FRIENDS of CANCER RESEARCH

Seamless Clinical Trial Designs in Rare Cancers: Leveraging Operational and Adaptive Strategies to Accelerate Drug Development

White Paper | 2025

Executive Summary

Rare cancers pose unique challenges for drug development. Small, heterogeneous patient populations can limit the feasibility of traditional randomized controlled trials, slowing evidence generation and resulting in delayed access to potentially life-saving therapies. Sequential evaluation of safety, dosage optimization, and efficacy in distinct phases can be slow and resource-intensive, creating inefficiencies in rare cancer development. More deliberate integration of these stages within a seamless framework can maximize learning from each patient, improve operational efficiency, and accelerate evidence generation. Additionally, development programs consisting of multiple distinct sequential clinical trials may not provide the ability to optimally leverage data from each patient, which is particularly crucial for rare cancer product development.

Seamless clinical trials build on common early-phase approaches—such as dose escalation and cohort expansion—by more thoughtfully integrating multiple development stages, including dosage optimization and efficacy evaluation, within a single framework. This approach can reduce downtime between phases, maximize learning from each patient, and allow adaptive modifications to the trial based on emerging data. Despite these advantages, seamless trial designs remain underutilized in rare cancer drug development.

To address these challenges, Friends of Cancer Research (*Friends*) convened a multi-stakeholder working group including experts from patient advocacy organizations, pharmaceutical companies, academia, National Cancer Institute (NCI) and the U.S. Food and Drug Administration (FDA) to identify critical design considerations and explore strategies for operationalizing these efficiencies offered by the seamless design framework in rare cancer development. The group explored several strategies and considerations:

- Seamless trial designs: These approaches integrate multiple development stages under a single framework, with inferential designs pooling data across stages for integrated analyses. Selecting the appropriate approach depends on objectives, patient population, and endpoints.
    - Operational considerations: Seamless designs can enable faster transitions from dose escalation to expansion, incorporate data from early-phase patients into later analyses, and can embed randomization, maximizing learning from each patient.
- Endpoints and adaptive features: Early, meaningful endpoints maximize the insights gained from each patient and can inform pre-specified adaptations, such as adjusting dose levels, expanding promising cohorts, or refining eligibility criteria. These adaptations occur according to predefined rules based on interim analyses, ensuring that decisions are guided by accumulating data while maintaining statistical rigor and trial integrity.
- Regulatory and patient engagement: Early and ongoing dialogue with regulatory authorities clarifies expectations around use of novel endpoints, adaptive features, and integrated analyses. Engaging patient advocates ensures trial designs reflect patient priorities, tolerability considerations, and operational feasibility, particularly in rare disease settings.

These insights highlight that seamless trials require careful planning, adaptive design, and close coordination with stakeholders to balance scientific rigor, operational feasibility, and patient benefit. By thoughtfully implementing these approaches, sponsors can accelerate patient access to new therapies, maximize evidence generation from limited populations, ensure safety, and provide a flexible yet rigorous framework for rare cancer drug development.

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This white paper was developed through discussions that included these experts and other perspectives representing academia, industry, the U.S. Food and Drug Administration, and the patient advocacy community. The views expressed here represent the collective insights from working group discussions and do not necessarily reflect the official positions of any individual organization.

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Introduction

Challenges of Rare Cancer Drug Development

Developing new therapies for rare cancers presents complex challenges that distinguish these diseases from more common malignancies. In many cases, the small number of eligible patients globally limits the feasibility of traditional randomized controlled trials (RCTs) and slows evidence generation. This rarity, combined with heterogeneity in disease biology, limited natural history data, low-prevalence biomarker-defined populations, and inadequate or absent standards of care (SOC), constrains trial enrollment, complicates trial design, and can reduce the generalizability of results. Additionally, limited financial incentives and constrained resources for conducting trials make efficient use of available patients and data even more critical. In rare cancers, inefficient trial designs or delays can have an outsized impact—slowing patient access, limiting evidence generation, and potentially missing opportunities to identify effective therapies.

Although challenges with traditional phased development are not unique to rare diseases, they are often magnified when patient numbers are small. Generally, traditional phased development starts with dose-finding studies and may be followed by registrational trials and confirmatory trials, which are often resource-intensive and time-consuming. Pauses between phases for protocol development and site activation may introduce delays that hinder patient access, risk losing the momentum of site engagement and patient recruitment, and limit efficient use of trial data across stages. Although randomization can be challenging to implement broadly in rare cancers due to small patient populations and often, because of the limitations of SOC which precludes clinical equipoise, it can be informative in certain context, such as when multiple dosages are under evaluation or within platform trials.

The significant unmet clinical need in rare cancer populations demands more agile approaches to drug development that maintain scientific rigor while improving efficiency. Patients with rare cancers are often enrolled in early-phase trials with broad study population (i.e., all solid tumors). As a result, the data are often fragmented, and hypothesis tests are underpowered, missing opportunities to generate meaningful evidence. Additionally, foundational knowledge about the patient population, treatment patterns, and clinical outcomes should be generated alongside the clinical trial itself. These realities highlight the need for trial designs that are efficient, representative of the intended population, and adaptable—maximizing insights from every enrolled patient while maintaining the robustness and reliability of the evidence.

