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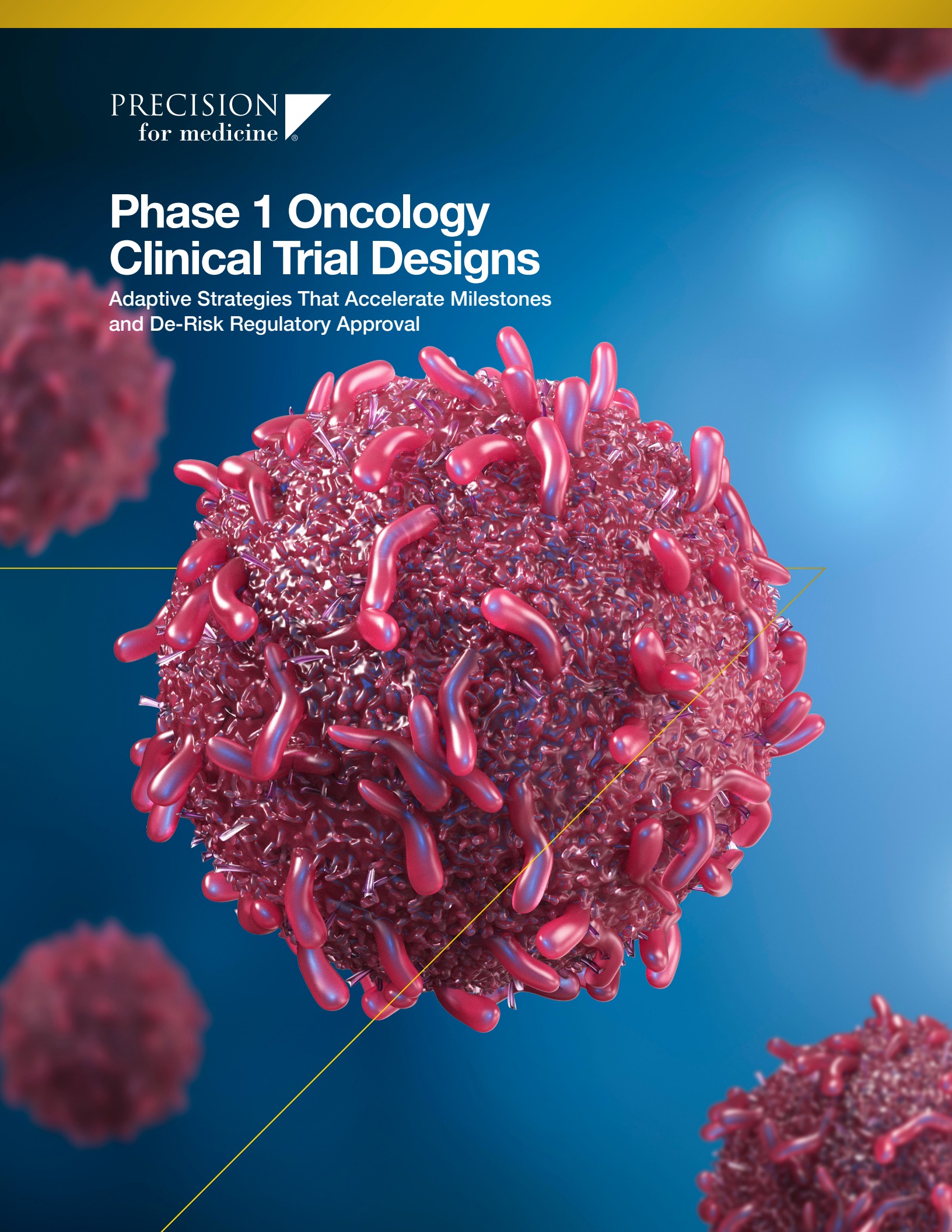
Phase 1 Oncology Clinical Trial Designs

Adaptive Strategies That Accelerate Milestones and De-Risk Regulatory Approval



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The Shifting Paradigm of Oncology Drug Development

For decades, the standard for first-in-human (FIH) Phase 1 oncology trials was the 3+3 dose escalation design. Originally introduced in the 1940s, this rule-based method has been widely utilized for its simplicity and robustness, providing a clear, step-by-step pathway to identifying a maximum tolerated dose (MTD) based on dose-limiting toxicities (DLTs). However, as targeted therapies, immunotherapies, and combination regimens reshape cancer care, this conventional design often fails to capture the complexity of these modern oncology therapeutics and may no longer meet regulatory expectations for dose optimization.

Today, oncology drug developers face unprecedented pressure to accelerate timelines, optimize resource utilization, and demonstrate not just the MTD but the optimal biological dose (OBD) that balances efficacy with tolerability. As regulatory expectations have shifted, developers are now faced with providing more robust dose-finding data and justifying their selected doses with greater rigor. Consequently, the industry is rapidly evolving beyond traditional designs toward more sophisticated, adaptive methodologies.

For emerging biotech and small-to-mid size pharmaceutical companies, this evolution presents both challenges and opportunities. Modern adaptive designs offer the potential for more efficient patient allocation, faster dose escalation, and stronger regulatory submissions—but they also require careful consideration of operational complexity, resource requirements, and implementation expertise.

This eBook is a strategic guide to navigating this complex landscape of modern adaptive methodologies. We will explore the most prevalent modern adaptive designs, review their mechanics, advantages, and applications, and offer practical guidance for selecting and implementing the approach that best aligns with the therapeutic hypothesis, patient population, and development goals.

At Precision for Medicine, where 76% of our trials focus on oncology, we have guided sponsors through the selection and implementation of diverse Phase 1 designs across therapeutic areas and modalities. With our deep domain expertise, agile operational model, and integrated clinical and laboratory capabilities, we are purpose-built to help developers proceed with precision in charting a course to oncology innovation.

Chapter 1

The Evolution of Phase 1 Oncology Clinical Trial Design

Historically, the primary objective of a Phase 1 oncology trial was to identify a maximum tolerated dose (MTD). Underpinning this objective was the assumption that higher doses would yield greater anti-tumor activity. While this assumption was rational for cytotoxic chemotherapies, where the therapeutic window is typically narrow and efficacy is often correlated with toxicity, it has been challenged by the emergence of modern oncology drugs.

Molecularly targeted agents and immunotherapies may demonstrate efficacy at doses well below their MTD, with toxicity profiles that differ fundamentally from traditional chemotherapy. Target saturation may occur at lower doses, and immune-mediated mechanisms of action may not follow traditional dose-response relationships. Recognition of these nuances has prompted a rethinking of Phase 1 objectives. Rather than pushing doses to toxicity limits, contemporary trials are increasingly seeking to identify the optimal biological dose (OBD)—the dose that provides the best balance of efficacy, safety, and tolerability.[2]

A Sea Change in the Regulatory Landscape

In 2021, the FDA's Oncology Center of Excellence launched Project Optimus, a landmark initiative that requires sponsors to generate more comprehensive dose optimization data, challenging the traditional practice of advancing the MTD into later-phase trials without thorough exploration of lower doses that might be equally effective.[3] The key objectives of Project Optimus are to:

- **Reform dose selection practices.** The core goal is to identify doses that maximize both efficacy and safety, ensuring that patients receive the optimal therapeutic dose that enhances outcomes while minimizing adverse effects.
- **Promote early dose optimization.** The aim is to determine the best dose before pivotal Phase III trials, potentially reducing post-market challenges.
- **Enhance collaboration.** The FDA encourages early engagement with regulatory authorities, with the expectation of discussions about dose-finding strategies prior to initiation of pivotal studies.
- **Incorporate patient-reported outcomes (PROs).** Understanding how different doses affect quality of life, tolerability, and real-world patient experiences is key to optimizing treatment.

Under this framework, the FDA expects dose-finding studies to:

- Explore a range of doses, not just a sequential escalation, in randomized studies—ideally before pivotal trials—to better understand the relationship between dose, efficacy, and toxicity.
- Incorporate efficacy endpoints alongside safety assessments.
- Consider long-term tolerability in dose selection.
- Provide robust justification for the recommended Phase 2 dose (R2PD).

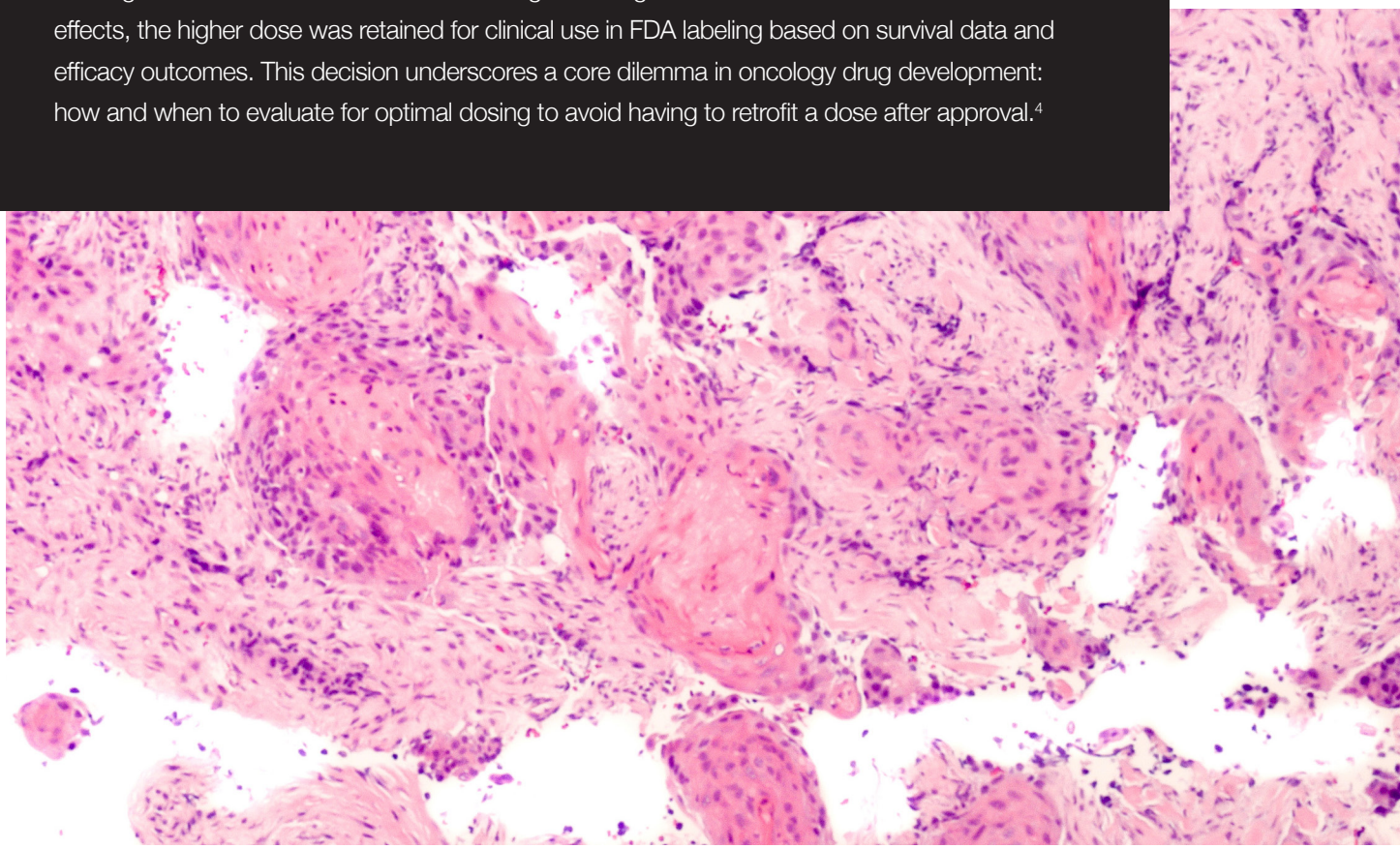
These expectations have profound implications for Phase 1 trial design as simple dose escalation schemes that only identify the MTD are no longer sufficient.

