



Adaptive Trials at the Mainstream of Drug Development

Cytel

INTRODUCTION

Traditionally associated with more efficient trials and better prospects for patients, adaptive trials continue to make revolutionary changes to drug development. While maintaining statistical rigor, adaptive trials are now more aligned with the overarching goals of human impact: improved clinical development, better pre-planning, greater patient safety, less medical waste, and increased knowledge. A deeper understanding of the adaptive concept can give trial sponsors the capacity to unlock an array of scientific, ethical, and financial benefits to drug and device development.



THE ADAPTIVE CONCEPT

Adaptive designs were initially conceived to devise novel ways to increase the efficiency and flexibility of clinical trials, while maintaining statistical rigor. Given a greater capacity to optimize resources and manage uncertainty, a number of trial designs have flourished and have changed the landscape of clinical trial execution and portfolio development. Adaptive designs can now tackle a range of challenges confronted during clinical development [Exhibit 1], resulting in more innovative designs becoming popular [Exhibit 2]. Therefore, familiarity with the scope of adaptive designs and their uses in forging strong pharmaceutical and financial strategy is an integral tool for clinical drug development.

According to the FDA, an adaptive design is any “study that includes a prospectively planned opportunity for modification,” where prospective refers to an adaptation that was determined with “details specified” prior to the unblinding of data¹ and preferably at the initial protocol-design stage. Such prospective planning can be implemented after a study has begun, as long as the data is not unblinded. Thus, building flexibility into a study design can enable a trial sponsor to maximize prospects across many eventualities.

When executed well, an adaptive design can ensure the best use of all the data collected during a clinical trial. An adaptive design may not only make trials faster, but also provide opportunities to obtain more information about a new drug or biologic. For example, **multi-arm** or **population enrichment** designs can yield highly specialized information during the execution of a trial, at decreased cost to trial sponsors. **Combined-phase** trials ensure that data collected from patients who enroll in early phases of a trial can also be used for late-stage confirmatory elements of a trial. In general, such trials facilitate the collection of important proprietary information that can be vital for strategy and decision-making.

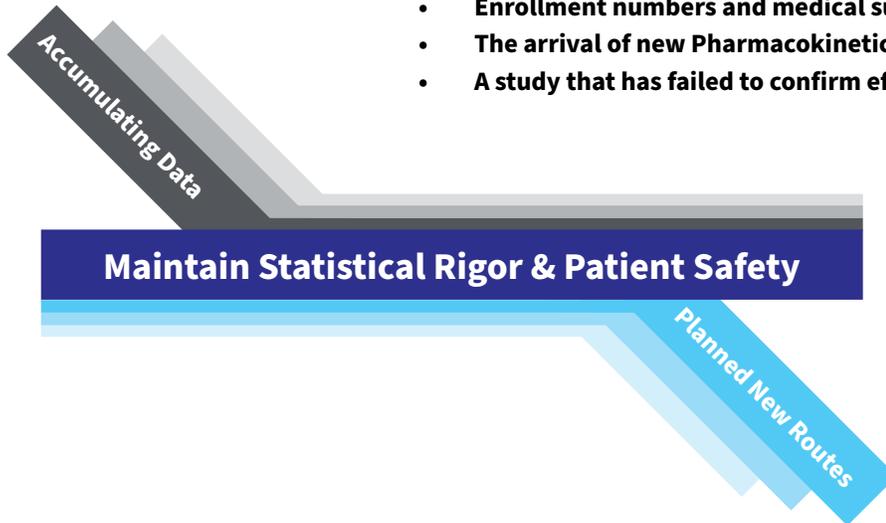
BENEFITS OF AN ADAPTIVE TRIAL

Scientific: Adaptive Trials Maintain Statistical Rigor and Increase Biological Knowledge

The main reason for a new drug or device to go to market is its proven effectiveness in supporting patients. Yet we also know that, in practice, several factors in a trial can interfere with confirmation of scientific viability.

