

A Precision for Medicine eBook

# Designing “Seamless Phase 1/2” Oncology Trials

Considerations and Best Practices

PRECISION  
for medicine®



## It's About Time

Drug development is an inherently risky endeavor with high attrition. This is especially true in oncology, where the rate of approval for novel treatments is low compared to other therapeutic areas.<sup>1</sup> Having a well-designed seamless Phase 1-2 study can allow for early identification of ineffective drug candidates, enabling appropriate No-Go decisions that save companies the cost of running additional trials. For developers of cancer treatments, it is imperative to

**Seamless trials require careful consideration of study design, objectives, statistical analyses, and trial oversight according to established ethical, scientific, and statistical standards.**

reliably establish the therapeutic potential and optimal dosage of a drug as quickly and efficiently as possible, allowing for accelerated development of the most promising interventions.

Traditionally, clinical trials were divided into separate, sequential phases, in which drugs were first evaluated for safety in Phase 1 and then for early signals of efficacy in Phase 2, before being investigated against standard of care in large, randomized Phase 3 studies. Over the past decade, seamless Phase 1/2 trials, which integrate the initial safety assessment of Phase 1 with the preliminary efficacy evaluations of Phase 2, have shifted the paradigm in cancer clinical

research. These trials offer a streamlined approach to drug development, potentially leading to earlier drug approval and bringing groundbreaking treatments to patients faster than ever before.

The popularity of seamless Phase 1/2 trials is inherent to their design. By conducting 2 clinical trials within a single study, researchers can swiftly transition from a First-In-Human (FIH) study design in Phase 1 to a more expansive Phase 2, in which the trial usually broadens to include more sites and either a larger or more targeted patient cohort for further testing of selected dose ranges. This approach also allows for fundamentally better answers about how safety and effectiveness of new products can be demonstrated, in faster time frames, with more certainty, and at lower cost.

**Precision for Medicine, a global leader in oncology clinical research, has been at the forefront of this paradigm shift, executing 46 seamless oncology clinical trials over the past 3 years.**

Developed by experienced project teams with deep organizational knowledge, this eBook sheds light on key considerations and best practices for seamless Phase 1/2 trials in oncology. From prestudy strategies to study execution nuances, we outline what it takes to successfully navigate these intricate trials.