Project Optimus promotes the use of innovative science and technology in drug development, with a focus on adaptive clinical trial designs and real-world data. Sponsors must now consider study methodologies that enable dose optimization, potentially including expansion cohorts at multiple dose levels and incorporating pharmacokinetic (PK)/pharmacodynamic (PD) modeling.

This initiative signals a major shift in the regulatory landscape, encouraging developers to make dose selection a data-driven, strategic decision rather than a reactive one and emphasizing that for many modern therapies, the MTD may not be the most effective or safest dose for long-term treatment. This shift extends beyond the FDA, with the European Medicines Agency (EMA) and other global regulatory agencies increasingly expecting comprehensive dose-finding strategies.

The Dose Dilemma: Lessons from Sotorasib

In early-phase trials, sotorasib, a targeted therapy, was found to be effective for treating KRAS-mutated non-small cell lung cancer at a 960 mg dose and was granted accelerated approval. Although later studies indicated that a 240 mg dose might offer similar benefits with fewer side effects, the higher dose was retained for clinical use in FDA labeling based on survival data and efficacy outcomes. This decision underscores a core dilemma in oncology drug development: how and when to evaluate for optimal dosing to avoid having to retrofit a dose after approval.[4]



Site Performance Monitoring

Application of the traditional 3+3 design to modern oncology therapeutics reveals its shortcomings for optimizing the dose of drugs that may not have a clear, dose-dependent toxicity profile:

- **Statistical inefficiency.** The 3+3 design treats a maximum of 3-6 patients per dose level, providing limited information about the dose-toxicity relationship and leading to high variability in MTD estimation.
- **Rigid cohort structure and low dose escalation.** The requirement to observe all patients in a cohort before escalating doses can significantly extend trial timelines, particularly with agents that have long dose-limiting toxicity (DLT) observation periods.
- **Limited flexibility.** The strict escalation rules of 3+3 designs cannot adapt to accumulating information about the dose-toxicity curve. This lack of flexibility may may result in slow dose escalation, with the inability to skip doses that show low toxicity.[5]
- **Poor dose selection.** Studies have shown that 3+3 designs correctly identify the true MTD only 30-60% of the time, depending on the underlying dose-toxicity relationship and the specific study scenario.[6]

The 3+3 design is also ill-suited for combination therapies, drugs with efficacy plateaus below the MTD, and trials in rare diseases where patient populations are inherently small.

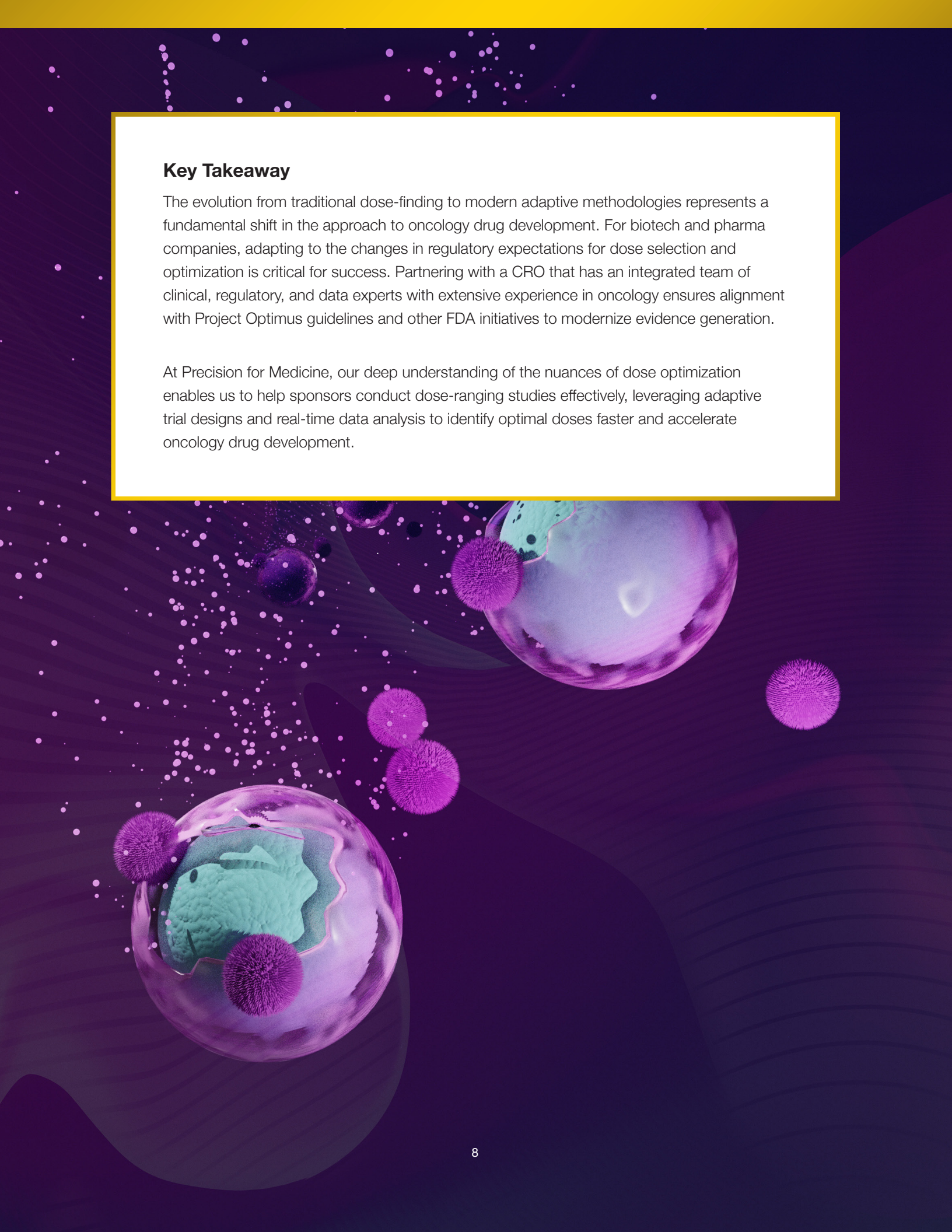
Value of Adaptive Designs

To address the limitations of the 3+3 design, a new generation of innovative, adaptive Phase 1 trials designs has emerged to facilitate compliance with the expectations of Project Optimus. These methodologies are dynamic and data-driven, using real-time information to inform dose decisions and optimize trial efficiency. They are also designed to accelerate the development timeline, improve patient safety, and better characterize the full profile of a drug, leading to more informed decisions in later phases.

Key Takeaway

The evolution from traditional dose-finding to modern adaptive methodologies represents a fundamental shift in the approach to oncology drug development. For biotech and pharma companies, adapting to the changes in regulatory expectations for dose selection and optimization is critical for success. Partnering with a CRO that has an integrated team of clinical, regulatory, and data experts with extensive experience in oncology ensures alignment with Project Optimus guidelines and other FDA initiatives to modernize evidence generation.

At Precision for Medicine, our deep understanding of the nuances of dose optimization enables us to help sponsors conduct dose-ranging studies effectively, leveraging adaptive trial designs and real-time data analysis to identify optimal doses faster and accelerate oncology drug development.



Chapter 2

Model-Assisted Designs

The traditional 3+3 design, and its numerous variants, has been the cornerstone of Phase 1 oncology dose-finding trials for decades despite its tendency to treat patients at potentially sub-therapeutic doses. The key advantage of this design lies in its simplicity as dose decisions are based on straightforward, prespecified rules that require no complex statistical modeling, making it easy to execute without any software or knowledge of basic statistical concepts.

