strategic partnership – an expression of a long-term commitment that can facilitate the demonstration of product value and the introduction of potentially transformative therapy.

Introduction

Strategic research and development decisions rely on integrating the perspectives of multiple disciplines in a coherent, highly effective project team. Key decision points extend across different phases of a clinical development program in an increasingly complex research and development environment populated with advanced therapeutics and nuanced patient populations. The interaction between sponsor and CRO should begin at the later stages of the drug discovery process, typically after the completion of a lead optimization process and identification of a drug candidate. Subsequently, a strategic partnership features a recursive review of enabling data and the creation of informed, technically competent regulatory-facing documents. The culmination of this workflow is an early phase development program that informs the remainder of a clinical development program, including both approval and commercialization.

The capacity to function globally in an increasingly international clinical research environment is mandatory. The ability to adjudicate and integrate multiple objectives into program design, with predictable metrics and efficient use of available resources, is critical. The following sections emphasize relevant concepts, including the creation of milestone-based development programs, the utilization of innovative regulatory programs, and the seminal importance of proof-of-concept study designs while thinking globally and acting locally. An efficient governance structure permits calibration and adjustments based on observed program metrics and facilitates the demonstration of product value and novelty.

Milestone-Based Development

In business, an inflection point is a time of significant change or a decisive moment. Drug development processes are often described as an arduous pathway with uncertain chances of success. Success rates vary significantly by phase and stage of development and reflect a well-described process of attrition in a product lifecycle (Figure 1). In fact, the Food and Drug Administration (FDA) estimates that only ~5% of candidates advance through Phase I, II, and III.[1]

However, with a milestone-based approach, the odds of success at each subsequent milestone can be greater than the cumulative probability of success. A drug candidate has a ~5% overall chance of success in completing Phase III. However, ~70%, ~33%, and ~25-30% of candidates advance beyond Phase I, II, and III trials, respectively. Information developed within each clinical research stage can be used to maximize the chance of success at each milestone.