### Table of Contents

#### Prestudy Strategy and Planning

- Regulatory Planning
- Study Planning

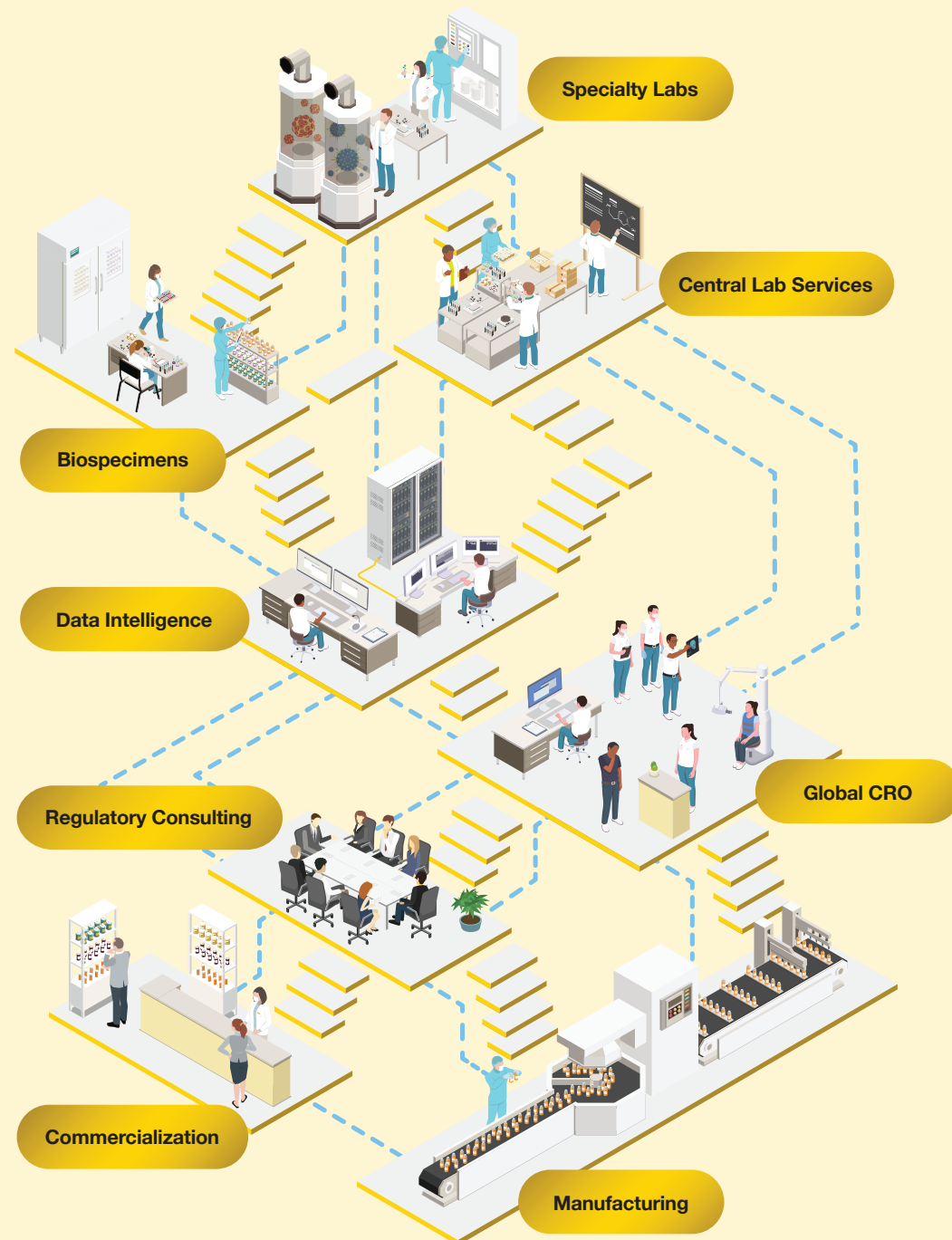
#### Execution Strategy

- Clinical Operations
- Data Management
- Medical Oversight
- Biostatistics
- Clinical Study Report
- Project Oversight



# Seamless Studies Require Seamless Solutions

Precision's integrated capabilities accelerate early phase programs from promising molecule to life-changing therapy.



## Prestudy Strategy and Planning

Seamless Phase 1/2 clinical trials intended to provide substantial evidence of safety and effectiveness require a robust prestudy strategy. Having a prestudy strategy sets the tone for trial success, ensuring every subsequent step is built on a solid foundation.

There are 2 key components of prestudy planning:

**1. Regulatory planning** provides a roadmap for maneuvering through the complex regulatory landscape, ensuring that the trial adheres to the stringent guidelines set forth by authorities such as the US Food and Drug Administration (FDA) and European Medicines Agency (EMA). Understanding regulatory agency expectations for establishing relationships among dosing, safety, and efficacy is important for obtaining meaningful data. Studies are often designed so that Phase 1 inclusion is for various advanced solid tumors and Phase 2 expansion is indication specific. If the program is target specific, it is important to incorporate requirements for establishing and validating relevant assays and cutoff points for inclusion. There are also special considerations for studies in which preliminary assessment of monotherapy safety is followed by addition of an immune checkpoint inhibitor.

**2. Protocol design** lays out the scientific and operational blueprint of the trial, detailing everything from patient selection criteria to dose escalation and expansion strategies. The design, conduct, and analysis of the study should be prespecified and should adequately control for the risk of erroneous conclusions, deliver a reliable estimation of treatment effects, and maintain appropriate trial integrity. Together, these elements form the bedrock of a successful seamless Phase 1/2 trial, ensuring that it is both compliant and scientifically sound.

Careful attention to these components of prestudy planning paves the way for efficient trial execution and enables smooth progress from dose finding through efficacy evaluation.

## Regulatory Planning

**Navigating the regulatory landscape is a critical step in the early phases of any study, but especially in seamless Phase 1/2 trials due to the unique challenges and intricacies.**

**Early and frequent consultations with regulators.** It is vital for pharmaceutical and biotech companies to proactively engage regulatory bodies. Initiating early dialogue, even prior to formal protocol submission, can provide invaluable insights into the regulatory perspective, ensuring that the trial design aligns with their expectations. For drug developers who are considering expedited programs, these consultations can also be useful for discussing program eligibility (see sidebar).

**Pre-IND and scientific advice meetings.** These preliminary meetings serve as platforms to discuss the scientific and regulatory aspects of the trial. They offer an opportunity to seek clarity on requirements, discuss potential challenges, and receive feedback on the proposed study design and endpoints.

**Adaptive design discussions.** Given the adaptive nature of seamless Phase 1/2 trials, it is crucial to discuss any proposed adaptive elements with

regulatory bodies. This ensures that the design is acceptable and should help mitigate regulatory hurdles down the line.

**Establishment of safety reporting protocols.** With seamless trials, there is a heightened focus on safety. Engaging with regulatory authorities to establish clear safety reporting protocols ensures timely and compliant adverse event reporting.

**Integration of feedback.** Following any meeting with a regulatory body, it is vital to integrate their feedback and recommendations into the trial design and execution strategy. This not only ensures compliance but also streamlines the approval process.