Mechanics of the 3+3 Design

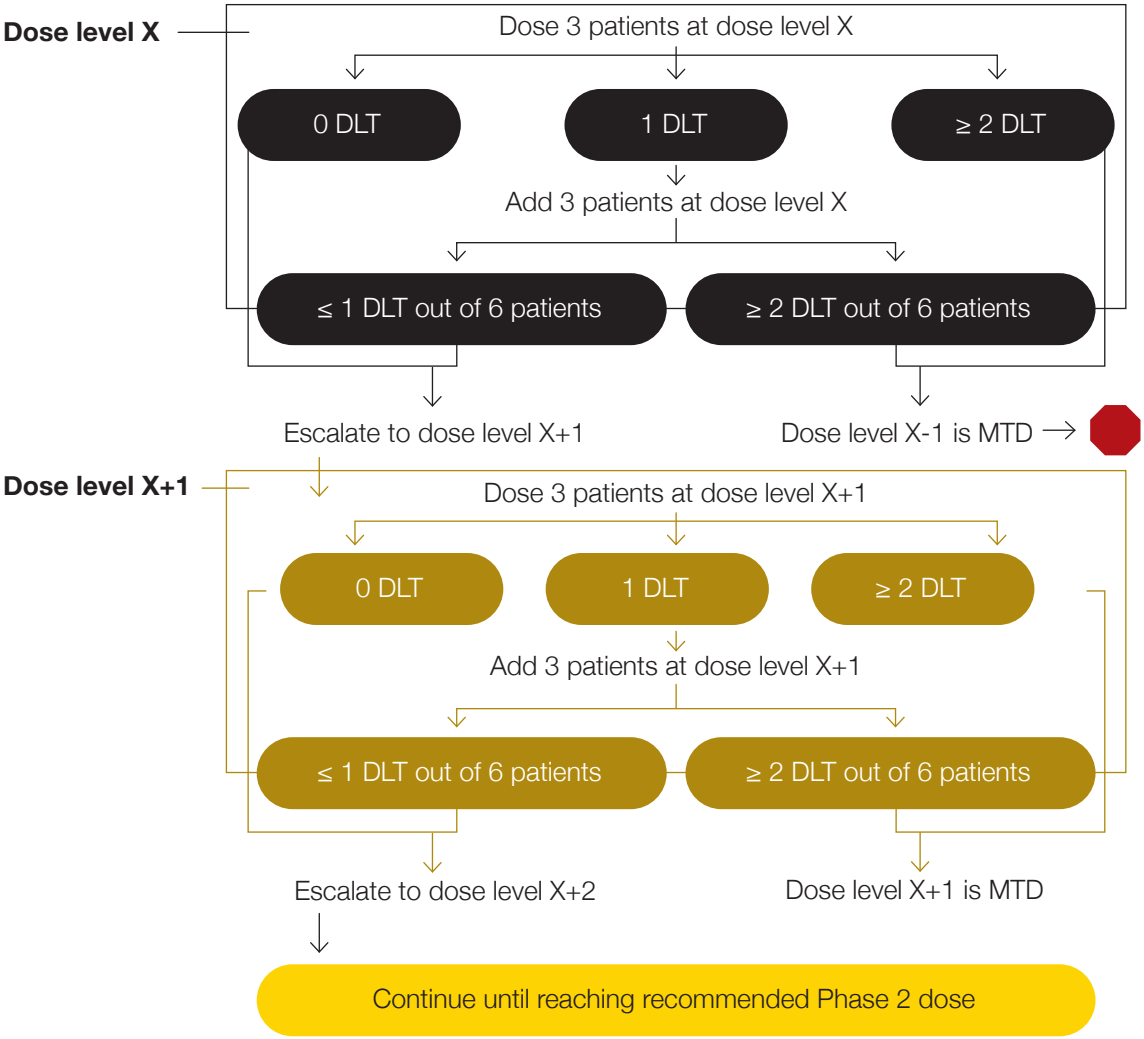
In the 3+3 design, pre-specified starting doses are selected based on toxicological data from animal studies or previous clinical trials. Of note, if toxicology data support sufficient safety of the starting dose, single person cohorts may be proposed for the initial dose cohorts.

The trial starts at the lowest dose and escalates to higher doses if toxicity remains within an acceptable range. The main goal is to find the MTD, where no more than one out of six patients experience a DLT.[7]

The 3+3 design follows a simple algorithm:

1. Treat 3 patients at the current dose level
2. If 0/3 patients experience DLT, escalate to the next dose level
3. If 1/3 patients experience DLT, treat 3 additional patients at the same dose
4. If ≤1/6 patients experience DLT, escalate to the next dose
5. If ≥2/3 or ≥2/6 patients experience DLT, the MTD has been exceeded

Figure 1. **Schema of 3+3 dose escalation design**



DLT: dose limiting toxicity **MTD:** maximum tolerated dose

Drawbacks of the 3+3 Design

The 3+3 design was developed to address the characteristics of traditional cytotoxic drugs, which have a predictable, dose-dependent relationship with toxicity. However, as oncology drug development has evolved, the shortcomings of this rigid design have become increasingly apparent, from sub-optimal dosing and statistical inefficiency to inflexibility and incompatibility with new modalities for which an MTD may not even be identifiable, or the OBD may be well below the MTD.

Advantages of Adaptive Design Methodologies

Contemporary approaches offer enhanced methods with a higher likelihood of identifying the true MTD and allow for the collection of information that can efficiently lead to dose optimization while maintaining patient safety. Modern adaptive designs are not a single method but a family of approaches that allow for pre-specified modifications to the design of a trial based on accumulating data. This flexibility allows for more efficient, ethical, and informative trials.

At a high level, adaptive designs can be classified into two main categories:

- **Model-assisted designs**, such as the Bayesian Optimal Interval (BOIN) design, use a pre-defined set of rules to make decisions but incorporate an underlying statistical model to guide those rules. They bridge the gap between simple rule-based designs and complex model-based ones, offering a balance of simplicity and efficiency.
- **Model-based designs**, such as Bayesian Logistic Regression Model (BLRM), use statistical models to estimate the dose-toxicity (and sometimes dose-efficacy) relationship, allowing adaptive dose escalation based on accumulating data rather than fixed rules. These designs are more complex but are also more statistically efficient, as they leverage all available data to continuously update the dose-toxicity curve.

The choice between model-assisted and model-based designs involves tradeoffs between statistical efficiency and operational complexity. Model-assisted designs offer improved performance over 3+3 while maintaining implementation simplicity. Model-based designs typically converge on the MTD more quickly and accurately but require significant statistical support.

When 3+3 Remains Appropriate

Despite the availability of more sophisticated alternatives, there remain scenarios where the traditional 3+3 design is a reasonable and appropriate choice:

- **Resource-constrained settings.** When statistical expertise or specialized software is unavailable, the simplicity and operational feasibility of the 3+3 design may outweigh its statistical limitations.
- **Well-characterized drug classes**. For agents with predictable dose-toxicity relationships based on extensive class experience, the limitations of the 3+3 design may be acceptable.
- **Regulatory requirements.** Some regulatory authorities or institutional review boards (IRBs) may specifically require or prefer traditional designs for certain contexts.
- **Pilot studies.** Early feasibility studies or dose-ranging experiments may use 3+3 designs before committing resources to more complex trials.

Key Takeaway

Choosing among the myriad approaches available for Phase 1 oncology trials can be daunting. Understanding the traditional 3+3 design provides essential context for evaluating modern alternatives. While its simplicity offers practical advantages in certain scenarios, sponsors must carefully weigh these benefits against its limitations in efficiency, ethics, and information generation.

At Precision for Medicine, we combine deep statistical knowledge with broad oncology experience to guide sponsors beyond traditional 3+3 limitations toward modern designs that optimize trial efficiency, enhance patient allocation, accelerate timelines, and support regulatory success—all while maintaining the highest safety standards.

In the following chapters, we will explore specific examples of these modern designs, outlining their unique features and strategic applications.

Bayesian Optimal Interval Design: A Balance of Simplicity and Efficiency

Novel designs provide drug developers with additional tools for conducting more flexible and efficient Phase 1 oncology trials. BOIN design is a model-assisted, rule-based approach that has gained significant traction due to its balance of statistical rigor and implementation simplicity. This approach was developed to overcome the inefficiencies of the 3+3 design while maintaining a clear, intuitive decision-making process. It can be used to determine the MTD of a study drug based on safety or the OBD based on both safety and efficacy. Beyond its utility for dose-finding in early phase trials, BOIN can also be extended to provide a unified framework for exploring toxicity, efficacy, continuous outcomes, delayed toxicity or efficacy, and drug combinations.[8]

How BOIN Works

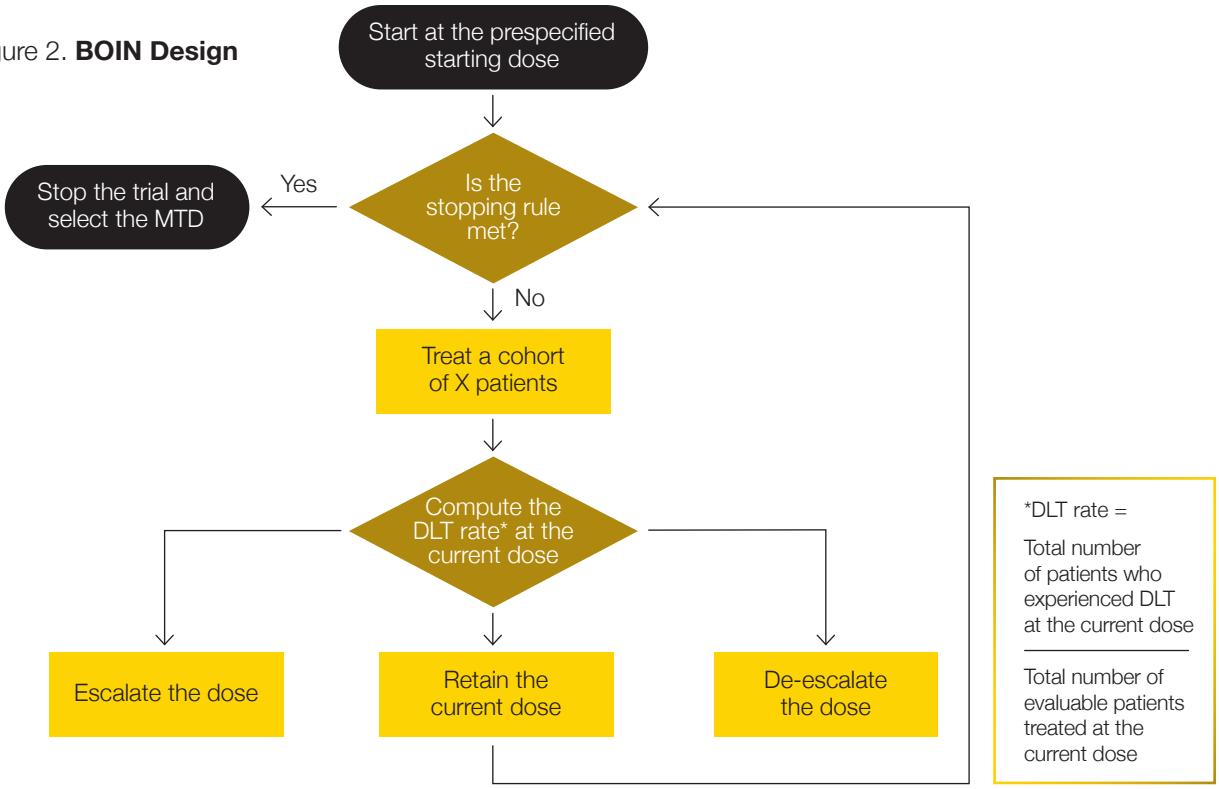
The first step in BOIN design is to specify a target toxicity rate and two alternative toxicity rates, one that would warrant dose escalation and another that would call for dose de-escalation. Using Bayesian probability models, these pre-specified toxicity rates are used to calculate escalation and de-escalation thresholds, with the aim of minimizing the probability of incorrect dosing decisions. Initial assumptions also include cohort size and maximum sample size.