Examples of such factors are:

- **Enrollment numbers and medical supply**
- **The arrival of new Pharmacokinetic/Pharmacodynamic (PK/PD) information**
- **A study that has failed to confirm effectiveness by only a small margin**



Financial Benefits

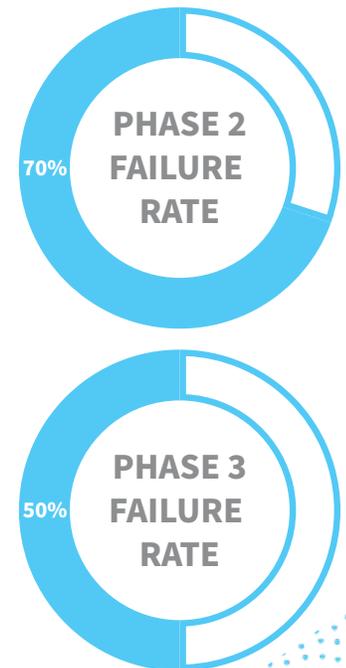
In planning an entire program of clinical development (preclinical phase to Phase 3), one of the challenges is predicting the aspects that could potentially go wrong. The inability to predict such problems accurately has led to a sobering backdrop of statistics on trial completion rates and trial success. Currently, about 70% of Phase 2 trials and 50% of Phase 3 trials are forecasted to fail.²

Adaptive designs can convert this uncertainty into an asset. By building flexibility into a trial, an adaptive design can help trial sponsors take advantage of promising results midway through a trial with the help of approaches such as sample size re-estimation, stratification, or other forms of protocol updates. (See, for example, the Champion Trial case study).³ Prospectively planned adaptations can yield strategic advantages while also being safe.

Adaptive strategies can constrain or increase sample size, allow for changes in dosage, and enable other modifications that allow sponsors to preserve the validity of a trial that would otherwise fail. Trial risks are mitigated through the use of adaptive strategies, while ensuring optimization of resources.

In both exploratory and confirmatory stages, adaptive designs are well-suited to managing uncertainty.

As mentioned earlier, adaptive trials ensure that sponsors can maximize net present value over the course of a trial by strategically planning possible decision-making as eventualities arise. An example of this scenario is sound go/no-go decision-making, where a “go” reflects an interim analysis into a seamless Phase 2/3 trial, or the start of other parts of the drug development process like beginning carcinogenicity or formulation evaluation studies. The financing of an adaptive trial can also benefit from strategic resource allocation and enrollment techniques.



Strategic Benefits

While it is important to ensure that any given trial obtains the best possible data, it is also imperative for pharmaceutical companies to optimize across a number of possible assets in a pipeline. Adaptive techniques can enhance clinical research and development strategy. Interim looks can inform simulations and forecasting, clarifying where scarce resources ought to be expended. Adaptive designs also allow planning for vulnerabilities in enrollment, medical supply, and other resource boundaries.

Early prospective planning enables adaptive strategies to maximize the expected net present value of a clinical portfolio. In order to accomplish this objective, adaptive strategies can complement rigorous forecasting, simulation, and intensive early-data collection. Adaptive strategies can also be tied to prospectively determined decision-rules that specify what action must be taken when an interim analysis reveals an unexpected finding.

In early phases, adaptive strategies align well with pharmacometric modeling to yield valuable insights that inform simulation and clinical development strategy. In particular, these strategies are pivotal for choosing the correct dose, without having to conduct multiple Phase 2 trials.

Adaptive designs can facilitate the collection of data that informs **go/no-go decision-making, dose-response modeling**, and other critical decision points in trial development. Adaptive designs can empower trial sponsors to make the most of the information collected during the trial.

In later phases, adaptive strategies allow trial sponsors to capitalize on data from earlier phases (for example, in a seamless Phase 2/3 trial, in biomarker-driven trials, or in population enrichment designs). They are important tools for mitigating Phase 3 risk.