**Taking a proactive and collaborative approach to regulatory planning can significantly influence the success of a seamless Phase 1/2 trial. By fostering open communication channels with regulatory authorities and leveraging their feedback, researchers can set trials on a path that prioritizes both patient safety and scientific rigor.**



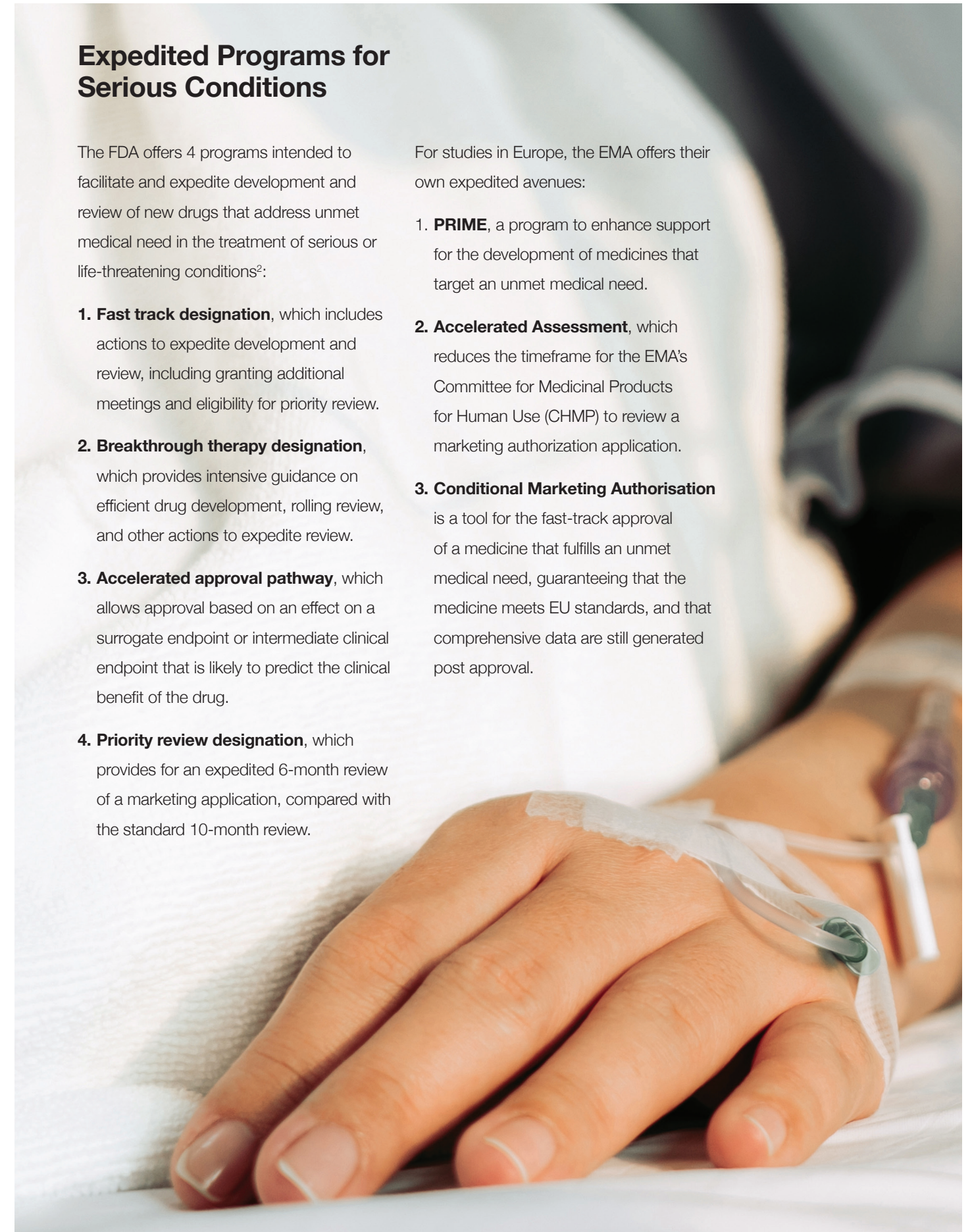
## Expedited Programs for Serious Conditions

The FDA offers 4 programs intended to facilitate and expedite development and review of new drugs that address unmet medical need in the treatment of serious or life-threatening conditions<sup>2</sup>:

- 1. Fast track designation**, which includes actions to expedite development and review, including granting additional meetings and eligibility for priority review.
- 2. Breakthrough therapy designation**, which provides intensive guidance on efficient drug development, rolling review, and other actions to expedite review.
- 3. Accelerated approval pathway**, which allows approval based on an effect on a surrogate endpoint or intermediate clinical endpoint that is likely to predict the clinical benefit of the drug.
- 4. Priority review designation**, which provides for an expedited 6-month review of a marketing application, compared with the standard 10-month review.