Regulatory and Scientific Trends

Over the past decade, the U.S. Food and Drug Administration (FDA) has issued guidance documents and demonstrated openness toward flexible strategies to generate evidence in settings of unmet medical need, including rare cancers.[1–4] Sponsors have often employed single-arm designs, intermediate clinical endpoints such as objective response, and adaptive trial designs in appropriate contexts. While early-phase oncology studies often include dose-finding and cohort expansion, more deliberate integration of additional seamless elements—such as adaptive cohort transitions or combined efficacy and safety assessments—remains limited in rare cancer development. Shared experience and best-practice frameworks for implementing these approaches are still sparse, creating uncertainty for sponsors and regulators. Broader adoption of seamless approaches in rare cancer development could enhance data continuity, maximize scientific and clinical insights, and accelerate access to promising therapies.

Scope

This white paper describes seamless clinical trials and design elements tailored to the challenges of rare cancers. These designs may integrate early-stage clinical evaluation with potential registrational intent into a single protocol, or they may be applied to specific portions of clinical development to enable more efficient evidence generation.

We describe what constitutes a seamless trial in this context, identify key considerations in trial structure and implementation, and outline specific use cases to illustrate when and how these strategies may be applied. The main objective is to provide a practical foundation to inform thoughtful, feasible, and scientifically robust trial designs that improve continuity, efficiency, and impact in rare cancer drug development.

Understanding Seamless Trials: Definitions, Benefits, and Relevance to Rare Cancers

Seamless clinical trials can accelerate and streamline drug development by integrating multiple trial stages within a single, continuous protocol. This approach can promote more efficient evidence generation, minimize delays between phases, and support real-time decision-making based on emerging data. For the purposes of this paper, we define a seamless clinical trial as:

"A clinical trial integrating multiple, sequential stages of drug development—such as dose escalation, dosage optimization, cohort expansion, and efficacy assessment—within a single framework."

By consolidating these stages, seamless trials can enhance efficiency, ensure consistency, and maximize the scientific and evidentiary value of each patient's participation. Seamless designs may incorporate pre-specified adaptive features, allowing modifications to aspects such as sample size, dosage optimization, or expansion criteria based on emerging data, provided these adaptations are pre-specified and carefully justified. Seamless designs vary in scope and complexity and can be broadly categorized as operationally or inferentially seamless, as summarized in Table 1.

Table 1. Seamless Trial Types, Key Features, and Benefits Relative to Traditional Single-Phase Trials

Approach	Description	Key Features	Purpose & Benefits
Operationally Seamless	Continuous trial conduct across multiple stages within a single protocol	Single continuous protocol; minimal enrollment gaps; early data informs later decisions; streamlined enrollment and data collection	Reduces delays, maintains trial momentum, and maximizes insights from each patient, addressing the primary challenges of rare cancers
Inferentially Seamless	Data from multiple stages are pooled and analyzed together to support unified conclusions	Combined analysis; integrated statistical plan	Enhances statistical efficiency, reduces sample size requirements, and supports cohesive decision-making across trial stages

In practice, all inferentially seamless trials are operationally seamless, but not all operationally seamless trials include inferential pooling. Operationally seamless designs may incorporate multiple expansion

cohorts, including those with potential registrational intent, and are often preferred in rare cancer settings when early-stage and later-stage endpoints differ, or when the limited scientific understanding of a novel agent warrants independent analyses—such as initiating with a dose-finding stage in a mixed tumor cohort before moving to a histology-specific expansion phase with different efficacy measures. By contrast, inferentially seamless features are most valuable when eligibility criteria, endpoints, and trial populations remain consistent across stages, allowing data to be combined—such as in a rare cancer trial where both the exploratory and confirmatory stages assess the same objective response endpoint in the same patient population.

Selecting the appropriate seamless features enables sponsors to optimize scarce patient resources, maintain statistical validity, and meet regulatory expectations while accelerating development in areas of unmet need.

Why Are Seamless Trials Important for Rare Cancers?

Seamless trials are particularly valuable for rare cancers because they help to:

- Minimize redundancy and enrollment delays: Avoiding separate protocols and site start-up processes helps preserve momentum, which is particularly important in rare cancers where recruitment is difficult, and patients may only be eligible for a single trial.
- Reduce patient exposure to ineffective therapies: By integrating early indicators of activity, seamless designs can identify ineffective interventions sooner, placing patient well-being at the center of trial efficiency.
- Enable real-time learning and adaptation: Seamless designs can accommodate multiple objectives from early and later stages, such as moving from early phase questions about dosage to objectives aimed at registration based on emerging signals.
- Maximize insights per patient enrolled: Given the limited number of eligible patients, integrating data across trial stages ensures that no clinical evidence is lost and data collected in early stages can inform later decisions and inferences.
- Support intermediate clinical endpoints or early measures of activity: Seamless trials allow incorporation of early signals to guide trial progress and inform dosage or cohort decisions.
- Leverage regulatory flexibility and enhance efficient evidence: Recent published FDA guidance reflects openness to well-justified, innovative trial designs.[1–4] Seamless trials may align well with approval pathways when thoughtfully planned and appropriately justified. For example, FDA OCE's Project FrontRunner highlights opportunities for using a seamless randomized approach to generate evidence for accelerated approval and verify clinical benefit for subsequent traditional approval in the front-line advanced/metastatic setting.[5]
- Facilitate faster patient access to promising therapies: By aiming to reduce pauses between phases and integrate registrational intent earlier, seamless trials can shorten timelines and provide patients with earlier access to potentially effective therapies.

Seamless design challenges relating to operational complexity, statistical considerations, and regulatory planning must be carefully managed to reduce bias impact and maintain trial integrity and interpretability. Their use in rare cancers must be grounded in both flexibility and rigor, balancing efficiency with meaningful evidence generation.

Challenges in Seamless Trials for Rare Cancer Drug Development

Despite the potential advantages of seamless trial designs, rare cancer development presents inherent challenges that can complicate trial approaches. These hurdles can make seamless designs more difficult to implement effectively. Table 2 summarizes the key challenges identified in both rare cancer and seamless trial contexts. Taken together, these challenges show that while seamless trials may reduce redundancy, they require deliberate planning to ensure interpretability and patient benefit.

Table 2. Key Challenges in Implementing Seamless Trials for Rare Cancer Drug Development

Scientific and Statistical Considerations	• Fully integrated seamless trial designs remain uncommon in rare cancer development. • Novel endpoints or adaptive rules require careful characterization. • Small populations amplify statistical uncertainty; traditional p-value frameworks may be underpowered, requiring alternative approaches
Operational Complexity	• Challenges coordinating early-phase developers with rare cancer disease experts. • Trials enrolling multiple rare cancer subtypes/tumors require coordination across investigators and institutions to ensure adequate representation and consistency. • Multi-regional trials face divergent regulations, SOC, and data collection requirements, which can disrupt enrollment and trial continuity.
Endpoint Selection and Evidence Generation	• Endpoints (ORR or DOR (e.g., objective response or duration of response)) for tumor activity in early phases can support go/no-go decisions; but their predictive value for long-term clinical benefit in rare cancers is not always typically established • Reliance on external or historical control data to inform go/no-go decisions can be challenging and unreliable in rapidly evolving treatment landscapes. • Traditional endpoints (e.g., OS, PFS) may require long follow-up, be underpowered and/or large sample sizes, or may be insufficient to capture other similarly meaningful aspects of patient experience; or may be impractical as patients transition through multiple therapies.
Dosage Optimization and Safety	• Limited prior clinical data and small patient cohorts complicate dosage optimization; may preclude extensive dosage optimization and safety monitoring. • Adaptive rules for dosage or cohort modifications must balance pre-specification with flexibility. • Higher risk of suboptimal dosage or missed safety signals compared with common cancers.

Abbreviations: SOC, standard of care; OS, overall survival; PFS, progression free survival.

Types of Seamless Approaches (Case Studies & Scenario Based)

Seamless trial strategies should be adapted to the unique context of each development program. Key factors such as disease rarity, heterogeneity of the patient population, robustness of understanding of the disease's natural history, prior knowledge of the therapeutic target, and regulatory goals shape both the feasibility of a seamless design and its implementation.

The following case studies illustrate a range of approaches: (1) early-phase dose-finding trials with efficacy signals; (2) seamless trials with registrational intent; and (3) seamless trials with randomized components. Together, they illustrate both the potential of seamless strategies to accelerate development in rare cancers and the operational challenges that can slow progress.

Early-Phase Dose-Finding Trials with Efficacy Signals

FIGHT-101

FIGHT-101 (NCT02393248) was a first-in-human (FiH) trial of pemigatinib, an FGFR inhibitor, in patients with advanced solid tumors (Table 3).[6] The trial progressed operationally seamlessly from dose-escalation into expansion cohorts that included rare cancers such as cholangiocarcinoma. Key operational considerations included balancing pharmacokinetic and broader drug development expertise alongside disease-specific insights, site selection, and protocol flexibility.

This trial exemplifies how seamless trial designs can inform subsequent registrational studies. Insights from FIGHT-101 supported the design of FIGHT-202, a dedicated study of pemigatinib monotherapy in FGFR-altered cholangiocarcinoma,[7] which ultimately supported FDA approval.[8,9]

Key Insight: Seamless early-phase trials can accelerate dose finding and provide early activity signals in rare cancers, but their success depends on aligning with experienced investigators in FiH trial conduct as well as early activity assessment, engaging trial sites equipped to manage complex protocols, and anticipating the operational trade-offs. They can generate critical pharmacology and safety data that can inform later trial decisions, and proactive regulatory engagement—through Investigational New Drug submissions, pre-New Drug Application meetings, and targeted feedback on dosing or safety questions—can help guide registrational planning. When combined with prior disease knowledge and clear regulatory engagement, seamless designs can set the stage for registrational trials and expand treatment options in areas of unmet need.