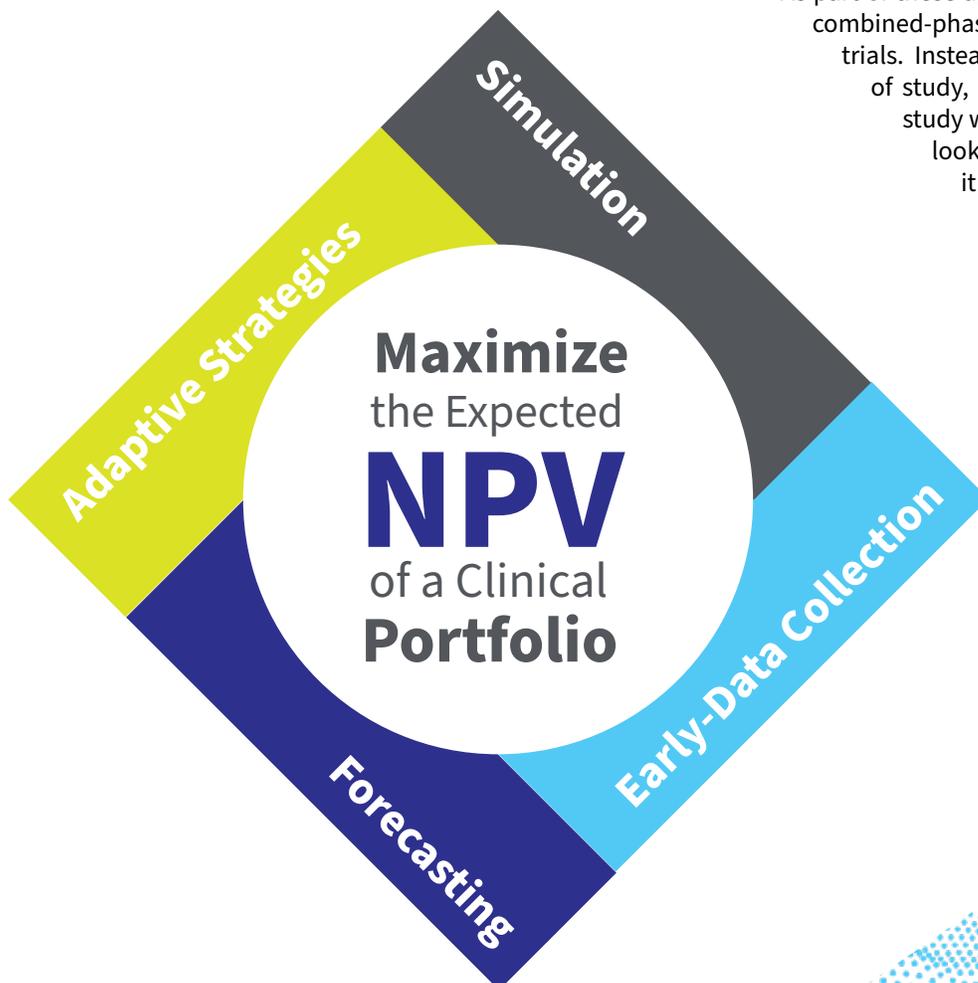
As part of these approaches, we're also seeing more use of combined-phase studies, what's referred to as seamless trials. Instead of conducting the usual three phases of study, seamless trials encompass one adaptive study where the phases are separated by interim looks. By using one large, continuous trial, it saves time and reduces costs. It also reduces the number of patients that have to be enrolled in a trial.⁴

Adaptive designs can enhance efficiency without compromising statistical rigor. A recent report shows that the average Phase 3 protocol now demands 60% more events than were required 15 years ago.² Prospective adaptive planning or using **"seamless" designs** can be a critical aspect of preserving scientific rigor while creating sound strategy and maximizing Phase 3 efficiency.