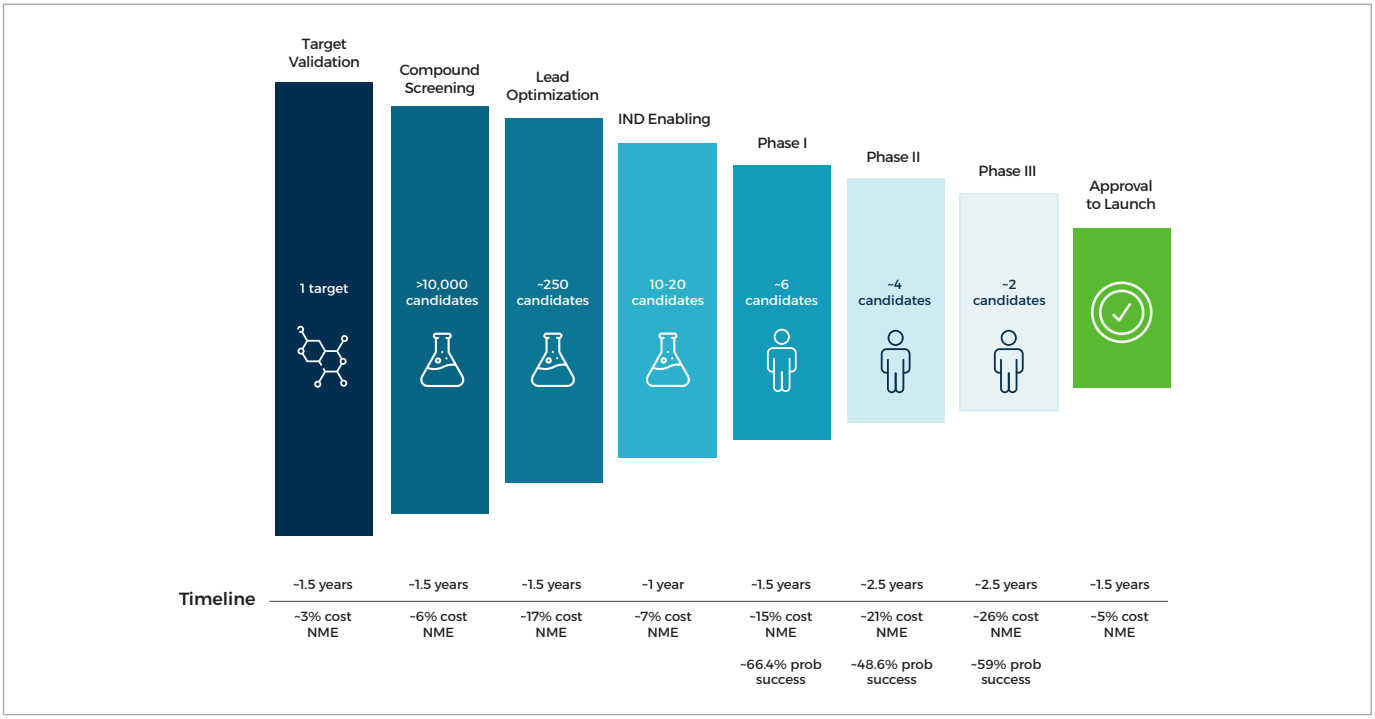
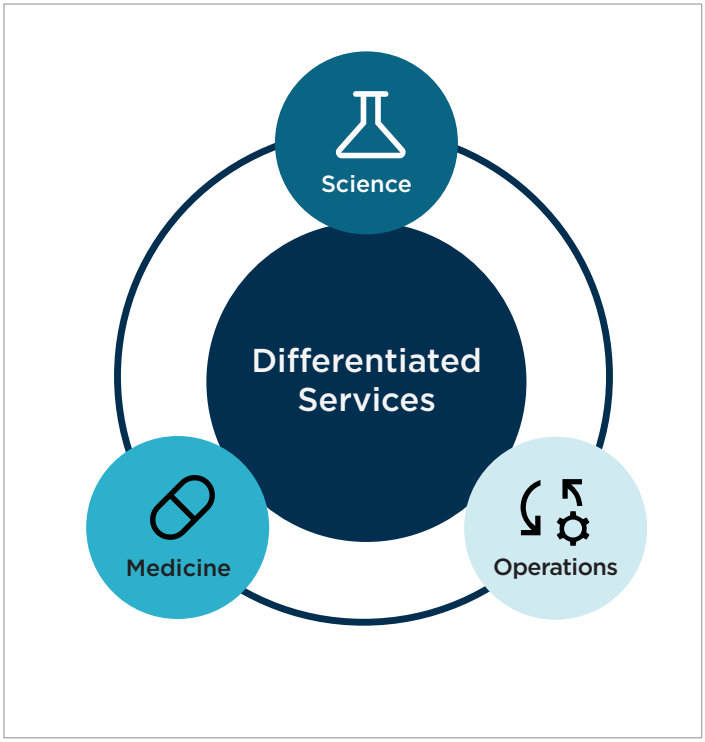


Figure 1. *Timeline for drug discovery and candidate compound attrition. (Adapted from Murphy & Badoux, 2023).*[2]

Natural Alliances: Science, Medicine, and Operations

An ability to appreciate and integrate potential product attributes within a clinical development program is essential in a partnership providing differentiated service.

A strategically based partnership between a sponsor and CRO, for example, complements the potential attributes of a novel drug candidate with savvy developmental acumen and staff who recognize that additive value is not an option but a necessity.[3] A foundation in science, medicine, and operations coupled with responsible resource management provides both sponsor and CRO with synergy.



Integrating multiple perspectives across functional disciplines contextualizes nonclinical data supporting product rationale while accommodating intuition and experience in the decision-making process. For example, an appreciation of the mechanism of action and molecular targets can prompt the development of a master protocol that may include concepts of both basket studies (multiple clinical targets) and umbrella designs (multiple therapeutic entities). This early phase design thus enhances product opportunity based on the anticipated pharmacological attributes of the test agent, acknowledging complex pathophysiology and operational demands.[4]

Thus, an initial engagement with a translational medicine team represents a required first step in the research and development partnership. Together, the sponsor and CRO can review product rationale, indication-specific nonclinical models, accessible clinical trial designs, and known and anticipated regulatory pathways leading to market authorization (MAA) or a New Drug Application (NDA). This task also includes an evaluation of the current clinical development landscapes as it might impact study metrics and expenditures, acknowledging both opportunities and encumbrances for product adoption and access. The above mosaic, including quantitative and qualitative assessments, is used to refine potential indications and patient populations.[5]

A sponsor may then closely align business planning with stages of development, available resources, and corporate objectives. One indication, for example, may be considered optimal concerning the totality of effort required within an overall program. However, the available "runway" for development may necessitate a brisk demonstration of target engagement to create enhanced investment opportunities.[6] Accordingly, partnerships that acknowledge each sponsor's specific goals tailored to scientific, medical, operational, and financial contributions are crucial.