The number of DLTs observed in enrolled patients determines which of three intervals the toxicity rate falls into and what the dose for the next cohort should be:

1. Under-dosing. The observed toxicity rate is below the target interval, and the dose should be escalated to the next level.
2. Optimal dosing. The observed toxicity rate falls within the optimal interval, and the dose should remain at the current level.
3. Over-dosing. The observed toxicity rate is above the target interval, and the dose should be de-escalated to a lower level.

The simplicity of this approach makes it easy for sites to implement in real-time since the rules are transparent and the logic behind each dose decision is clear.

Figure 2. **BOIN Design**



Practical Advantages and Key Considerations

What sets BOIN apart is the way it uses the observed DLT rate at the current dose to determine dose escalation and de-escalation, in addition to the flexibility to chose the maximum number of patients that can be enrolled at a given dose. This approach is more transparent and assessable for non-statisticians and is easy to calibrate to fit a design goal.

The BOIN design offers several advantages:

- **Improved efficiency.** BOIN enrolls a higher percentage of patients at the optimal dose compared to the 3+3 design, leading to a more efficient trial.
- **Ease of study execution.** The straightforward rules make it less complex to operationalize than fully model-based designs, reducing the need for extensive real-time statistical support. The accessibility of this design is also enhanced by its simulation software. With the assistance of Precision for Medicine's experienced biostatisticians, the user-friendly simulation platform can assist in the design and implementation of the BOIN design in Phase 1 clinical trials, including single agent and drug combination studies.

- **Robust performance.** Extensive simulations have shown that BOIN performs well in identifying the MTD across a wide range of scenarios, making it a reliable and robust choice.

Though some have raised concerns about the possibility of aggressive dose escalation in BOIN trials, studies have shown that BOIN has a lower risk of overdosing patients than other designs and generally a higher probability of correctly selecting the MTD.

Moreover, BOIN is among the top-performing designs for mitigating the risk of sub-therapeutic dosing.[9]

While BOIN offers many benefits, it is essential to consider its limitations. As a model-assisted design, it is less flexible than a fully model-based approach and may not be the optimal choice for trials with complex objectives.

Table 1. **Summary of BOIN design**

Strengths	Limitations
• Higher probability of selecting the true maximum tolerated dose • Clear implementation guidelines that teams can execute without advanced statistical knowledge • Model assisted framework supporting various endpoints and safety data integration • Established regulatory acceptance • Overdose control built into design	• May not suit trials requiring extensive dose-response modeling • Performance depends on initial escalation boundary setting *Optimal use: Phase 1 oncology trials requiring balanced statistical strength and operational efficiency, particularly with sites new to adaptive designs.*

Key Takeaway

BOIN balances statistical sophistication and operational practicality, delivering efficiency without derailing implementation. This design is a powerful tool for dose-finding in Phase 1 oncology clinical trials, but as with any model, it is not one-size-fits-all.

Precision's data science experts can assist sponsors in selecting the right design for their unique requirements, allowing them to unlock insights and harvest the most impactful data to propel their programs forward. With our experience delivering BOIN across diverse therapeutic contexts, we understand the critical factors that determine success, from site training through regulatory submission, ensuring that theoretical advantages translate into practical trial benefits.

Other Model-Assisted Designs

While BOIN, Continuous Reassessment Method (CRM), and BLRM are among the most popular adaptive designs, other methodologies offer unique advantages and applications.

Understanding these alternatives can help sponsors select the most appropriate design for their specific trial.

Modified Toxicity Probability Interval

The modified toxicity probability interval-2 (mTPI-2) design, a variant of the traditional 3+3 design, is a model-assisted approach that is similar to BOIN in terms of its straightforward design and ease of implementation. This design is an upgrade to the mTPI, with a substantially lower risk of over- or under-dosing and a more precise estimate of the MTD. In mTPI-2, a posterior probability interval for the toxicity rate is calculated at each dose level, and a dose decision is made based on where the observed toxicity rate falls within this interval.

Advantages of the mTPI-1 design are that it is more flexible than the 3+3 and it possesses superior operating characteristics that are comparable to more complex model-based designs. However, it requires more statistical support and may need larger patient populations than model-based approaches.

Table 2. **Summary of mTPI-2 design**

Strengths	Limitations
• Enhanced precision over rule-based designs • Simpler implementation than CRM • Effective balance of statistical power and operational feasibility	• Requires more statistical support than basic designs • May need larger patient populations than model-based approaches

Optimal use: Programs seeking enhanced statistical rigor while avoiding full model-based complexity.

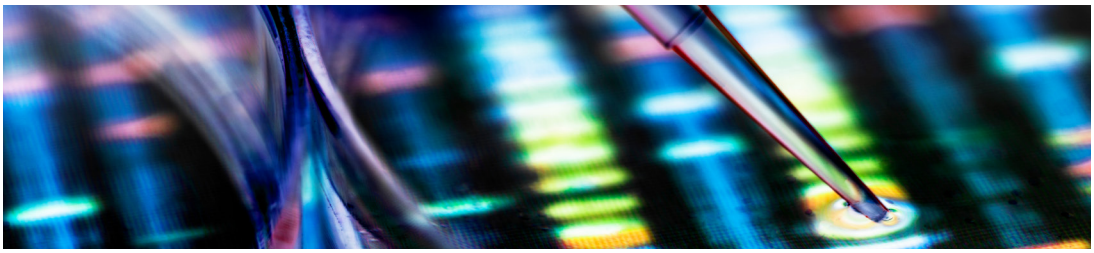
Backfill i3+3

The Backfill i3+3 (Bi3+3) design is an innovative hybrid approach that combines elements of the traditional 3+3 design with adaptive features.[10] It is a more robust alternative to the simple 3+3 design that allows for the backfilling of cohorts, with the goal of collecting information at different doses during dose escalation to help inform dose optimization decisions.

Bi3+3 uses a dose escalation algorithm that combines the model-free i3+3 design approach with a Bayesian model-based probability of decision (POD) framework. In this design, patients are first enrolled at the current dose level. Once this main cohort has completed enrollment, patients are randomly allocated to backfill cohort doses, which must be lower than the current dose level. Backfill cohort doses must also be considered safe and demonstrate sufficient efficacy.

After DLT is observed in the main cohort, a dosing decision for the next cohort is made using the i3+3 design. At the same time—and prior to acting on the decision for the main cohort—the dosing decision for all the backfill doses is also determined:

- If none of the subjects in the backfill cohorts have pending DLT outcomes, the i3+3 design is used to make dosing decisions for the backfill doses.
- If at least one subject has a pending DLT outcome, the POD framework is used to determine if trial enrollment should be suspended for all doses.



If trial enrollment is suspended, patients with pending DLT outcomes are followed up. Once sufficient DLT outcomes are observed such that trial enrollment is no longer suspended, the POD framework is then used to make dosing decisions for all the backfill doses.

Based on the findings from the backfill doses and main cohort, a dosing decision for the next main cohort is made. This process continues until no doses are left either due to safety rules being met or the number of patients in the main cohort reaching a pre-determined maximum sample size.

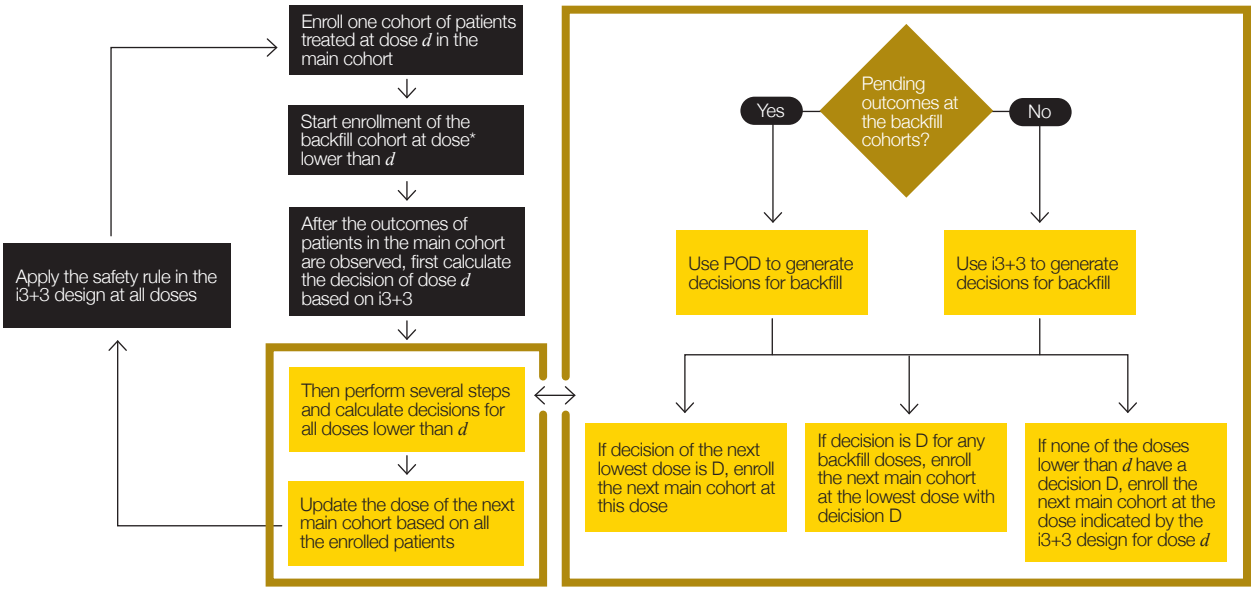


Figure 3. **Bi3+3 design workflow**

Bi3+3 may be a good option for sponsors who are comfortable with the traditional 3+3 framework but want to incorporate some of the benefits of modern adaptive designs.