Table 3. Key Features of FIGHT-101 Trial

Key design, operational, and patient population features

Feature	Details
Population / Rarity	• Advanced, refractory malignancies with or without FGF/FGFR alterations, including NSCLC, cholangiocarcinoma, urothelial, pancreatic, head and neck, and other solid tumors ○ Alterations are uncommon (generally ~8–15% in urothelial and cholangiocarcinoma, and <5% in NSCLC, pancreatic, and head and neck cancers). • Rare molecular subtypes; later cohort enriched by FGFR status. • Data from 128 patients who received pemigatinib monotherapy (dose escalation Part 1: n=49; dose expansion Part 2: n=79), with patients receiving either intermittent (n=70) or continuous (n=58) dosing.
Seamless Features	• Dose escalation stage transitioned directly into expansion. • Multiple expansion cohorts defined by tumor type and FGFR alteration status; enrollment adapted based on emerging activity signals.
Key Design / Operational Decisions	• Standard 3+3 dose-escalation scheme to determine MTD and recommended dosage. • Safety monitoring (dose interruptions/reductions for TEAEs) • Operational flexibility to evaluate a broad spectrum of tumors and FGFR alterations within one study.
Endpoints	• Escalation: MTD, RP2D, safety, PK/PD, and biomarker correlations. • Expansion: activity (primary endpoint: ORR), DOR, PFS, OS, and safety; and exploratory assessment of predictive biomarkers and FGFR alteration–driven responses.
Regulatory Interactions / Outcomes	• Data from patients informed dosage selection for subsequent studies. ○ FIGHT-101 was conducted prior to the FDA's Project Optimus initiative. • Signals of antitumor activity and safety across multiple tumor types supported initiation of a registrational trial (FIGHT-202), with a primary endpoint that differed from FIGHT-101.

Abbreviations: NSCLC, non-small cell lung cancer; MTD, maximum tolerated dose; TEAE, treatment-emergent adverse event; RP2D, recommended phase two dose; PK/PD, pharmacokinetics/ pharmacodynamics; OR, objective response, DOR, duration of response; PFS, progression-free survival; OS, overall survival.

Seamless with Registrational Intent

ARROW

ARROW (NCT03037385) evaluated pralsetinib, a RET tyrosine kinase inhibitor, in RET fusion-positive non-small cell lung cancer (NSCLC), thyroid cancer, and other RET-altered tumors using an inferentially seamless design with registrational intent (Table 4).[10] Patients who received the recommended dosage during the dose-finding portion were integrated into pivotal analyses. The design combined dose escalation and

multiple expansion cohorts, allowing early data to guide enrollment and cohort adaptations. This structure enabled data generation within a unified study framework.

The trial ultimately supported FDA approval of pralsetinib for treatment of RET fusion-positive NSCLC and thyroid cancers, with additional expansion cohorts exploring other RET-altered tumors.[11–13]

Table 4. Key Features of ARROW Trial

Key design, operational, and patient population features

Feature	Details
Population / Rarity	• Patients with advanced RET-altered solid tumors including NSCLC (~1–2% prevalence), medullary thyroid cancer (50–80% RET mutations), and other RET-fusion tumors • Data from 647 total patients (dose-escalation: 62; expansion and registrational cohorts: 585). ○ Data from 471 patients at selected dose (NSCLC: 233; thyroid cancer: 162; other RET-fusion tumors: 76)
Seamless Features	• Inferentially seamless design integrating first-in-human dose escalation, cohort expansion, and registrational intent within a single protocol • Data from patients at recommended dosage included in dataset to support approval • Multiple expansion cohorts defined by tumor type and prior therapy; cohort sizes adapted in response to emerging data.
Key Design / Operational Decisions	• BOIN dose-escalation in small cohorts, with selected dosage determined by tolerability and activity. • Adaptive cohort sizing (e.g., Group 2 NSCLC increased from ~80 → 200) was not prespecified and occurred via protocol amendments based on emerging data. • Operational flexibility achieved through protocol amendments • Safety monitoring tailored to tumor type and prior therapy
Endpoints	• Escalation: MTD, RP2D, safety, OR, PK/PD, biomarker correlations • Expansion and registrational (NSCLC cohorts): activity (primary endpoint: OR), DOR, CB, DC, PFS, OS, intracranial response, safety
Regulatory Interactions / Outcomes	• Data from patients who received the proposed recommended dosage supported U.S. approvals for RET fusion-positive NSCLC and thyroid cancers.

Abbreviations: NSCLC, non-small cell lung cancer; BOIN, Bayesian Optimal Interval; MTD, maximum tolerated dose; OR, overall response; PK/PD, pharmacokinetics/pharmacodynamics; DOR, duration of response; CB, clinical benefit; DC, disease control; PFS, progression-free survival; OS, overall survival.