Regulatory Engagements: Extensions of the Partnership Concept

Early phase studies are characterized by relatively restrictive inclusion/exclusion criteria to create a homogenous patient population. Enriching a population with a leveraged phenotype may facilitate the demonstration of treatment effects by maximizing assay sensitivity, which assures safety in the context of potential benefit with an acceptable impact upon generalizability.

In this process, a clinical development team may also contribute to creating strategic regulatory handshakes such as FastTrack, Orphan Drug, Breakthrough, and Prime designations, amongst others. These programs exist under the umbrella of regulatory incentives within the United States and the European Union and can accelerate program completion.[7,8]

Representative Regulatory Incentives

FastTrack (FDA)[9]

For treating serious conditions or life-threatening disease, with the potential to address an unmet medical need, based on nonclinical or clinical data available or mechanistic rationale. In addition to increased opportunities for regulatory interaction, the product is eligible for priority review. Ideal submission range is at the time of IND through pre-IND meeting.

Breakthrough therapy (FDA)[10]

For treatment of a serious condition with preliminary clinical evidence of therapeutic benefit either in Phase I or II. Increased regulatory interaction with cross disciplinary review team, with eligibility for rolling review or priority review. Submitted with an IND or as an amendment to an IND but no later than the end of a Phase II meeting.

PRIority MEdicines;[11] PRIME (EMA)

For treating conditions with an unmet medical need. Requires non-clinical and exploratory clinical data that shows potential for therapeutic benefit or substantial clinical improvement. This requires early and intensive multidisciplinary communication to inform development plans, provide scientific and study design advice. Ability of non-clinical and preliminary clinical evidence (FIH safety/tolerability data) to inform the timing of application.

Innovative Licensing and Access Pathway;[12] ILAP (MHRA)

For treating life-threatening disease or debilitating conditions with significant patient or public health need. To be eligible, the product fulfils at least 1 of the following criteria: innovative medicine, clinically significant new indication for approved medicine, rare disease and/or other special populations, aligns with objectives for UK public health priorities. This offers the potential to reduce time to marketing authorization, market access and patient access. Engaging early in development, availability of non-clinical data, and the three-step process to submit all impact decisions for timing of the application.

Proof-of-Concept: Building the Bridge Carefully to Cross it Quickly

Proof-of-concept (PoC) study planning requires discussion between multiple stakeholders regarding the optimal patient phenotype, most sensitive assessments, and the potential dose exposure-response relationship. These discussions are bounded by the framework of enabling GLP toxicology data and the feasibility of study conduct. Facility with both bespoke and more traditional study designs in proof-of-concept studies is essential.

Often, proof of concept may necessitate a duration of patient exposure beyond the framework of enabling GLP toxicology data, with sample sizes that cannot be pragmatically obtained. Thus, incorporating sensitive fluid, electrophysiological, or imaging endpoints in addition to clinical outcomes in a "fit for purpose" biomarker signature program becomes an alternative stratagem. This approach may accommodate a shorter duration of exposure with a smaller number of patients. The emerging interest in using external or synthetic controls is emblematic of opportunities and challenges in this regard.[13] However, the success of the planned study design remains highly contingent upon the collaborative expertise of staff within bioanalysis, drug discovery, biostatistics, and clinical operations.[14]

A balanced and 'de-risked' approach also includes including primary endpoint(s) that are approachable, meaningful, and sensitive to change in a given timeframe. Exploratory secondary endpoints(s) and analyses may further demonstrate product attributes and inform subsequent trial designs. Proof of concept designs may be aimed at 'hypothesis generation' in addition to testing. This approach significantly increases patient burden, encumbers study metrics, and increases overall expenditures, although it may accommodate multiple program objectives.[15]

All the above considerations require integrating clinical operations, biostatistics, finance, and medical and scientific affairs to coherently integrate concepts into a 'de-risked' development stratagem.

Thinking Globally, Acting Locally

Accentuating a trend in its third decade of evolution requires incorporating program enhancements based on an efficient global operational structure. The globalization of clinical research, appropriate to the stage of development, can provide distinct advantages of lowering costs (e.g., tax incentives, investigator fees) or accelerating drug development (e.g., regulatory flexibility in initial program implementation) while improving diversity in clinical research.[16]

Choosing a development partner with experience across therapeutic areas, geographic regions, and different regulatory agencies will allow a sponsor to pursue parallel workstreams to accelerate development timelines. For example, a developer may pursue a Phase I trial in Australia due to economic incentives and a relatively simplified regulatory interface to begin clinical trials efficiently. Simultaneously, the sponsor may initiate a traditional IND or CTA process within the United States or European Union, respectively, to introduce a global footprint into business planning.[17] Such parallel workstreams allow a product to continuously move forward, reducing the "white space" between subsequent phases of development.