The Average Phase 3
Protocol Now Demands



Than Were Required 15 Years Ago



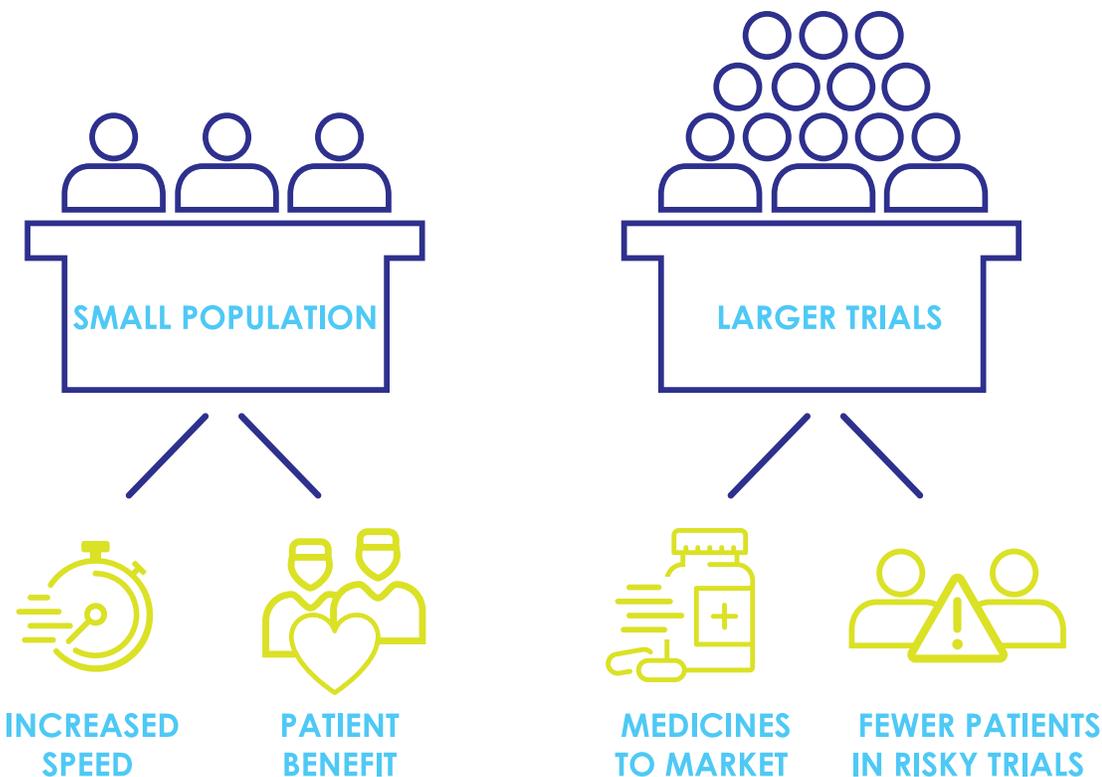
Ethical Benefits

According to a 2015 study,⁵ consultant biostatisticians and clinicians believe that adaptive designs are more ethical than standard designs. The reasons for this belief are varied. Some of the subjects of the research highlight the fact that adaptive designs enable a trial to stop early if there are signs that a candidate drug or therapeutic is not effective, thus allowing patients to enroll in other trials that might have more effective therapies. Others cite the fact that patient prospects might improve in some adaptive settings, particularly if they are enrolled after an interim analysis.

At the population level, rather than the clinical level, adaptive trials can provide additional ethical benefits to patients and members of other vulnerable populations. Let us consider rare disease trials, where the population sample is sometimes considered too small to justify market investment. The efficiency of certain adaptive designs—for example, combined-phase designs or sample size re-estimation trials—can result in better use of sample size and increased speed of trials, without sacrificing statistical rigor. The TRACON TRC105 trial for angiosarcoma demonstrated this advantage. Created by Cytel statisticians in collaboration with TRACON Pharmaceuticals, the trial combined population enrichment with an adaptive design to ensure that the small population sample could benefit from the study.

In larger trials, such efficiency results in new medicines based on the best available technology getting to market more quickly, thereby having life-saving impact. Simulations and forecasts performed by Cytel biostatisticians also confirm that multi-arm combined-phase designs are better at predicting which assets are likely to reflect efficacy. As a result, fewer patients are enrolled into unnecessarily risky trials.

“ **BETTER USE OF SAMPLE SIZE AND INCREASED SPEED OF TRIALS, WITHOUT SACRIFICING STATISTICAL RIGOR** ”



OPERATIONAL CONSIDERATIONS

When deciding whether to adapt, it is helpful to keep in mind the operational considerations in implementing an adaptive trial, including the regulatory environment, clinical operations, and finance.

Regulatory Environment

Regulators across the world have embraced adaptive designs in their full complexity. Since the FDA published its guidance on adaptive designs (2010), trial planners have been designing trials that are safe, efficient, and statistically rigorous using flexible approaches. For sponsors considering an adaptive trial, proactive and early engagement with regulators is critical. For example, Cytel provided support to TRACON Pharmaceuticals in their interactions with EMA and FDA for the TAPPAS trial, an innovative adaptive enrichment design that was approved for adoption by both agencies.