Table 3. **Summary of Bi3+3 design**

Strengths	Limitations
• Recognizable framework facilitating stakeholder acceptance • Enhanced safety protocols • Implementation possible without specialized tools	• Longer time to completion compared to rule-based approaches • Conservative methodology may miss optimal dosing levels • Requires deep statistical experience to perform simulation work for the development of design operating characteristics

Optimal use: Programs prioritizing safety considerations or regulatory compliance, and organizations transitioning from traditional designs.

Key Takeaway

Both mTPI-2 and Bi3+3 demonstrate efficiency gains over traditional approaches, including sample size reduction, timeline acceleration, and operational simplicity, making them accessible to a broad range of sponsors. While these designs are generally preferred over conventional 3+3 designs in early-phase oncology trials due to their statistical superiority, they may also be preferred over modern adaptive designs due to their transparency and operational simplicity.

Chapter 3

Model-Based Designs

Continuous Reassessment Method: A Model-Based Approach

As a fully model-based design that uses all available patient data to continuously update the dose-toxicity relationship, the CRM represents a significant leap forward in dose-finding methodology. Due to its statistical sophistication, CRM uses real-time toxicity data to update dose recommendations, protecting patient safety while shortening the time to identifying the right dose.

Despite studies showing that CRM is more effective than other designs at finding the MTD, adoption of this approach has been low since its introduction in 1990. From 2008 to 2014, only 5.4% of Phase 1 trials used model-based designs.[11] Though advancements in software and additional evidence have increased its use, many sponsors still prefer more familiar methods.

Power of Bayesian Modeling

CRM is a Bayesian design that starts with an initial prior belief about the dose-toxicity curve. As each patient is enrolled and their toxicity data becomes known, the model uses this new information to reassess its understanding of the curve. When a patient experiences a DLT, the model recalculates.

This constant feedback loop and continuous reassessment results in a posterior probability distribution that provides a more accurate estimate of the dose-toxicity relationship and the OBD.

Step-by-Step CRM Process

The CRM process is comprised of five steps:

1. **Pre-trial setup.** A dose-toxicity model is selected, and the initial dose levels and a target toxicity rate are defined.
2. **First patient enrollment.** The first patient is assigned to a dose level. Once their DLT status is known, the data is added to the model.
3. **Continuous reassessment.** The model is updated, and a new probability of toxicity is calculated for each dose level.
4. **Next patient assignment.** The next patient is assigned to the dose level that is estimated to be closest to the target toxicity rate.
5. **Iteration.** This process repeats with each patient, with the model becoming increasingly precise over time, until pre-specified stopping criteria are achieved.

Key Strengths and Implementation Challenges

The primary strength of CRM is its statistical efficiency. By leveraging all available data, it can quickly and accurately pinpoint the MTD, often with a smaller sample size than rule-based designs. It also has an ethical advantage, as it tends to assign more patients to doses at or near the MTD, thus increasing their chances of a therapeutic benefit.

However, the implementation of CRM can be challenging. A biostatistician with a deep understanding of Bayesian modeling is needed for both protocol design and real-time study execution, and some regulatory agencies require additional documentation to approve these designs. Modern software packages have simplified CRM setup, with these tools handling complex calculations and guiding real-time decisions. However, proper training remains essential. Small choices in setup can significantly impact trial outcomes as initial assumptions of the model can influence its future behavior, so careful calibration is critical.

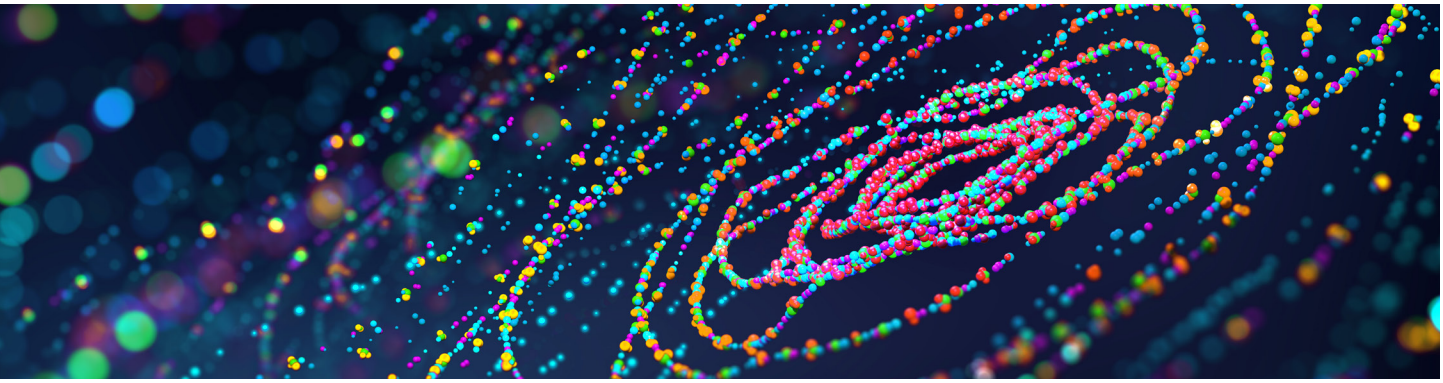


Table 4. **Summary of CRM design**

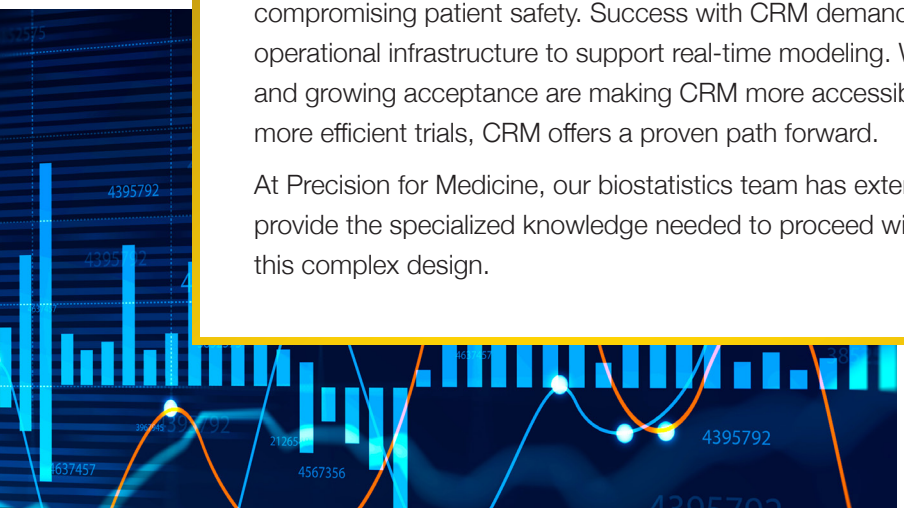
Strengths	Limitations
• Efficient maximum tolerated dose identification • Strategic patient allocation to effective dose levels • Robust handling of complex dose-response relationships	• Requires dedicated statistical expertise • More complex stakeholder communication • Higher implementation costs

Optimal use: Programs where precise dose-finding is essential, especially for new drug classes or non-linear dose-response relationships.

Key Takeaway

CRM finds effective doses more quickly than traditional methods, increasing trial efficiency without compromising patient safety. Success with CRM demands both statistical expertise and the operational infrastructure to support real-time modeling. While challenges remain, improved tools and growing acceptance are making CRM more accessible. For organizations committed to safer, more efficient trials, CRM offers a proven path forward.

At Precision for Medicine, our biostatistics team has extensive experience with CRM and can provide the specialized knowledge needed to proceed with precision and successfully implement this complex design.



Bayesian Logistic Regression Model: An Advanced Dose-Finding Methodology

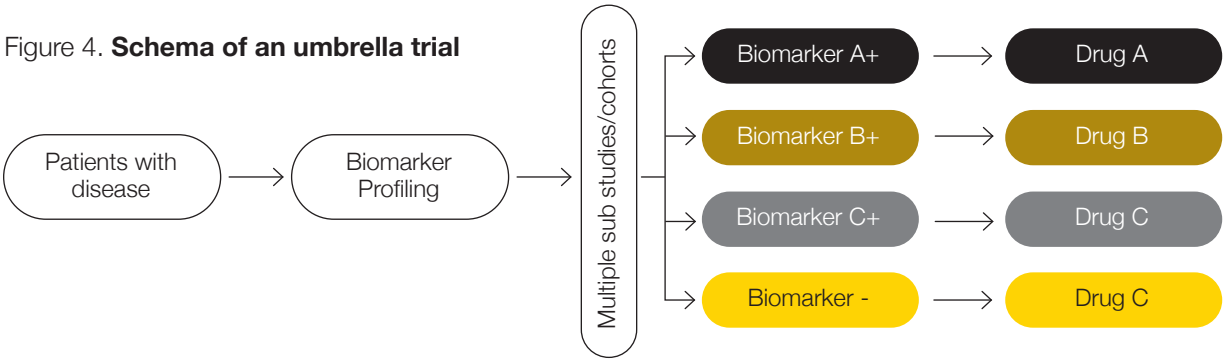
The Bayesian Logistic Regression Model is a versatile and powerful model-based design that is well-suited for complex oncology trials. It builds on the principles of the Continuous Reassessment Method (CRM) by using a logistic regression curve to model the dose-toxicity relationship, providing a more robust and flexible framework for informed dose adjustments.