Correspondingly, in an era of increasingly sophisticated therapies and niche patient populations, clinical monitoring has moved beyond foundational requirements for basic services into a sophisticated, informed site-level engagement. Study monitors must be conversational with the characteristics of an

investigational product in the context of a given patient population. For example, in cell and gene therapies, particularly within oncology, physician-led training of study coordinators with senior operations staff and site monitors on product and protocol characteristics provides a differentiated service, exemplified by a Clinical Research Associate (CRA) Academy.[18]

Regional representation across countries or regions universally is also a requirement in which cultural and linguistic capabilities are married to an appreciation of differences in standards of care (Figure 2). This includes eliciting feedback from patient advocacy groups, indication-specific organizations facilitating research, and commercial, not-for-profit, and academic organizations that may interface with contract research organizations.[19] Establishing a global operational footprint that facilitates contributions from multiple stakeholders is a differentiating aspect of international research.

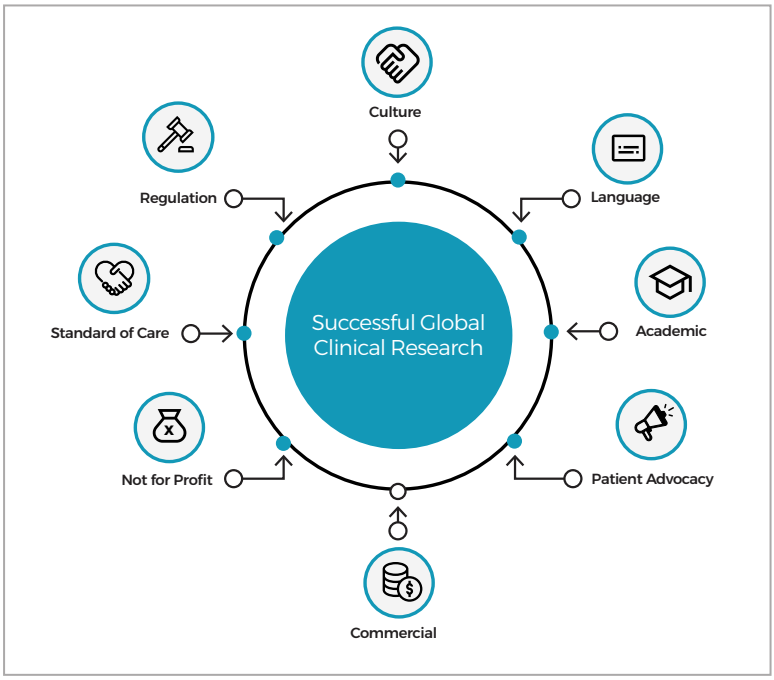


Figure 2. *Integrating the perspectives of multiple stakeholders in global clinical research.*

An informed Governance Structure

An ideal interaction between a sponsor and CRO involves interconnected activities empowering all participants based on corporate objectives, regulatory requirements, and the need for increasingly sophisticated clinical oversight assuring data integrity. The most efficient corporate governance thus results in a matrix of reciprocal responsibilities within the strategic partnership. As an example, a hierarchical escalation scheme is created where individuals possessing different subject matter expertise remain on a team for the duration of a program, with varying levels of contribution throughout the program's evolution (Figure 3).