With regard to regulatory interaction, at least one study confirms that sponsors who approach agencies early in the context of their trial designs are more likely to receive market authorization for a study that is adaptive.⁶

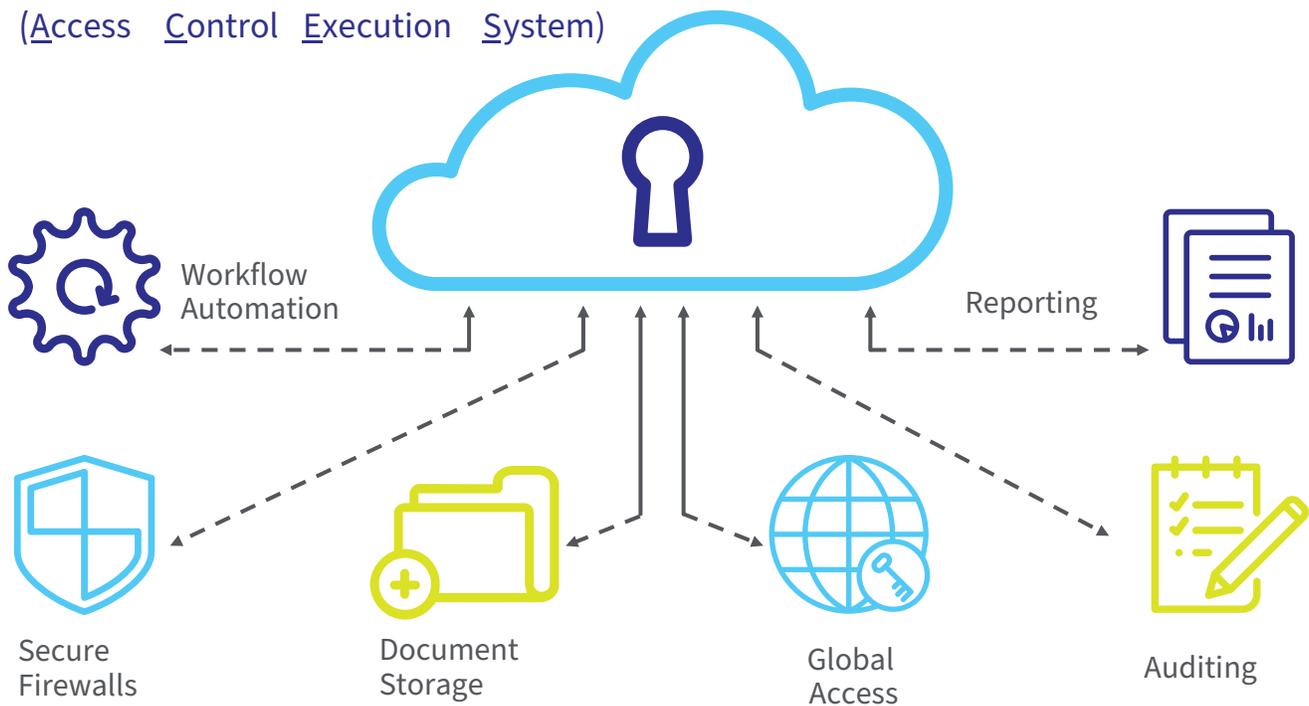
“ WITH REGARD TO REGULATORY INTERACTION, AT LEAST ONE STUDY CONFIRMS THAT SPONSORS WHO APPROACH AGENCIES EARLY IN THE CONTEXT OF THEIR TRIAL DESIGNS ARE MORE LIKELY TO RECEIVE MARKET AUTHORIZATION FOR A STUDY THAT IS ADAPTIVE. ”

Clinical Operations

Clinical operations for adaptive trials have specific requirements. Care must be taken to plan interim analyses prospectively and to ensure that data monitoring committees are able to analyze data without corrupting it. In general, the more complex the design, the more carefully operational logistics ought to be planned ahead of time. Therefore, it is important to have clinical operations specialists at the table early when planning for an adaptive trial.

ACES

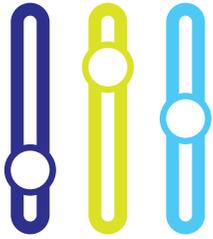
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The very existence of interim analyses requires adaptations to the trial process. All interim analyses should theoretically implement a “soft lock” in which the data management team ensures that all data is entered and monitored, without additional enrollments being included in the interim analysis data files during the analysis process. Therefore, the period of time allocated to data monitoring committees should be rather short to ensure that a minimal number of patients enroll as data monitoring is taking place.⁷ Further, adaptive trials require secure firewalls so that only members of the data monitoring committee have access to trial data during interim analyses. Trial platforms like the Access Control Execution System (ACES) ensure such discretionary practices, while also streamlining workflow and providing a clear system to manage document exchange. Such platforms can also help data managers handle more sensitive issues. For example, a recent complex trial design implemented by Cytel’s data management team had a feature whereby patients randomized into one trial arm were allowed to switch into another.