For studies in Europe, the EMA offers their own expedited avenues:

- 1. PRIME**, a program to enhance support for the development of medicines that target an unmet medical need.
- 2. Accelerated Assessment**, which reduces the timeframe for the EMA's Committee for Medicinal Products for Human Use (CHMP) to review a marketing authorization application.
- 3. Conditional Marketing Authorisation** is a tool for the fast-track approval of a medicine that fulfills an unmet medical need, guaranteeing that the medicine meets EU standards, and that comprehensive data are still generated post approval.





## Study Planning

**Arguably the most crucial step in safeguarding study success is the planning phase. With seamless Phase 1/2 trials, designing a protocol that accommodates both phases, each with different objectives and endpoints, demands a thorough understanding of the investigational product and a meticulous attention to detail.**

### Protocol design considerations

Protocol design is a cross-functional, multistakeholder process that involves medical monitors, investigators, internal and external subject matter experts, regulatory personnel, clinical operations, data management, statistics, pharmacokinetics (PK), and pharmacodynamics, where applicable, and patient advocacy groups.

A single protocol that incorporates elements of both a Phase 1 and a Phase 2 study, including dose escalation and dose expansion cohorts, requires clinical research organization (CRO) teams that can anticipate potential challenges and propose solutions that are comprehensive, scientifically rigorous, and adherent to regulatory requirements.

### Utilizing adaptive dose-finding designs

- **Consideration:** While traditional rule-based designs such as 3+3 are easy to execute without any software or sophisticated statistics, they have limitations in accuracy and sample size requirements for dose finding.
- **Best Practice:** Use adaptive designs such as Bayesian optimal interval (BOIN), modified toxicity probability interval-2 (mTPI-2), or Backfill i3+3 (Bi3+3), which allow dose decisions based on ongoing results and interim analyses. These have better accuracy, reduce the number of total patient exposures, and expedite finding of the maximum tolerated dose (MTD). Computational models and simulations can be used to inform or validate the adaptive dose-finding design.

Potential applications of these simulations include selecting the number and timing of analyses, determining the appropriate critical value of a test statistic for declaring efficacy or futility, comparing the performance of alternative designs, or estimating trial operating characteristics.

### It is important to keep in mind that adaptive designs can:

- Increase the probability of a type 1 error. This risk can be mitigated by applying methods that determine the appropriate significance levels for interim and final analyses.
- Lead to statistical bias in the treatment effects estimate. Prospective planning that takes into account trial adaptations by adjusting estimates to reduce or remove bias can help to improve the performance on measures.
- Require controlling for the chance of erroneous conclusions. It is important to plan for aspects of the adaptive design by prespecifying appropriate statistical methods and decision-making rules. Once trial data have been collected, the appropriate statistical methods required to produce reliable estimates may no longer be feasible. Any unplanned adaptations may undermine the confidence that these decisions were based on accumulating knowledge in a planned way.
- Create operational trial complications. For example, maintaining the confidentiality of interim results may be difficult if the trial design includes adaptive features. Consider the potential sources of trial issues and the consequences of conducting an adaptive trial and generate processes and plans to avoid issues.

### Establishing decision rules

- **Consideration:** Unclear or inconsistent decision rules at the end of Phase 1/2 studies can lead to mismatches between data interpretation and next steps.
- **Best Practice:** Have clearly defined, reproducible criteria for decision-making aligned to study objectives up front, enabling unambiguous determinations.

### Minimizing patient burden

- **Consideration:** Patients participating in seamless Phase 1/2 clinical trials may experience varying levels of burden due to the combined nature and longer duration of these studies. Participants may also face challenges associated with the intensive safety assessments and dose escalations typical of Phase 1, followed by the immediate transition to efficacy evaluations in Phase 2. The potential of frequent protocol amendments and adaptations may also contribute to uncertainty and changes in patient commitment.
- **Best Practice:** Develop robust informed consent forms and educational materials to help patients understand study expectations. Involve patients, caregivers, and patient advocacy groups in protocol design. This can be valuable for garnering insight into how study participation may impact the lives of patients and their loved ones and determining which assessments are required to generate the data needed to reach study endpoints. It can also be useful for understanding what can be done to reduce the burden of participation and enhance the overall study experience.

### Planning for diversity

- **Consideration:** Ensuring population diversity in clinical trials is essential to obtaining more generalizable results and optimizing the external validity of trial findings. In addition, analyzing trial outcomes within subgroups can uncover potential variations in treatment responses, contributing to a more comprehensive and nuanced understanding of the intervention's effectiveness across diverse populations.
- **Best Practice:** Proactively engage with diverse communities and collaborate with regulatory authorities to align on diversity goals and to achieve broad access and inclusivity in seamless Phase 1/2 trials. The FDA has issued guidance titled Enhancing the Diversity of Clinical Trial Populations—Eligibility Criteria, Enrollment Practices, and Trial Designs, which recommends approaches to increasing enrollment of underrepresented populations in clinical trials.<sup>3</sup>
- **Consideration:** Unexpected changes can lead to delays, which impact resources and the value of trial data.