Mechanics of BLRM

BLRM uses a logistic regression curve to model the probability of a DLT as a function of dose. As with CRM, this design starts with prior beliefs about dose safety, drawn from prior research, but BLRM is better-suited for evaluating the complex dose relationships involved in combination therapies. Additionally, we can use Bayesian "priors" to encode information into the design – such as ensuring a monotonic relationship between dose and DLT rate (DLT rate will always increase as a function of dose).

These effectively act as guardrails and prevent the model from returning "backwards" curves when data are sparse. The parameters of the model are updated using Bayesian inference as patient data becomes available, allowing for a continuous, data-driven reassessment of the dose-toxicity relationship. Importantly, BLRM looks beyond severe side effects to track mild and moderate reactions, building a more comprehensive safety profile.

Figure 4. **Schema of an umbrella trial**



Practical Advantages and Key Considerations

A key advantage of BLRM is its ability to incorporate a wide range of prior information, including data from preclinical studies or previous trials. This helps to stabilize the model and improve its performance, especially in the early stages of a trial with limited data. Additionally, covariates can be included within the model, which allow for differing toxicity risks based on a patients' characteristics, and can also be used to account for increased toxicity risk with drug interactions for combination studies. The output of BLRM is not just a single dose recommendation but a set of probabilities for each dose level, which provides a more complete picture for decision-making. The adaptive nature of the model also results in more patients receiving a dose that is closer to the OBD.

As a model-based design, BLRM can be more resource-intensive than traditional methods due to the need to set up the model and its computational requirements. Poor or inaccurate initial assumptions can mislead the model, so extensive simulation testing to demonstrate control of patient risk and operating characteristics is essential. Implementation and management of BLRM also requires significant statistical knowledge.

Table 5. **Summary of BLRM design**

Strengths	Limitations
• Incorporates information gained on study to extend model strength • Effective integration of historical data • Strong performance with complex dose-response patterns • Clear toxicity risk assessment	• Demands statistical implementation support • Resource-intensive computing requirements • Requires thorough prior assumption validation

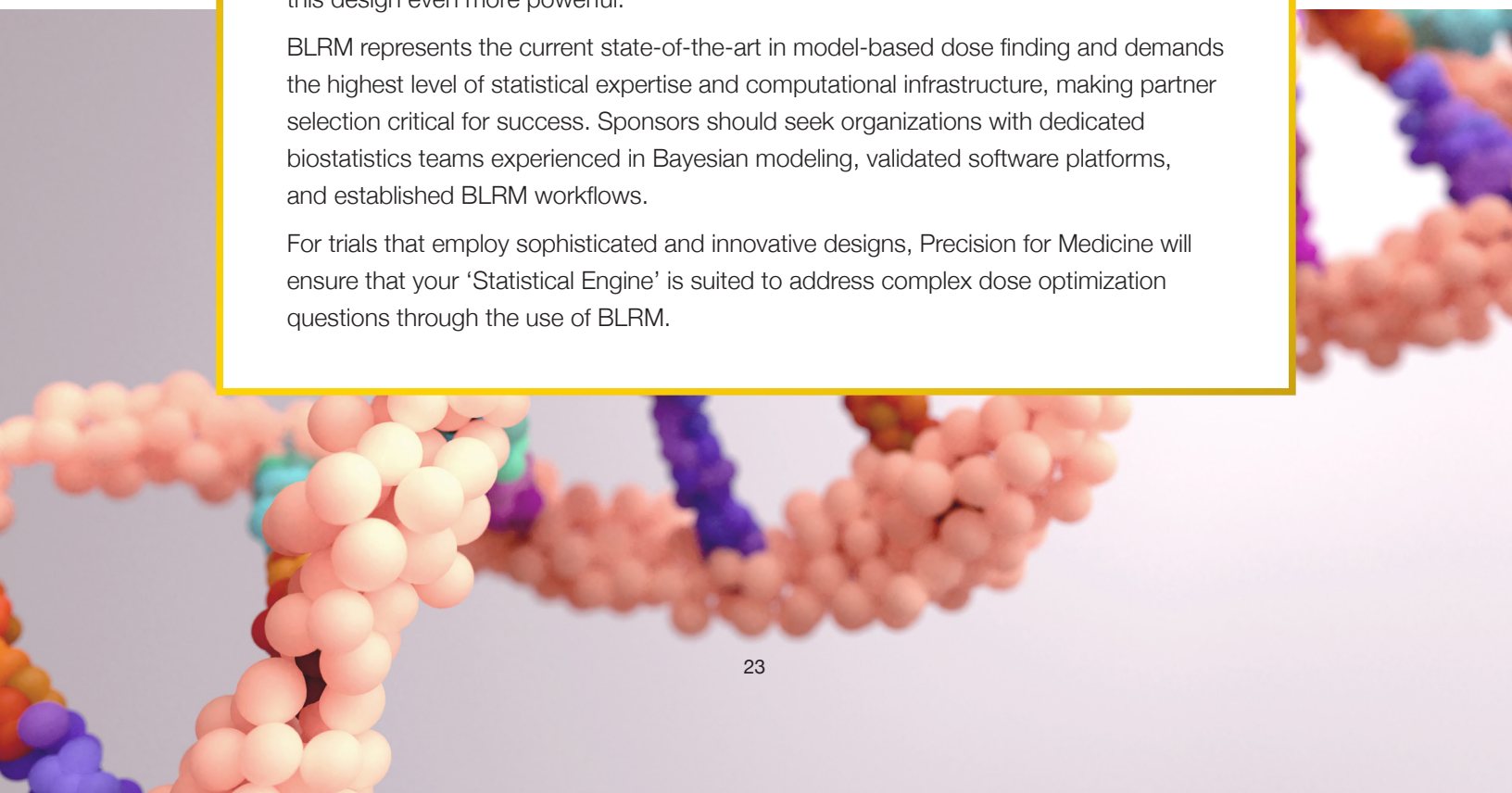
Optimal use: Programs with substantial prior data, combination therapy studies, or work in well-documented therapeutic areas.

Key Takeaway

Successful BLRM designs balance speed and safety. Computing advances continue to expand BLRM capabilities with new statistical methods that can handle more complex drug interactions. Machine learning integration may further refine dose selection, making this design even more powerful.

BLRM represents the current state-of-the-art in model-based dose finding and demands the highest level of statistical expertise and computational infrastructure, making partner selection critical for success. Sponsors should seek organizations with dedicated biostatistics teams experienced in Bayesian modeling, validated software platforms, and established BLRM workflows.

For trials that employ sophisticated and innovative designs, Precision for Medicine will ensure that your ‘Statistical Engine’ is suited to address complex dose optimization questions through the use of BLRM.



Chapter 4

Selecting the Right Phase 1 Oncology Trial Design

Selecting the optimal Phase 1 design is one of the most consequential decisions in oncology drug development. No single design dominates all scenarios. Instead, success requires matching design sophistication to the drug developer's specific therapeutic context, operational capabilities, and strategic objectives. This decision impacts not only the immediate efficiency of dose-finding but also the quality of data supporting regulatory submissions, the foundation for Phase 2 planning, and the competitive positioning of the development program.

A Strategic Decision-Making Framework

The therapeutic characteristics of the investigational agent fundamentally shape design selection. Cytotoxic agents with steep dose-toxicity curves often benefit from model-based designs like CRM or BLRM that can efficiently navigate narrow therapeutic windows through continuous learning. These designs excel when small dose changes produce significant toxicity differences, requiring precise MTD identification. In contrast, targeted therapies with wider therapeutic indices and plateau effects may be better served by model-assisted designs like BOIN or mTPI-2, which offer statistical efficiency without excessive complexity.

The expected toxicity profile also drives design choice. Predictable, acute toxicities that manifest within standard DLT windows align well with any modern design, while complex, delayed, or cumulative toxicities demand more sophisticated approaches that can incorporate partial information from patients still under observation.

For combination therapies, the complexity increases exponentially. Multi-dimensional dose-finding requires specialized designs capable of efficiently exploring the dose space of two or more agents simultaneously. The choice depends on the expected interaction between agents, the size of the dose space to explore, and available patient numbers.

Patient population characteristics also influence design selection. In rare diseases, the superior efficiency of adaptive designs becomes essential. CRM might enroll 25-40% fewer patients than a traditional 3+3 while providing better MTD estimates, a critical advantage when the global patient pool is inherently limited.[12] Heavily pretreated populations with few treatment alternatives may justify more aggressive dose escalation enabled by model-based designs, while treatment-naïve populations might warrant more conservative approaches with more stringent safety constraints.

Balancing Risk, Efficiency, and Data Value

The evaluation of different designs requires careful consideration of multiple dimensions of risk and benefit. Safety remains paramount, particularly for first-in-human studies where conservative approaches appropriately dominate. However, being too conservative raises ethical concerns if it results in treating a large number of patients at sub-therapeutic doses. Modern designs address this tension through sophisticated dosing control mechanisms that maintain safety while improving efficiency.

Efficiency manifests in multiple ways beyond simple sample size. The proportion of patients treated at or near therapeutic doses represents both an ethical imperative and a practical consideration for trial recruitment and retention. Adaptive designs typically assign 40-60% of patients near the MTD compared to 20-30% for traditional 3+3 designs.[13] This improvement in patient allocation translates to better informed consent discussions, enhanced investigator engagement, and potentially improved recruitment rates.

The data generated by different designs varies in richness and regulatory value. While 3+3 designs provide minimal information about the dose-toxicity curve, model-based approaches generate a more detailed characterization. This comprehensive information is essential for regulatory submissions, particularly under the dose optimization expectations of Project Optimus. The ability to incorporate biomarker data, PK/PD relationships, and efficacy signals further distinguishes modern designs in their capacity to support integrated development strategies.

Strategic considerations are often the deciding factor in design selection. In competitive indications where multiple agents are in development, the time saved through efficient dose-finding may determine commercial success. In addition, portfolio-level resource allocation might favor standardizing on specific design approaches to build institutional expertise. However, global development strategies must account for regional regulatory preferences, with some authorities showing clear preferences for certain design types.