TO ADAPT OR NOT TO ADAPT?

Here is a 10-point decision framework that can help you decide whether your next trial should be adaptive:



1. Are there any regulatory concerns or complexities?

In order to answer this question, it is advisable to approach regulators early to receive statistical guidance and advice on protocol. There is growing evidence that adaptive trials that have received regulatory guidance on the design of the protocol are more likely to win approvability to take a new medicine to market.¹⁰

2. Is there any reason to believe that decision-making will be driven by population enrichment, biomarkers, or surrogates?

This factor will clearly help determine which particular adaptive strategies are best suited for your needs. If a new drug or biologic is aimed at a certain subgroup, then opening a trial to the full population can dilute the power of the therapy. An adaptive arm-dropping design can be used to ensure that this does not occur.⁸



3. What are the resource constraints in areas such as drug supply and enrollment?

Forecasting or simulation can help determine which adaptive designs or strategies are best suited to accommodate your specific needs.

4. Can the data monitoring committee receive and evaluate data in a timely manner?

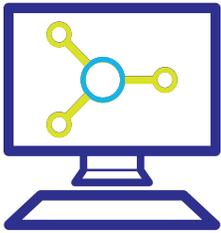
If not, an interim look might hold up the trial for longer than expected. Adaptive trial design can be used to ensure that this does not occur.



5. Is statistical expertise available to you?

Generally, adaptive trials benefit from having a biostatistician work alongside the trial design team and other members of a clinical operations team.

TO ADAPT OR NOT TO ADAPT?



6. Are forecasting tools available to you?

Using simulations, a trial sponsor should be able to predict the potential trial outcomes and many of the critical decisions required during the course of a trial, and to choose decision rules that allow for strategic and quantitatively rigorous decision-making.

7. How would adaptive designs optimize your financial strategy?

Adaptive designs are an important part of a tool kit that aims to optimize program and portfolio design. Thus, adaptive strategies can inform financial strategy



8. What are the statistical needs?

For example, if a trial would benefit from the use of conditional probabilities at interim analysis, adaptive designs might be superior. Some products (e.g., pediatric drugs) are better candidates for Bayesian trials. Some trials, such as cardiovascular outcome trials (CVOTs), are so large that early stopping will be more central to strategy. Such strategy can be adopted at both the financial and the statistical levels.

9. How much improvement in areas like cost and efficiency do adaptive designs achieve when compared to more traditional designs?

Platforms like Solara and East can now help sponsors quantify trade-offs in speed, cost and power to make designs Pareto optimal.



10. Will historical or real-world data be helpful in supporting regulatory submissions?

The wealth of historical, observable, and real-world data can enhance regulatory submissions by strengthening evidentiary packages. This, in turn, will influence the efficiency and effectiveness of an adaptive trial.

Digital Transformation

Cytel is channeling the current wave of digital transformation toward mainstream issues in clinical trial strategy, highlighting opportunities to transform linear trial development into synergistic, multi-stakeholder strategy.

These opportunities arise because the clinical trial industry is quickly learning the value of the holistic approaches made possible through digital transformation. In studies of organizational behavior, the force of digital transformation is largely delivered through the ability of enterprise-level technology platforms that streamline various elements of an organization's structure. Organizations like Netflix, Tesla, and Glassdoor have used digital transformation to connect R&D with customer insights, diffuse product safety technology remotely, and to generate billions of dollars in revenue from streamlining processes.

In the case of the clinical trial, industry digital transformation enables the unification of statistics with strategy. This means a clinical development journey where uncertainties about safety, treatment effects, and other clinical questions are resolved on the same platform that answers questions about trial design, such as endpoint selection, interim looks, and stratification of target populations. This places clinicians and statisticians into a mutually advantageous dialogue, and results in more optimized clinical strategies.