- **Best Practice:** Incorporate flexibility into the protocol to allow for adaptive modifications based on emerging safety or efficacy data, ensuring the study remains responsive to evolving clinical insights.

### Enabling Protocol Flexibility

- **Consideration:** Unexpected changes can lead to delays, which impact resources and the value of trial data.
- **Best Practice:** Incorporate flexibility into the protocol to allow for adaptive modifications based on emerging safety or efficacy data, ensuring the study remains responsive to evolving clinical insights.

An early investment of time in the prestudy strategy planning phase sets the right tone for the entire trial. By adopting a meticulous approach, informed by the latest methodologies and best practices, researchers can maximize the likelihood of seamless Phase 1/2 trial success.



## Execution Strategy

**Once the foundational elements of a seamless oncology Phase 1/2 clinical trial have been established, the focus shifts to the execution phase. This is where the meticulously crafted study plans are brought to life, and trial success hinges on a well-orchestrated strategy.**

Execution is more than just implementing the protocol; it is navigating the dynamic nature of clinical research, adapting to unforeseen challenges, and ensuring that every step aligns with the trial's stated objectives.

From clinical operations and data management to medical oversight and biostatistics, each component of the execution strategy plays

a pivotal role in ensuring the trial progresses smoothly, remains compliant, and ultimately achieves its scientific goals. Here we highlight challenges, best practices, and the importance of a cohesive approach to trial execution.



### Biomarker Assay Development and Validation

**Isolate and enrich circulating tumor cells (CTC) with Precision's Proprietary ApoStream® technology.**

ApoStream was developed as part of a National Cancer Institute (NCI) initiative to support the development of a rare cell enrichment device for the isolation of CTCs from whole blood. Today, laboratories at the NCI use this technology to enable biomarker detection using liquid biopsies for oncology therapeutic development.

# Clinical Operations

**Clinical operations form the backbone of any clinical trial. Operationalizing a seamless Phase 1/2 trial requires careful planning and execution, from site selection to patient recruitment and monitoring.**

## Investigative site management

- **Consideration:** Selecting qualified investigators and sites is always critical to study success; this is especially true in seamless Phase 1/2 studies due to their duration, complexity, and the common desire to rapidly achieve FPI.
- **Best Practice:** When selecting investigative sites, seek those with a strong background in the specific cancer type(s) under study, previous experience in conducting early-phase trials, and a track record of quick study start-up. Consider sites that have a proven history of successful patient recruitment and high-quality, timely data entry. It is also important to build strong relationships with site staff, ensuring they stay well informed regarding trial objectives and protocols throughout the study, to enhance patient care, data quality, and timeliness of first patient enrollment.

## Site start-up strategies

- **Consideration:** Effective site start-up expedites patient recruitment and data collection.
- **Best Practice:** Engage with regulators early to allow adequate time for approvals. Use risk-based site selection focused on recruitment feasibility. Develop comprehensive training plans tailored to the experience level(s) of site staff. Confirm site readiness before

enrollment begins. Sites should have the necessary infrastructure in place ahead of trial commencement.

## Site activation

- **Consideration:** It is important to recognize the diversity in site profiles between phase 1 and phase 2 portions of seamless trials. Phase 1 investigators typically have access to a range of advanced treatment-resistant tumor types, while phase 2 investigators may need access to a more restricted patient population due to specificity in the type of cancer and a greater number of patients. Therefore, sponsors need to intelligently match the trial requirements with the site capabilities, ensuring that each site can contribute effectively to the trial's objectives
- **Best Practice:** We recommend a tailored approach to site activation that considers the unique characteristics and patient populations of phase 1 and 2 sites. For phase 1, select sites with the capability to enroll a range of advanced tumor types. For phase 2, ensure there are enough sites with the capability of enrolling a limited range of tumor types and the necessary patient volume to meet the study's efficacy objectives. When possible, engage the same sites used in phase 1 for phase 2 to maintain consistency and for efficiency. However, activate additional sites to support the higher patient numbers typically required for phase 2.

This strategic activation ensures any potential issues are identified and addressed before the trial progresses, allowing for smoother transitions and more robust data collection.

## Site monitoring

- **Consideration:** Ensuring that the trial is conducted according to the protocol and that any deviations are promptly addressed is essential.

- **Best Practice:** Regularly monitor sites to drive not only patient safety but data integrity. With the advent of remote monitoring technologies, clinical operations teams can now oversee trial activities in real time, allowing for quicker and more informed decision-making.

With the manifold complexities inherent to seamless Phase 1/2 oncology trials, a robust clinical operations strategy can mean the difference between study success and failure.