Navigating the Regulatory Landscape

The regulatory environment has shifted decisively toward sophisticated dose-finding approaches. Project Optimus reflects longstanding FDA concerns about inadequate dose optimization, effectively mandating more comprehensive Phase 1 programs. This shift extends beyond simple expectations for multiple dose exploration, with regulators increasingly expecting integrated analysis of safety, efficacy, PK/PD relationships, and biomarker data to justify dose selection.

Different designs carry varying levels of regulatory precedent and acceptance:

- **BOIN** design has achieved broad FDA endorsement with published guidance and numerous successful implementations across therapeutic areas. The agency's comfort with BOIN stems from its transparent decision rules, robust safety properties, and extensive simulation studies demonstrating superior performance.
- **CRM** also has decades of regulatory history but requires careful justification of model specifications and prior distributions.
- **BLRM** is gaining acceptance but demands comprehensive documentation of modeling assumptions and sensitivity analyses.

Novel or hybrid designs typically require early FDA consultation to ensure alignment on acceptability.

Documentation requirements for adaptive designs extend well beyond traditional protocols:

- **Comprehensive simulation reports** must demonstrate operating characteristics across plausible scenarios, including stress tests of unusual dose-toxicity curves.
- **Clear specification of decision rules** eliminates ambiguity in dose escalation decisions.
- **Sensitivity analyses** for key assumptions, particularly prior specifications in Bayesian designs, provide confidence in robustness.
- **Risk mitigation strategies** should address potential design limitations.

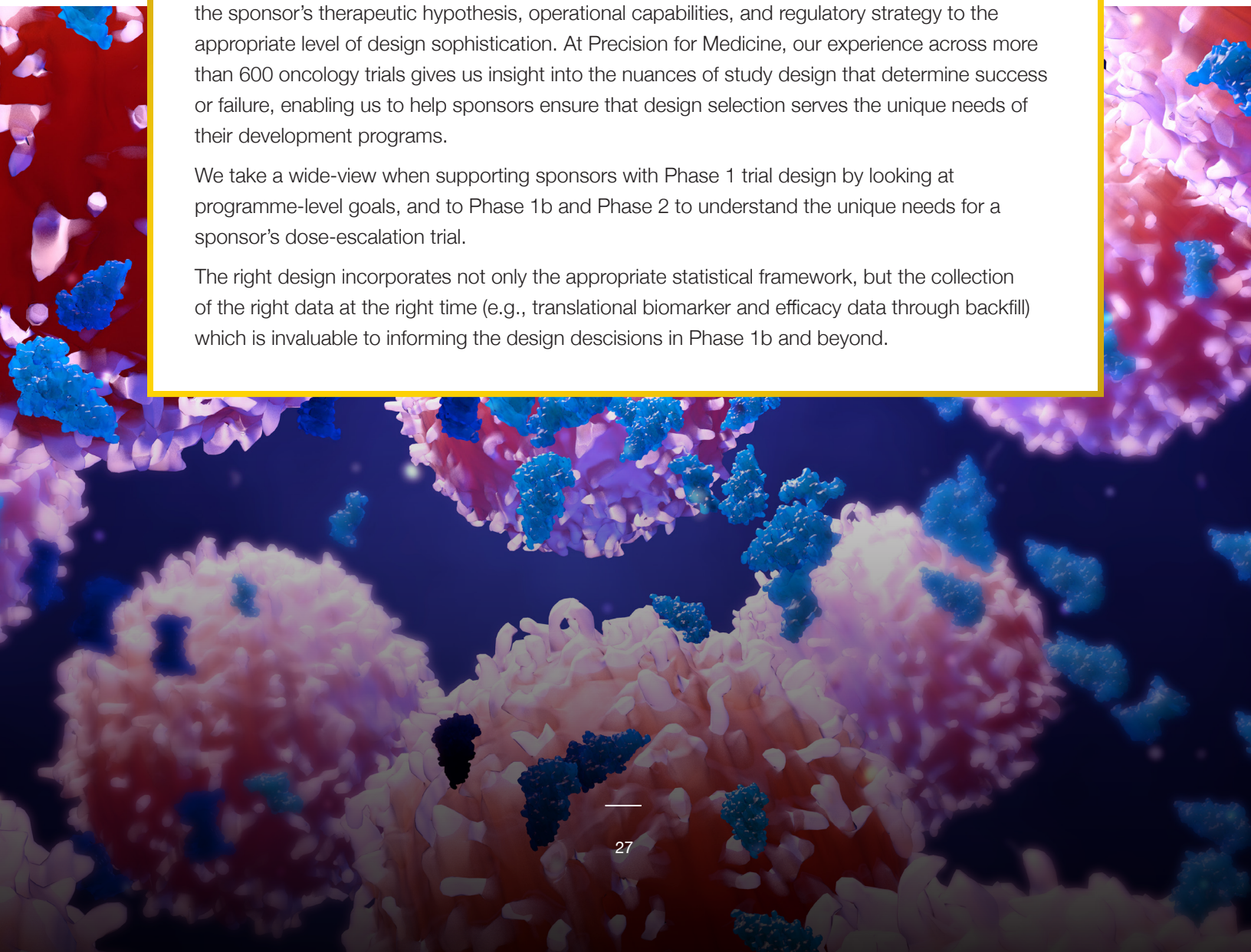
Global development programs must navigate varying regional expectations. The EMA increasingly emphasizes dose optimization in initial approvals, often requesting additional dose-finding data during review. Japanese authorities maintain specific requirements for bridging studies that may influence Phase 1 design choices. Emerging markets present their own considerations around design complexity and local implementation capabilities. Harmonizing these requirements while maintaining trial efficiency requires thoughtful design selection and careful regulatory strategy.

Key Takeaway

The selection of a Phase 1 trial design is more than a statistical decision—it is a strategic choice that influences every aspect of a development program. The right design is one that matches the sponsor's therapeutic hypothesis, operational capabilities, and regulatory strategy to the appropriate level of design sophistication. At Precision for Medicine, our experience across more than 600 oncology trials gives us insight into the nuances of study design that determine success or failure, enabling us to help sponsors ensure that design selection serves the unique needs of their development programs.

We take a wide-view when supporting sponsors with Phase 1 trial design by looking at programme-level goals, and to Phase 1b and Phase 2 to understand the unique needs for a sponsor's dose-escalation trial.

The right design incorporates not only the appropriate statistical framework, but the collection of the right data at the right time (e.g., translational biomarker and efficacy data through backfill) which is invaluable to informing the design descisions in Phase 1b and beyond.



Chapter 5

Operationalizing Modern Adaptive Methodologies

While modern adaptive designs offer significant strategic advantages, they can be challenging to implement. These trials are dynamic and data-driven, demanding a different level of precision and integration than traditional designs. Thus, successfully operationalizing modern Phase 1 designs demands more than statistical sophistication—it requires bringing together the right team, technology, and training to translate the protocol into practice.

Building the Implementation Team

The composition and preparation of the implementation team often determine the difference between smooth execution and operational challenges that compromise trial integrity.

- **Medical leadership** provides the clinical judgment essential for translating statistical recommendations into patient care decisions. Oncologists experienced with dose escalation trials understand the nuances of DLT assessment, the importance of timely safety evaluations, and the clinical implications of different dose levels. This clinical expertise is crucial when unexpected toxicity patterns emerge or when difficult decisions arise about dose escalation in the face of ambiguous safety signals.
- **The biostatistical team** serves as the backbone of adaptive designs. For model-based approaches like the CRM or the BLRM, PhD-level statisticians with Bayesian expertise are responsible not only for initial design specification but also for ongoing dose recommendations and model diagnostics. Even model-assisted designs benefit from experienced statistical support to ensure proper implementation and interpretation.
- **Clinical operations** transform the conceptual design into operational reality. The real-time nature of adaptive trials means that clinical data, including toxicity information and biomarker results, must flow seamlessly from the site to the biostatistics team. The data management team must implement the accelerated cleaning processes essential for real-time dose decisions. Their ability to rapidly identify and resolve queries directly impacts the timeliness of dose escalation decisions.

Ensuring Trial Site Excellence

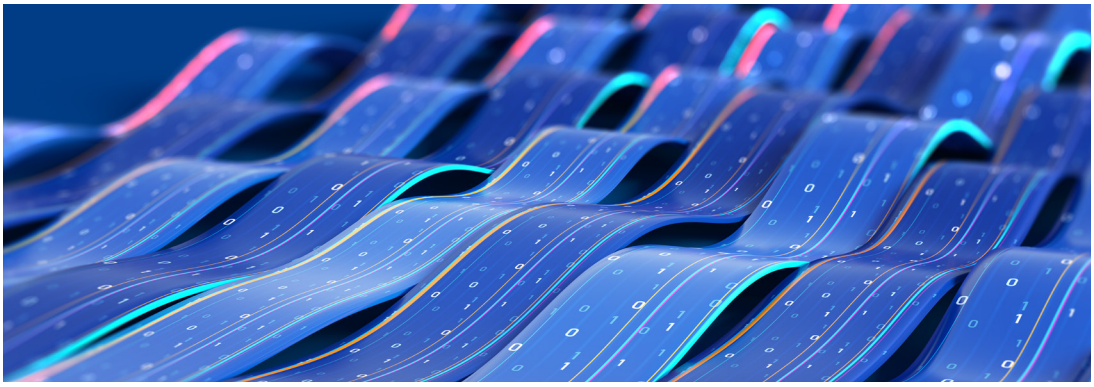
The technological infrastructure supporting modern Phase 1 designs extends far beyond basic electronic data capture (EDC). Real-time data flow, integrated analytical systems, and robust communication platforms are critical for enabling adaptive decision-making.

EDC systems must prioritize critical fields required for dose decisions while still supporting comprehensive data collection. This means configuring edit checks to flag DLT-related inconsistencies immediately, automating query generation for safety data, and enabling rapid data export for statistical analysis. Seamless integration of the EDC, randomization, and drug supply management systems prevents delays and provides the audit trail needed for capturing the decision-making process for dose escalation.

Statistical computing infrastructure ranges from validated commercial software packages to custom-developed solutions. No matter what tool is used, the system must generate dose recommendations reliably and rapidly, often within 24-48 hours of data lock for a cohort. For Bayesian designs, computational resources for Markov chain Monte Carlo (MCMC) sampling or other intensive calculations must be readily available.