The Future

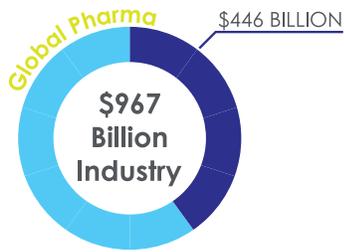
We have now entered a new era where the adaptive paradigm is not simply a method or a tactic, but a tool kit with the potential to resolve a wide range of challenges faced by trial sponsors and patients. Smaller trials like rare disease studies are now achieving statistical rigor with limited sample sizes, while larger trials like CVOTs are executed more quickly. Adaptive designs are used in biomarker-driven trials, for precision medicine, and in numerous other trials reflecting scientific innovations. They have also become a key component of ethical drug development by generating efficient designs in oncology, safer dose-selection, and more manageable population sizes for rare disease treatment. Financially, adaptive designs allow stakeholders to leverage more knowledge, particularly from early-phase data and through the use of pharmacometric models. These tools are allowing the industry to create shorter, cheaper trials while maintaining statistical rigor, thus creating new optimism for driving down the costs of medicine and bringing life-changing therapies to patients more quickly.

“ THESE TOOLS ARE ALLOWING THE INDUSTRY TO CREATE SHORTER, CHEAPER TRIALS WHILE MAINTAINING STATISTICAL RIGOR, THUS CREATING NEW OPTIMISM FOR DRIVING DOWN THE COSTS OF MEDICINE AND BRINGING LIFE-CHANGING THERAPIES TO PATIENTS MORE QUICKLY.

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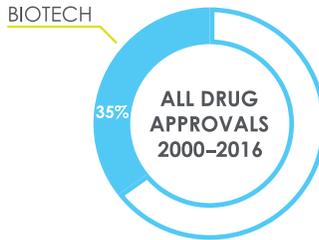
Exhibit 1:

INDUSTRY SIZE

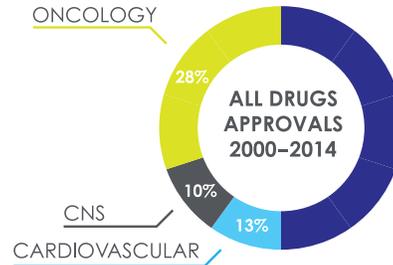


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APPROVAL RATE



10



11, 12, 13

AVERAGE NUMBER OF PHASE 3 TRIAL PROCEDURES REQUIRED

15 years ago

67

Today

167

60% Increase

MAKING CONFIRMATORY TRIALS MUCH LONGER

14

AVERAGE COST OF NEW DRUGS

\$2.6 BILLION & **15 YEARS**

15, 16

TRIALS ENROLLING PATIENTS



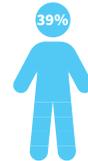
See Enrollment Now, but Not in a Timely Manner