# Data Management

**There is no margin for error in the way data are collected, stored, and analyzed. For seamless oncology Phase 1/2 oncology trials, data management can be even more complicated due to combined safety and efficacy objectives.**

## Length of Time to reach clinical endpoints and variability in study duration

- **Consideration:** In early-phase oncology studies, including seamless Phase 1/2 trials, patients may undergo multiple cycles of treatment until either disease progression, or another withdrawal criterion is met. The multiple cycles result in high data volume and variability among subjects in study duration.
- **Best Practice:** Ensure close collaboration between the data management and statistics teams during case report form (CRF) creation

to ensure no duplicate data are collected. The clinical data manager must check that eCRFs are designed to facilitate accurate and timely data collection. Regular data cleaning, both automatic and manual, is also crucial for preparing data for interim or final analysis.



### Complexity of data collection

- **Consideration:** In seamless Phase 1/2 trials, the data collected can be multifaceted, especially when capturing dose-limiting toxicities, efficacy endpoints, and PK data.
- **Best Practice:** Modular CRF design can be beneficial. Break down the CRF into sections or modules specific to each phase or type of data to make it more manageable and user-friendly, thus reducing the probability of errors.

### Evolving data needs

- **Consideration:** As the trial progresses from Phase 1 to Phase 2, the data requirements may evolve, necessitating changes to the CRF.
- **Best Practice:** Design adaptive CRFs that can be easily modified without disrupting previously entered data. This requires collaboration between data management, clinical operations, and IT teams.

### Medical coding of combination therapies

- **Consideration:** Chemotherapy treatments often consist of various drug combinations, which might not all be covered by the WHODrug dictionary.

- **Best Practice:** The WHODrug dictionary allows the addition of new terms upon request. The coding team should proactively submit requests. Consider planning for dictionary upgrades to the latest version to incorporate new codes prior to finalizing the database and include this in early data management plan discussions.

### High volume of AEs and SAEs

- **Consideration:** There are typically a large number of adverse events (AEs) and serious adverse events (SAEs) among oncology patient populations, including those involved in seamless Phase 1/2 studies. SAE data are usually stored in a separate safety database from the clinical trial data, necessitating regular reconciliation of the 2 datasets.
- **Best Practice:** Implement automated SAE reconciliation listings through tools like SAS. Conducting more frequent reconciliations can also help ensure that essential safety data are reported consistently and accurately.

### Consistent capture and analysis of efficacy data

- **Consideration:** Compliance with standardized criteria is necessary for consistent and accurate tumor assessments. Although Phase 1 studies focus on characterizing a safety profile with efficacy assessment as a preliminary evaluation, it's still important to perform the assessment properly. In the phase 2 part of a seamless study, efficacy assessment may be based on statistical assumptions and must be approached with a high degree of rigor. Therefore, it's important to ensure clarity regarding all aspects of efficacy assessment and reporting. This is a critical aspect of ensuring that investigators, independent radiologic review committees, and sponsors can draw conclusions about the study's efficacy outcomes and make decisions with confidence.

- **Best Practice:** Ensure all involved study team members—including clinical research associates, data management, statistics, and clinical sites—are comprehensively trained on the appropriate guidelines both at study outset and throughout study execution. Implement electronic data capture system checks to automatically flag deviations from baseline data, enabling rapid query generation for inaccuracies. Additionally, Phase 2 studies, which are more focused on efficacy, should include statistical requirements and response-based decisions (such as futility testing) in their design to ensure accuracy and compliance. Decisions about phase 3 are often based on efficacy outcomes in phase 2. Therefore, an independent review process may be implemented and must be supported by compliance with the efficacy requirements and the submission of high-quality image data.

Effective data management is pivotal in ensuring the success of seamless Phase 1/2 trials, particularly in data-heavy oncology studies. By addressing the unique challenges these trials present and implementing robust strategies, researchers can preserve the integrity and accuracy of their data.

### Building Biomarker Data Intelligence

Clinical trials can hit bottlenecks when facing the complex web of sample and biomarker data that flows throughout your study and program's lifecycle. Precision QuartzBio's Biomarker Intelligence Platform, powered by AI, provides clinical trial decision support by centralizing all data in a unified data ecosystem. Extract insights using natural language today, with a path to even more powerful predictive intelligence tomorrow.



## Medical Oversight

The importance of ensuring both patient safety and the scientific integrity of the study cannot be overstated. In seamless Phase 1/2 oncology trials, the need for strong medical oversight is heightened due to the complexities and potential risks involved.

### Safety monitoring

- **Consideration:** It can be a challenge to comprehensively monitor the large volume of safety data generated from patients on investigational therapies.
- **Best Practice:** Implement centralized, real-time data monitoring systems and leverage AI analytics to efficiently process safety signals across multiple parameters.

### Interim efficacy assessments

- **Consideration:** Determining efficacy with limited, imbalanced patient samples and maturing Phase 2 data is difficult at interim analysis stages.
- **Best Practice:** Implement an adaptive statistical analysis plan that accounts for evolving Phase 2 enrollment and leverages Bayesian methodologies. Efficacy analysis on Phase 1 and Phase 2 data should be pooled when appropriate, but also done separately to allow assessment of early signals, even if Phase 2 maturity is limited.