Communication platforms facilitate the complex coordination required for dose decisions. Secure portals allow dose escalation committees to review patient data, statistical analyses, and safety summaries regardless of geographic location. Document management systems maintain version control for protocols, statistical analysis plans, and meeting minutes. Video conferencing enables real-time discussion among global team members, while automated notifications ensure critical information reaches decision-makers promptly.

The data flow architecture connecting these systems determines operational efficiency. Standardized data formats, particularly CDISC compliance, facilitate integration across systems and vendors. Application program interfaces (APIs) that enable real-time data transfer eliminate the batch processing delays that historically slowed adaptive trials.



Technology Infrastructure and Operational Systems

Site preparation and ongoing support are key determinants of whether sophisticated designs translate into successful trials. Even the best statistical design fails if sites cannot execute it properly, making site readiness a critical success factor.

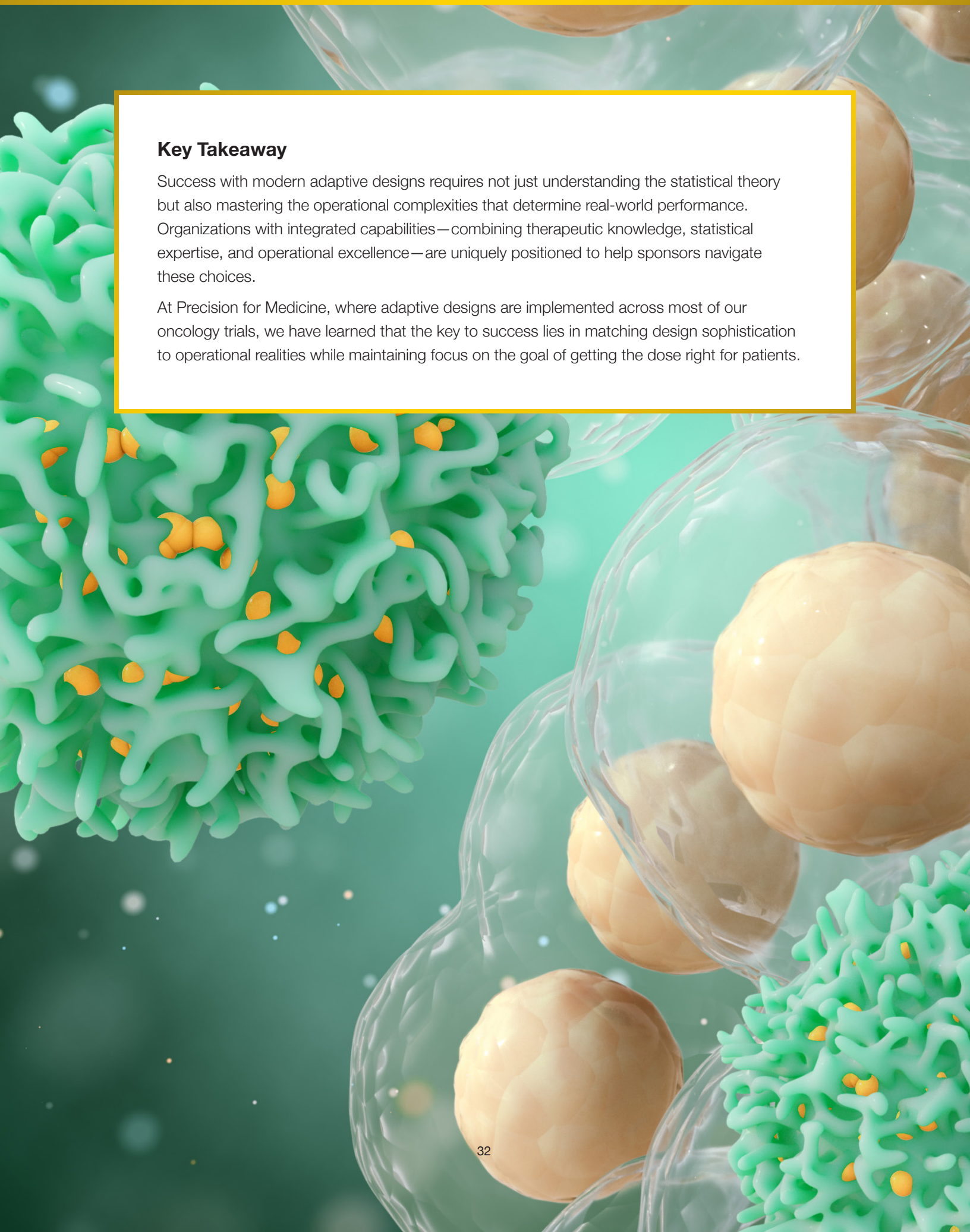
Site selection for adaptive trials requires careful evaluation beyond traditional metrics. Previous Phase 1 experience provides a foundation, but hands-on experience with adaptive designs offers an additional advantage. Sites must demonstrate not only clinical expertise and access to the target patient population but also operational capabilities including rapid data entry, timely query resolution, and flexibility for dose decision meetings. Further, infrastructure requirements—from laboratory capabilities to imaging facilities—must align with protocol demands.

The readiness assessment process should evaluate both tangible capabilities, such as technology infrastructure and resource availability, and intangible factors like enthusiasm and commitment. Competing trials may dilute site attention or create patient recruitment challenges. Staff experience influences training needs and ongoing support requirements.

Site activation for adaptive trials demands comprehensive preparation beyond standard protocols. Site initiation visits must cover not only protocol procedures but also design-specific requirements like DLT assessment timelines and dose decision processes. Hands-on training with decision tools and EDC systems builds practical competence, and mock patient scenarios allow sites to practice the rapid data entry and query resolution essential for adaptive designs.

Ongoing support throughout the trial maintains site engagement and performance. Regular check-ins during early cohorts helps identify and address challenges before they become systematic problems. Refresher training as the trial progresses maintains competency, particularly for sites with lower enrollment.

Our Precision Site Network demonstrates how systematic site preparation translates into measurable performance improvements, with participating sites achieving 6% faster IRB/ethics committee (EC) approval and 12% faster first patient in compared to non-network sites. This operational excellence, combined with deep statistical expertise across the spectrum of adaptive designs, enables successful implementation of even the most sophisticated Phase 1 protocols.



Key Takeaway

Success with modern adaptive designs requires not just understanding the statistical theory but also mastering the operational complexities that determine real-world performance. Organizations with integrated capabilities—combining therapeutic knowledge, statistical expertise, and operational excellence—are uniquely positioned to help sponsors navigate these choices.

At Precision for Medicine, where adaptive designs are implemented across most of our oncology trials, we have learned that the key to success lies in matching design sophistication to operational realities while maintaining focus on the goal of getting the dose right for patients.

Charting the Right Course with the Right Strategic Partner

Successful Phase 1 trials demand a combination of scientific rigor, operational feasibility, and seamless execution. In the lifecycle of breakthrough oncology therapies, the choice of Phase 1 trial design has become a critical strategic decision that impacts not only the near-term success of dose-finding but also the long-term trajectory of the entire drug development program. The one-size-fits-all 3+3 design is being replaced by adaptive trial methodologies that accelerate development, improve patient outcomes, and meet the evolving regulatory requirements on dose optimization. These designs are often complex, requiring a strategic partner with a unique blend of statistical expertise, therapeutic area knowledge, and integrated operational capabilities.

The future of oncology drug development lies in embracing innovation—whether through novel trial designs or adaptive dosing strategies. By working closely with regulatory bodies and leveraging adaptive designs, drug developers can optimize treatments faster and more effectively. For those navigating these complexities, partnering with the right CRO is a critical first step.

Precision for Medicine specializes in guiding our partners through the intricacies of oncology drug development, from pre-IND meetings to post-approval studies. Our experience ensures that every decision is informed by data and aligned with regulatory requirements, helping to bring the best therapies to patients faster and more effectively.

Optimize your development strategy by partnering with Precision experts for your next oncology program.

References

1. Kurzrock R, et al. Moving Beyond 3+3: The Future of Clinical Trial Design. *Am Soc Clin Oncol Educ Book*. 2021;41:e133-e144.

2. Fraisse J, et al. Optimal biological dose: a systematic review in cancer phase I clinical trials. *BMC Cancer*; 2021;21(1):60. US Food and Drug Administration.

3. Project Optimus. Available at https://www.fda.gov/about-fda/oncology-center-excellence/project-optimus.

4. Singh H, Vellanki PJ, Pazdur. The Retrofit: Lessons From Sotorasib's Dosing Conundrum. *J Clin Oncol.* 2025;43(3):248-250.

5. Simon R, et al. Accelerated titration designs for phase I clinical trials in oncology. *J Natl Cancer Inst*. 1997;89:1138-1147.

6. Reiner J, Paoletti X, O'Quigley J. Operating characteristics of the standard phase I clinical design. *Comput Stat Data Anal.* 1999;30:303-315.

7. Chen Z, et al. Interactive calculator for operating characteristics of phase I cancer clinical trials using standard 3+3 designs. *Contemp Clin Trials Commun.* 2018;12:145-153.

8. Ananthakrishnan R, et al. An overview of the BOIN design and its current extensions for novel early-phase oncology trials. *Contempt Clin Trials Commun.* 2022;28:100943.

9. Zhou H, Yuan Y, Nie L. Accuracy, Safety, and Reliability of Novel Phase I Trial Designs. *Clin Cancer Res*. 2018;24(18):4357-4364.

10. Liu J, et al. The Backfill i3+ 3 Design for Dose-Finding Trials in Oncology. *N Engl J Stat Data Sci.* 2024;3:271-283.

11. Li N, Zhou X, Yan D. Phase I clinical trial designs in oncology: A systematic literature review from 2020 to 2022. *J Clin Transl Sci*. 2024;8(1):e134.

12. James GD. Continual reassessment method for dose escalation clinical trials in oncology: a comparison of prior skeleton approaches using AZD3514 data. *BMC Cancer.* 2016;16(1):703.

13. Wheeler GM, et al. How to design a dose-finding study using the continual reassessment method. *BMC Med Res Methodol*. 2019;19(1):18.

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