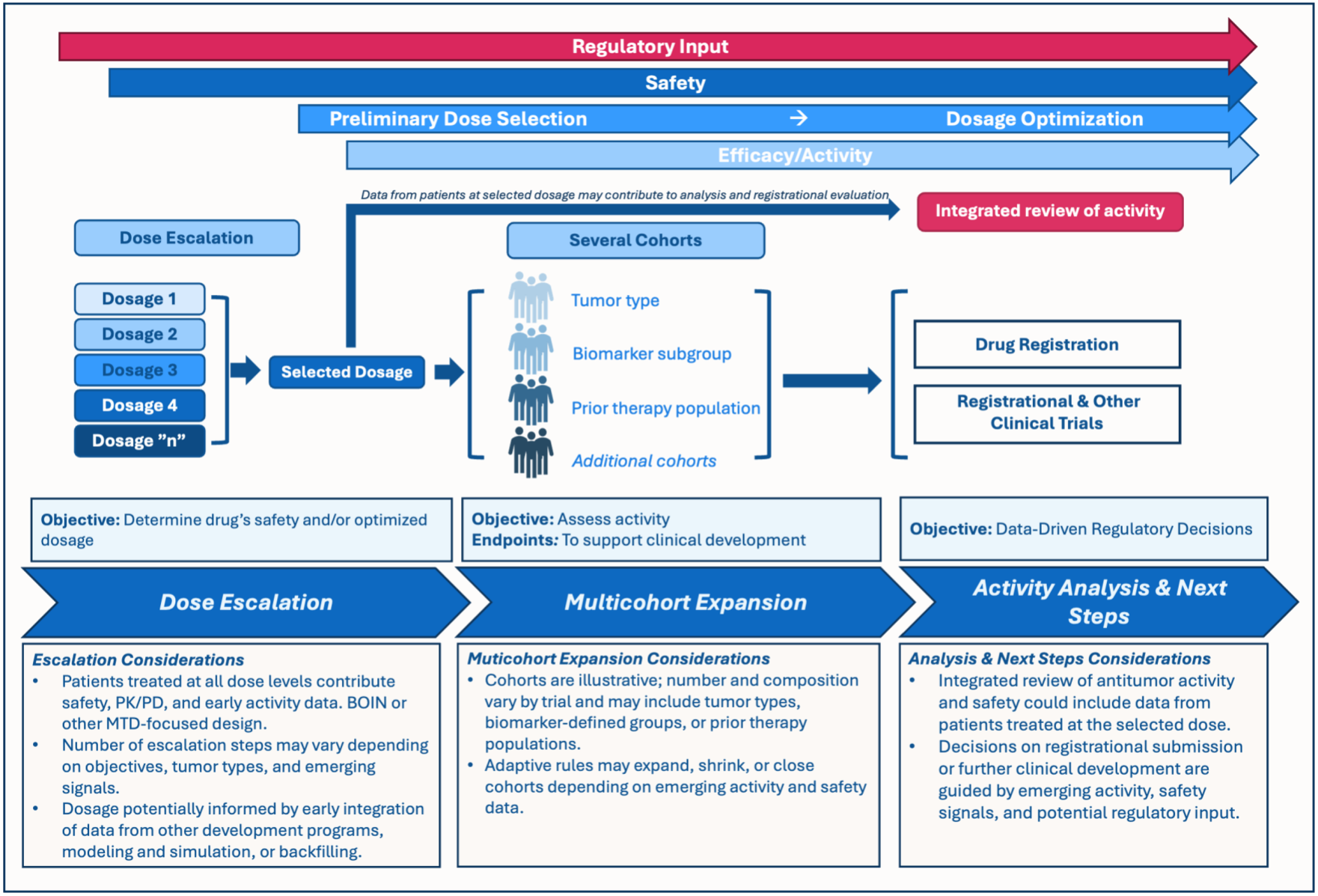
Key Insight: Seamless designs can enable faster development and support multiple approvals when expansion cohorts show consistent, high response rates. When robust efficacy is observed across tumor types, treatment lines, or specific biomarkers, efficiencies in development may be largely driven by the drug itself. Integrating patients who received the RP2D from early cohorts into analyses to support the approval can shorten timelines but requires clear regulatory alignment on dosage optimization, adaptive rules, and safety monitoring. Single studies can include multiple expansion cohorts that could support distinct

indications, though successful implementation depends on structured dosage-optimization strategies, careful endpoint selection, and balancing pre-specified elements with necessary flexibility to maintain statistical rigor and operational feasibility.

ARROW applied a seamless trial design in RET fusion-positive NSCLC, integrating adaptive dose escalation with multiple expansion cohorts and pooling patients treated at the RP2D to support registration. Other drugs used a similar approach, including LIBRETTO-001; this inferentially seamless trial was designed to evaluate selpercatinib in patients with previously treated and treatment-naive RET fusion-positive NSCLC, and incorporated data from the dose escalation portion into the primary efficacy analysis to maximize data and follow-up.[14–16] TRIDENT-1 also used an inferentially seamless design in ROS1 fusion-positive NSCLC, enrolling multiple molecularly defined cohorts—including TKI-naive and pretreated patients—and pooled data from patients enrolled in dose-finding to optimize sample size and evaluate efficacy across diverse populations.[17–19] It is important to note that these studies were conducted prior to the FDA's Project Optimus initiative final guidance, emphasizing systematic dosage optimization.