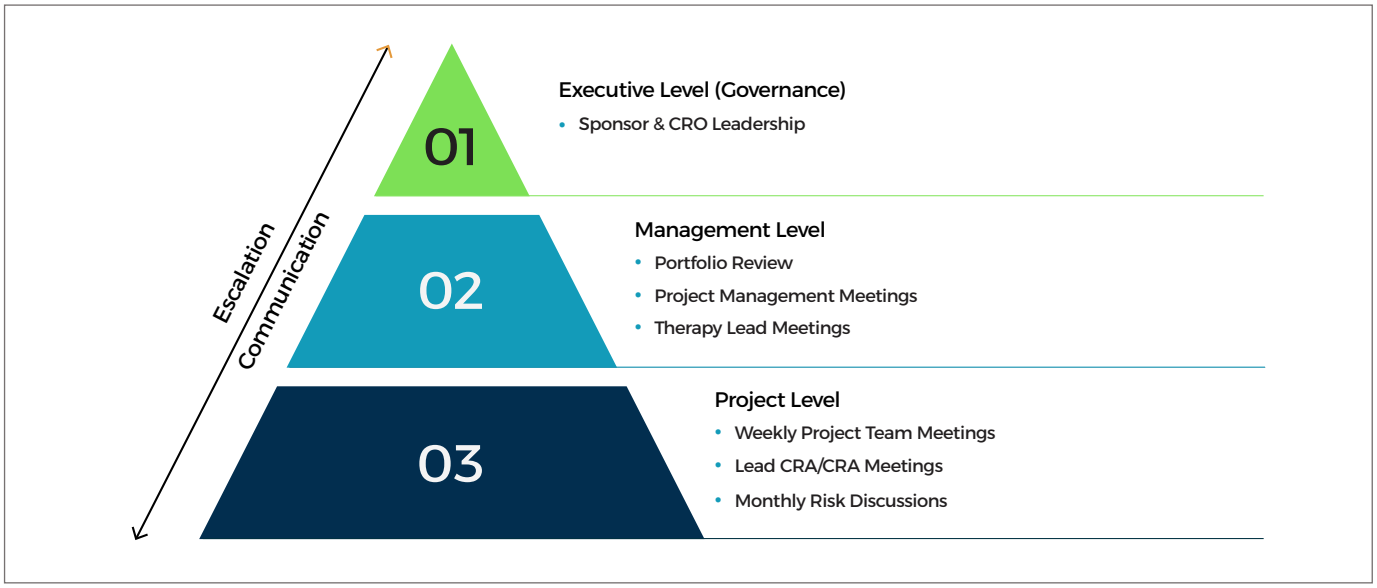


Figure 3. *Governance structure within strategic partnerships.*

Demonstrating Value Beyond Novelty

Early phase studies appropriately inform safety, dose range, and efficacy. However, innovative early phase programs achieve this success while simultaneously limiting the generalizability of data relevant to standards of care in more representative patient populations.[20] Potentially pivotal studies, in contrast, build on confirmed safety and efficacy obtained from ideal investigative sites and patients and examine "effectiveness" in an environment which is more representative of that likely encountered following product approval. Incorporating patient, physician, and payer perspectives into a development program thus converge to ensure approval (a regulatory function) and adoption (a physician prerogative), with access increasingly dominated by commercial and government organizations dictating formulary placement and reimbursement.

The clinical development team can serve multiple needs in this process. For example, data collected during open-label extensions in support of a mandatory clinical safety base would also allow for the collection of 'pilot' data to inform healthcare utilization (both direct and indirect costs) over longer-term observations.[21,22] An interlocking set of questions, implemented in the context of a clinical development program, thus helps to establish patient access at a targeted price (Figure 4).

- Regional differences – U.S. (budget impact) / E.U. (cost-effectiveness)
- Differences by plan; e.g., commercial plans, self-insured, or government
- Does the product fit into existing reimbursement systems, or will it need new codes?
- Will the target price be compatible with available reimbursement?
- What is the perceived value from each key stakeholder
- Are there opportunities to access additional reimbursement?
- What clinical evidence is required to establish patient access at the targeted price?

Figure 4. *Important questions for consideration in clinical development programs.*

Conclusion

Strategic partnerships enhance research and development at multiple touchpoints during a product's lifecycle. When constituted properly and operated efficiently, each stage of a milestone development program enhances the prospects for delineating product value at subsequent steps. The collective effort maximizes guidance available from sophisticated regulatory programs that can accelerate product development, utilizes study innovation where appropriate to maximize assay sensitivity, and exploits opportunities afforded by an international footprint for trial operations with linguistically and culturally competent professional staff. A strategic partnership thus results in a matrix of engagements with subject matter experts across functional groups, providing expertise and experience throughout a program's evolution.

What begins as a "business handshake" for transactional services extends into a comprehensive development program with dedicated staff who are contributory at each stage of product development from late phase discovery through all phases of clinical research, culminating in successful commercialization. Strategic partnerships efficiently position candidate therapeutics for success with predictable metrics and expenditures and optimal opportunities for product differentiation. Partnerships provide synergy and momentum in drug development, affording patients, their families, and healthcare providers new treatment opportunities for improved quality of life.

Contact us today for more information or to discuss methods for optimizing your clinical research strategy.

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