### Protocol deviations and amendments

- **Consideration:** Given the adaptive nature of Phase 1/2 trials, protocol deviations or the need for protocol amendments may arise.
- **Best Practice:** Establish a robust medical oversight process, which can ensure that any deviations are appropriately documented and justified and that necessary protocol amendments are made in a timely manner, ensuring patient safety and trial integrity.

Medical oversight is a key driver of success and safety of seamless Phase 1/2 trials in oncology. By addressing the challenges these trials present and implementing robust oversight strategies, researchers can ensure the well-being of patients and the scientific validity of the trial.



## Biostatistics

Biostatistics impact the design of clinical trials and the interpretation of clinical trial data. In seamless Phase 1/2 oncology trials, the role of biostatistics becomes even more critical due to the adaptive nature of these trials and the need for appropriate statistical methodologies.

### Dose-finding designs

- **Consideration:** Dose levels and escalation schemes appropriate for efficacy may require adjustments from the original Phase 1 protocol as safety and initial efficacy signals emerge in Phase 2.
- **Best Practice:** Employ dose-finding designs, such as model-based adaptive designs, to identify an optimal dose in the context of specified study goals, whether based on safety, target engagement, or early signs of efficacy.

### Sample size

- **Consideration:** A power analysis and assumptions for sample size considerations are crucial when planning a seamless Phase 1/2 design. However, insufficient information about efficacy and toxicity may lead to an inadequately planned sample size.

- **Best Practice:** Use appropriate adaptive designs to allow for the re-estimation of the sample size during study conduct, if needed, based on results from interim analysis.

### Interim analyses

- **Consideration:** Given the adaptive nature of seamless Phase 1/2 trials, interim analyses are often required to make decisions about cohort expansion or trial termination.
- **Best Practice:** Use prespecified interim analysis time points, coupled with an adaptive design, modifications to the study, or predefined stopping rules, to keep the trial on track and prioritize patient safety.

## Dose optimization

- **Consideration:** The FDA recommends formal dose optimization, which is the process of evaluating 2 or more dose levels, when selecting an optimal dose for expansion. Seamless Phase 1/2 study designs need to determine when and how to perform dose optimization.
- **Best Practice:** The selection of an appropriate study design and relevant data is critical when selecting a dose optimization strategy. Conduct simulation studies by varying assumptions regarding toxicity and

efficacy to guide final selection of the dose optimization approach. Close collaboration between biostatisticians and clinical teams is crucial for employing the right statistical approaches and interpreting the results correctly. With the proper biostatistical foundation in place—including the right tools and methodologies—researchers can conduct rigorous, scientifically valid seamless trials that efficiently advance new oncology treatments.



## GMP Infrastructure and Startup

Good Manufacturing Process (GMP) programs, policies, procedures and more. For GMP facility startup and operation, right-sizing quality management systems and the procedures that govern the use of these systems is a key input into clinical and commercial manufacturing compliance.



## Clinical Study Report

**The Clinical Study Report (CSR) is a comprehensive document that provides a detailed overview of the design, execution, results, and conclusions of a clinical trial. In seamless Phase 1/2 oncology trials, the CSR becomes particularly intricate due to the adaptive nature of these trials and the need to report on both the dose-finding and the efficacy components.**

### Structure and organization

- **Consideration:** Given the complexity of seamless Phase 1/2 trials, organizing the CSR in a manner that clearly delineates the results and conclusions of each phase can be challenging.
- **Best Practice:** Consider structuring the CSR in a modular format, with separate sections dedicated to Phase 1 and Phase 2. This ensures clarity and allows readers to easily navigate to relevant sections.

### Data presentation

- **Consideration:** It is important to present data from both phases in a cohesive manner, especially when considering dose-response relationships, safety profiles, and efficacy endpoints.
- **Best Practice:** Utilize graphical representations, such as dose-response curves, to visually depict findings. Pay attention to clearly labeling tables and figures to indicate the phase to which they pertain.

## Discussion and interpretation

- **Consideration:** The CSR should provide a clear interpretation of the results from both phases and draw overarching conclusions about the safety and efficacy of the investigational product.
- **Best Practice:** Dedicate separate discussion sections for Phase 1 and Phase 2, followed by a combined discussion that synthesizes the findings from both phases. This allows for a comprehensive analysis of the trial's outcomes.

## Incorporation of feedback from regulatory authorities

- **Consideration:** The CSR should also address feedback and recommendations from regulatory authorities, such as the FDA or EMA, especially when considering dose recommendations, protocol development, or safety concerns.

- **Best Practice:** Maintain open communication with regulatory authorities throughout the trial and incorporate their feedback into the CSR. Crafting a comprehensive and clear CSR for seamless Phase 1/2 trials in oncology is critical for conveying the trial's findings to stakeholders, including regulatory authorities, clinicians, and the scientific community.