Across these trials, the seamless design strategy—combining dose-escalation, adaptive cohort expansion, and integrated analyses to support registration—demonstrates a flexible and pragmatic approach, which can incorporate elements such as pooling patients across development and tailoring dosage finding to accelerate development. This structure can help enable faster development, support multiple patient populations within a single protocol, and provide a framework for efficiently generating the evidence needed for regulatory approval. Figure 1 illustrates a potential general structure for trial designs, highlighting key elements such as cohort expansion, dose escalation, and pooling strategies, while demonstrating the adaptability of seamless designs across different disease contexts.

Figure 1. Conceptual Model of Seamless Trial Structure with Registrational Intent



Abbreviations: BOIN, Bayesian optimal interval; MTD, maximum tolerated dose; ORR, overall response rate; PK/PD, pharmacokinetics/pharmacodynamics; DOR, duration of response; PFS, progression-free survival.

Seamless with Randomized Components

RINGSIDE

RINGSIDE (NCT04871282) is an ongoing clinical trial evaluating AL102, a γ-secretase inhibitor, in patients with desmoid tumors, a rare and locally aggressive fibroblastic neoplasm (Table 5).[20] The trial was designed as an integrated Phase II/III study: an open-label Phase II dose-finding stage explored multiple dosing regimens, while a randomized, double-blind, placebo-controlled Phase III is underway to confirm efficacy and safety of the selected regimen.

Table 5. Key Features of RINGSIDE Trial

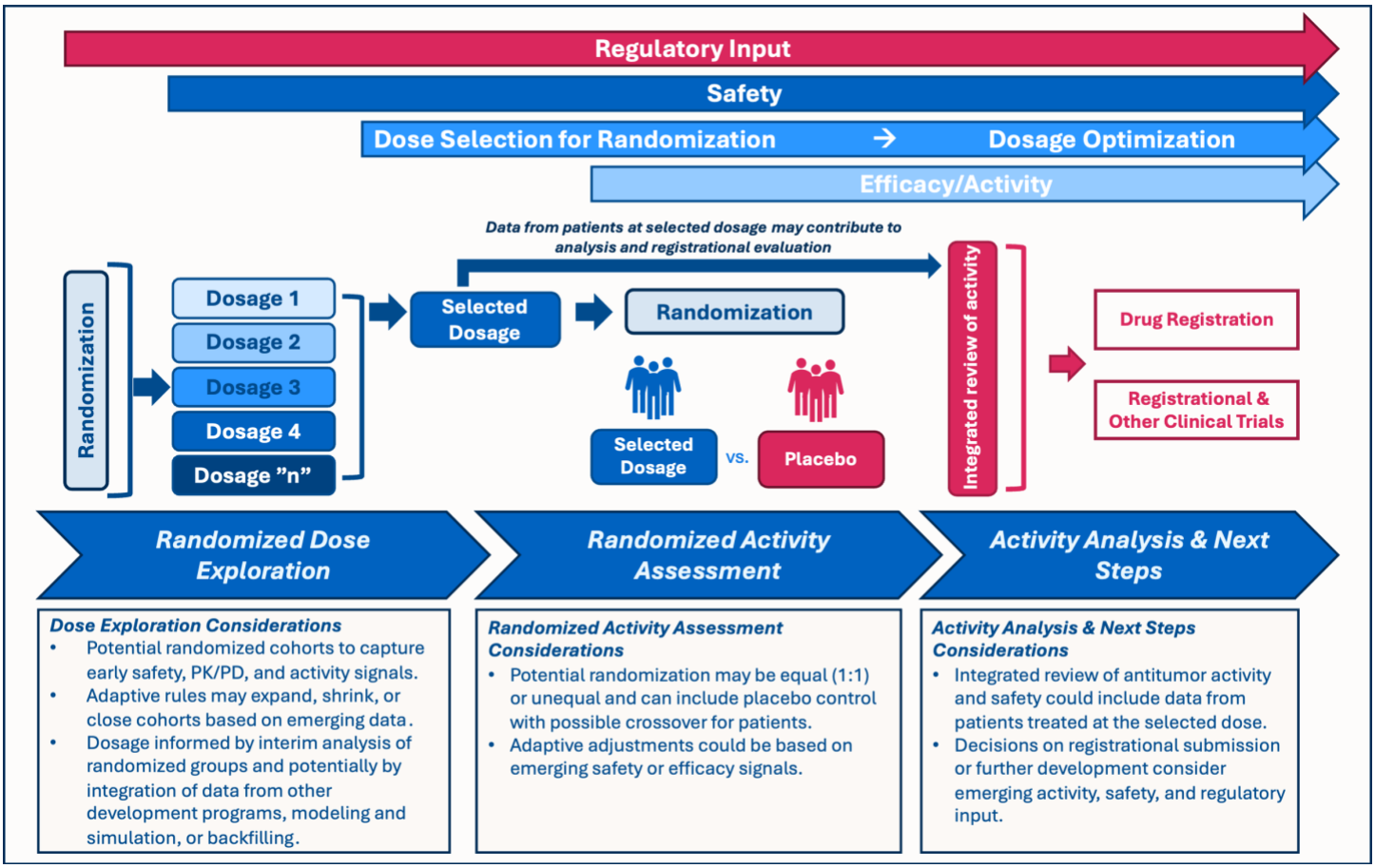
Key design, operational, and patient population features

Feature	Details
Population / Rarity	• Adults with progressing desmoid tumors (aggressive fibromatosis); 42 patients enrolled in initial activity assessment; multi-country pivotal stage ongoing. • Ultra-rare soft-tissue tumors (~2–4 per million annually)
Seamless Features	• Initial randomized evaluation of multiple doses to identify optimal regimen. • Randomization embedded at both activity/efficacy and registrational stages. • Operationally seamless design, without carryover of patients.
Key Design / Operational Decisions	• Randomized, placebo-controlled assessment to evaluate antitumor activity and safety. • Adaptive dosing and cohort selection based on emerging activity data.
Endpoints	• Early evaluation: tumor response, disease control rate, tumor volume change, T2 signal intensity; safety and tolerability. • Confirmatory evaluation: progression-free survival (primary), symptom control, quality of life, overall safety.
Regulatory Interactions / Outcomes	• Dosage selection for the ongoing Phase III study.

Key Insight: Seamless trials are not confined to single-arm expansion strategies; they can also integrate randomization at pivotal stages. By embedding randomized cohorts within a seamless framework, sponsors can capture early safety and activity signals while simultaneously generating the confirmatory evidence regulators require. Randomized seamless designs may be particularly valuable in rare cancers, where efficient use of limited patient populations must be weighed against the need for credible, comparative evidence.

Figure 2 illustrates a potential structure for seamless Phase II/III trial designs, highlighting key elements such as randomized dose exploration, dosage selection, and activity evaluation, while showing how randomization can be embedded at multiple stages to generate early safety and efficacy signals alongside confirmatory evidence.

Figure 2. Conceptual Model of Seamless Trial Structure with Randomized Components



Abbreviations: PK/PD, pharmacokinetics/pharmacodynamics

Key Design and Operational Considerations

Patient and Advocate Engagement

Engaging patient advocacy groups early in trial planning is particularly critical in rare cancers. Advocates can provide insights on patient priorities, tolerability, and feasibility, particularly in limited populations. Inclusion of patient advocates and key opinion leaders in FDA meetings allows discussion of complex trade-offs in trial design, dosing, and treatment considerations. Input from advocates helps ensure seamless trial elements are meaningful from the patient perspective, including early endpoints, adaptive features, and pragmatic design elements. By combining iterative learning, flexible frameworks, and patient-centered input, seamless designs can accelerate drug development while generating high-quality evidence that addresses both clinical and patient priorities.

Regulatory Engagement and Global Considerations

Early and ongoing engagement with regulators is essential for employing seamless trial designs to facilitate rare cancer drug development. In rare cancers, proactive regulatory dialogue can help clarify expectations on important elements of trial design and other aspects of development, such as inferentially designed elements (e.g., pool strategies) or dosage optimization strategies, thus reducing the risk of late-stage redesigns or delays. Formal FDA meetings, such as Type B, C, or D meetings, provide a structured forum for

clear guidance on trial design, adaptive features, dosage optimization, and regulatory expectations, and allow sponsors to align adaptations with regulatory priorities and ensure trial integrity despite mid-course adjustments.[21,22]

Beyond FDA, global regulatory coordination is increasingly important. Many rare cancer trials recruit globally to achieve sufficient enrollment, which introduces complexities related to varying SOCs, ethical frameworks, and data collection practices. Divergent expectations around acceptable endpoints or evidence thresholds can create hurdles for sponsors aiming to generate unified evidence packages. International engagement early in trial planning—through initiatives like parallel scientific advice meetings—can help facilitate international development, reduce duplication, and expand access to clinical trials. Seamless designs, by nature of integrating multiple phases and endpoints, amplify the importance of early discussions to aid in achieving an international development program that can satisfy regulatory expectations of multiple regulatory authorities.

Feasibility: Safety Assessments and Dosage Optimization

Dosage optimization presents unique challenges in rare cancers. Because reliable early measures of antitumor activity are often lacking, dosage selection may be primarily guided by toxicity, which can hinder dosage optimization.