By addressing the unique challenges these trials present and implementing structured reporting strategies, researchers can ensure the CSR effectively communicates the trial's outcomes.

- **Best Practice:** Perform regular resource reviews and adjustments based on trial needs to ensure that all aspects of the trial are adequately supported.

## Stakeholder communication

- **Consideration:** Maintaining open communication with all stakeholders, including sponsors, regulatory authorities, site investigators, and patients, is paramount.
- **Best Practice:** Establish regular communication channels, such as weekly or monthly update meetings, to ensure that all stakeholders are informed and aligned.

## Risk management

- **Consideration:** Trial success involves identifying and mitigating potential risks, whether they pertain to patient safety, data integrity, or trial execution.

- **Best Practice:** Implement a proactive risk management strategy, which includes regular risk assessments and predefined mitigation plans, to ensure that potential issues are promptly addressed.

## Adaptive trial adjustments

- **Consideration:** Seamless Phase 1/2 trials require adjustments based on interim analyses or other trial findings without compromising the trial's integrity.
- **Best Practice:** Have a predefined adaptive trial protocol, which outlines potential adjustments and the criteria for making them, to ensure that the trial remains scientifically valid while being flexible.

Effective project oversight is pivotal for addressing the unique challenges of seamless Phase 1/2 oncology studies. Implementing robust oversight strategies allows researchers to safeguard timely and successful trial completion.

## Project Oversight

**Smooth execution and successful completion of a clinical trial require experience and oversight. This need is exacerbated with seamless Phase 1/2 trials using adaptive protocols.**

### Timeline management

- **Consideration:** Choreographing timelines in seamless Phase 1/2 trials, especially when transitioning between phases, can be tedious.
- **Best Practice:** Implement robust project management software that allows for real-time tracking and adjustments. Regularly

update stakeholders on progress and potential delays to ensure transparency and proactive problem-solving.

### Resource allocation

- **Consideration:** Checking resources—both human and financial—are appropriately allocated throughout the trial is critical.



## Conclusion

**Seamless Phase 1/2 trials offer the potential for accelerated drug development and patient access to novel treatments, but they come with their unique set of challenges.**

From the intricacies of study design and data management to the nuances of medical oversight and project management, every aspect of these trials demands expertise and precision. To navigate the challenges of these trials successfully, it is imperative to partner with a CRO with the right experience:

- 1 Understands the oncology space.** Oncology trials are distinct from trials in other therapeutic areas. Disease heterogeneity, evolving treatment paradigms, and unique patient populations demand a deep understanding of the oncology landscape.
- 2 Has expertise in seamless Phase 1/2 trials.** The adaptive nature of seamless Phase 1/2 trials requires a CRO that has hands-on experience with such designs. The CRO should have a track record of successfully executing these trials, from dose-finding strategies to seamless transitions between phases.
- 3 Can meet the evolving needs of your program.** With responsive CRO operations teams and integrated end-to-end capabilities, Precision is built to deliver early phase oncology program success.
- 4 Has a track-record of success.** Precision ran 46 seamless oncology clinical trials over the past 3 years. Project teams are backed by organizational knowledge and have been at the forefront of advancing oncology research through projects like these.
- 5 Brings domain expertise and practical experience.** This ensures that the complexities of seamless trials are navigated with precision, ultimately benefiting both the scientific community and the patients awaiting novel treatments.

## Authors



**Ivan Barrera, MD**  
Senior Medical Director



**Vann Parker, PhD**  
Executive Director,  
Regulatory



**Ana Magalhaes**  
Senior Manager,  
Medical Writing



**Meredith Latino, PhD**  
Director,  
Medical Writing



**Veronica Ruvolo**  
Senior Manager,  
Biostatistics



**Vandana Sundaram**  
Principal Statistician

---

### References

1. Jaki T, et al. Early phase clinical trials in oncology: realising the potential of seamless designs. *Eur J Cancer*. 2023;189:112916.
2. US Food and Drug Administration. *Guidance for Industry: Expedited Programs for Serious Conditions—Drugs and Biologics*. May 2014. <https://www.fda.gov/media/86377/download>.
3. US Food and Drug Administration. *Enhancing the Diversity of Clinical Trial Populations—Eligibility Criteria, Enrollment Practices, and Trial Designs: Guidance for Industry*. November 2020. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enhancing-diversity-clinical-trial-populations-eligibility-criteria-enrollment-practices-and-trial>.

CLIENT SERVICE • PURPOSE • ACCOUNTABILITY • MUTUAL RESPECT • COLLABORATION

**A partner with shared principles and shared passion for patients.**



Download your  
digital copy

[precisionformedicine.com](https://precisionformedicine.com)

© 2024. All rights reserved.  
Rev. 01

PRECISION  
for medicine®