Thoughtful use of validated clinical outcome assessments (COAs) can provide additional insight into tolerability and symptom burden, helping guide dosage optimization. Pre-specified dose-finding schemes may require mid-course adjustments as accumulating data refine understanding of dose- and exposure- and response relationships for safety and activity. Safety run-ins can be considered for monitoring, dosage selection, and seamless trial conduct. When a drug is already approved in other indications, extensive safety evaluations may not be needed; however, assessing potential safety issues or key pharmacokinetics (PK) interactions with new treatment regimens remain essential. Adaptive evaluations of multiple doses, supported by early PK and exposure–response analyses, can maximize learning from each patient. Dosage optimization strategies must balance scientific rigor with feasibility given small cohorts, competing SOCs, and heterogeneous trial sites.

Pediatric Considerations

For pediatric populations, potential differences in PK, between very young and older pediatric patients due to ontogeny, age-appropriate formulation considerations, and developmental-specific safety concerns for some products can affect dosage optimization and adaptive strategies. Adaptive strategies may include adjusting dosages, cohort progression, or enrollment criteria based on accumulating pediatric PK, safety, or activity data. While safety profiles are often similar in pediatric and adult patients, seamless trial designs may require modifications—such as staggered cohort enrollment or additional monitoring—to ensure integrated dose-escalation and expansion elements are safe and appropriate for younger patients.

Balancing Pre-Specification and Flexibility

Balancing pre-specification with the need for protocol amendments is a central challenge in seamless trials. Pre-specifying rules for dose expansion, dropping arms, or patient pooling across phases help maintain statistical rigor and enable confidence in the resulting data. However, in rare cancers, limited early data and evolving knowledge of patient response often make amendments inevitable. Midstream protocol amendments such as adding biomarker-defined cohorts, adjusting eligibility criteria, or incorporating new

endpoints may be necessary as insights emerge. Sponsors may consider prospectively identifying which elements can realistically be pre-specified and where amendments to the protocol and regulatory interaction may be necessary to preserve trial feasibility, efficiency, and integrity. **Addressing this challenge proactively through pre-specified interim assessment of data generated in the trial and timely regulatory engagement when needed is key to increasing adoption of seamless approaches.**

Endpoints

In rare cancer drug development, endpoints are especially important when employing seamless trial designs that integrate early- and late-phase objectives to guide dosage optimization, safety evaluation, and adaptive trial decisions. While early endpoints could provide valuable insight into drug activity and support trial adaptations, they generally lack the validation necessary for standalone regulatory approval. In settings of high unmet medical need, regulators may allow some flexibility in accepting novel early endpoints, but these must be clearly justified, interpretable, and linked to meaningful clinical outcomes.

Endpoint selection should consider feasibility, biological and clinical relevance, anticipated drug activity, interpretability, and precedent from similar rare disease settings. When traditional endpoints are not suitable or feasible, complementary endpoints can help characterize drug activity. In some rare cancers, traditional measures may show modest effect yet traditional approval can be achieved if a clinically meaningful supportive endpoint reinforces the evidence of benefit.[23] In contrast, in diseases without accepted early endpoints, such as glioblastoma, trials often rely on overall survival, which can limit opportunities for early adaptation and dosage optimization within seamless designs. Incorporating COAs can further strengthen evidence in this setting by providing longitudinal data across phases. Measures of patient experience—if collected consistently from early stages through registration—can offer early insights into tolerability and build a more comprehensive view of clinical benefit over time. Remote data collection may also reduce site burden and improve feasibility, complementing efficacy and safety endpoints as part of the totality of evidence. **Selecting endpoints that maximize learning from each patient and thoughtfully integrating both supportive and primary endpoints can help seamless trials remain efficient while generating credible evidence to inform regulatory decisions.**

Conclusions and Future Directions

Seamless clinical trials represent a paradigm shift in rare cancer drug development, addressing the limitations of conventional phased approaches by integrating multiple stages of clinical evaluation into a single protocol. When thoughtfully designed, seamless trials can accelerate timelines, reduce redundancy, and generate robust evidence from limited populations without compromising scientific integrity.

Beyond operational efficiency, seamless designs support patient-centered considerations, including early engagement with advocacy groups, meaningful endpoints, and pragmatic trial elements. As regulatory agencies increasingly embrace innovative methodologies in areas of high unmet need, seamless trials provide a practical, patient-centered framework that balances innovation with regulatory expectations.

Realizing the full potential of seamless trials requires collaboration among sponsors, investigators, regulators, and patient advocates. As experience grows, stakeholders can iteratively refine trial elements—learning from successes and challenges to improve efficiency, adaptive decision-making, and endpoint

selection. Sharing best practices and proactively seeking FDA guidance further ensures that adaptive designs remain feasible, meaningful, and aligned with regulatory priorities.

Looking forward, broader frameworks, including platform trials and other consolidated designs, offer opportunities to integrate new hypotheses, emerging patient subgroups, and novel indications within a single adaptive structure. Such approaches are particularly valuable in rare cancers, where limited populations demand careful resource allocation and coordination. By combining iterative learning, flexible frameworks, and patient-centered input, seamless trials can become increasingly efficient, informative, and aligned with both clinical and patient priorities, ultimately accelerating meaningful therapeutic advances in rare malignancies.

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