Fail to Enroll Any Patients



Are Under-Enrolled



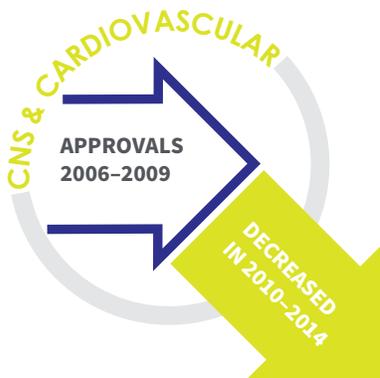
Meet Enrollment Targets



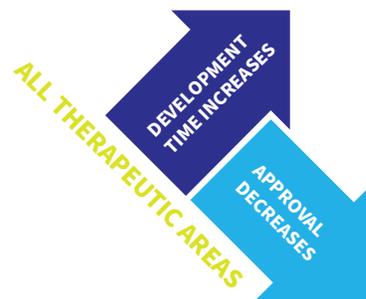
Exceed Enrollment Targets

17

DRUG APPROVAL RATES



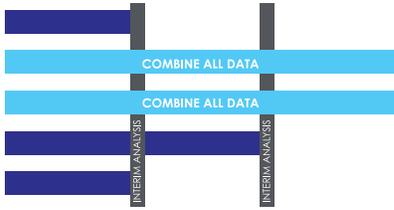
18



19, 20

Exhibit 2: Types of Adaptive Designs

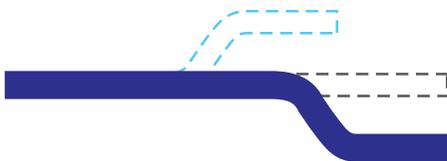
SEAMLESS PHASE 2/3



ARM-DROPPING AND DROP-THE-LOSER DESIGNS



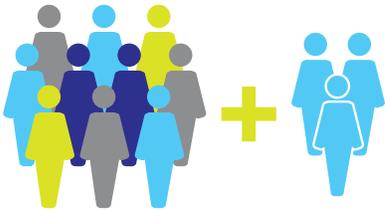
CHANGE OF PRIMARY ENDPOINT



SAMPLE SIZE RE-ESTIMATION



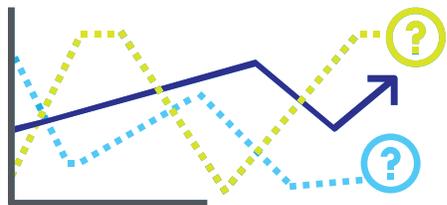
POPULATION ENRICHMENT



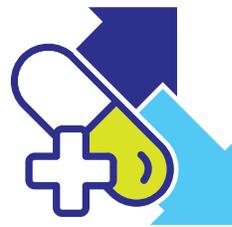
ADAPTIVE DOSE-FINDING



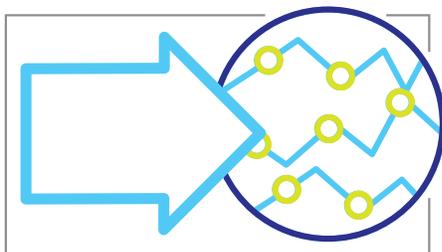
MULTIPLE ADAPTATIONS REQUIRING SIMULATIONS AND FORECASTING



CHANGE IN DOSAGE OR EXPOSURE



BAYESIAN PREDICTIVE PROBABILITY



BIOMARKER-DRIVEN ADAPTIVE DESIGNS



Design Examples

Early-Phase Dose-Finding Trials:

One of the challenges identified in the 2010 guidance on adaptive clinical trials was the possible use of adaptive strategies for clinical development in the early phases. In particular, the guidance identified dose-finding trials as particular beneficiaries of strategies, even while labeling the specific methodologies “less understood.”

In traditional rule-based dose-finding trials like 3+3, the design allows for rules that are easy to identify but are imprecise and/or limited in finding the maximum tolerated dose. Thus, two disadvantages arise: fewer patients receive the right dose (or a dose close to the right dose), and more patients are needed to hone in on the right dose(s). Adaptive strategies add the benefits of both more efficient trials and more accurate dose-finding.

Cytel has deployed a number of methods to improve on rule-based dose-finding. Product of Independent beta Prior probabilities dose Escalation (PIPE), a hybrid of rule-based models and Bayesian methods, has been particularly useful for early-phase (Phase 1/2a) trials in oncology.²² In 2021, Cytel scientists also developed the i3+3 early-phase rule for dose-escalation.

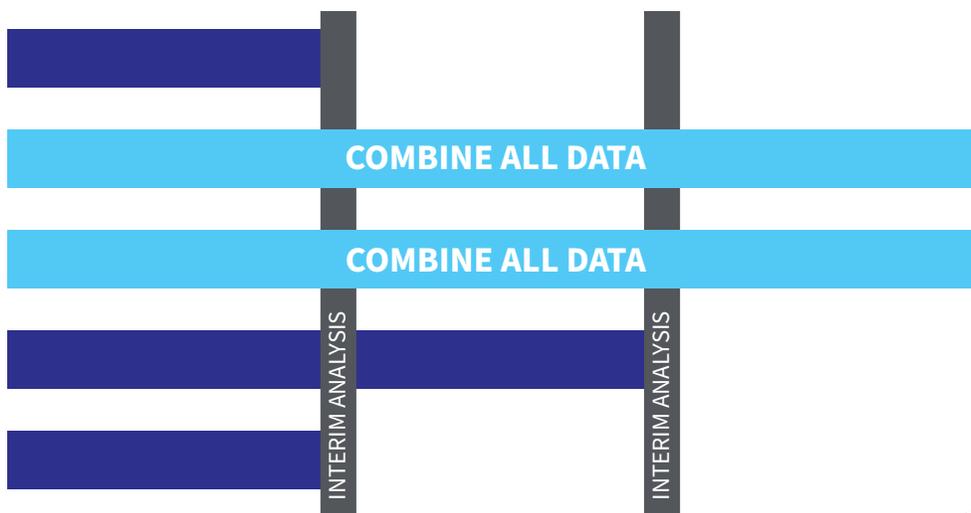
Other designs include BOIN, Ji3+3, Hi3+3, MUCE, TITE Toxicity, and others. In addition, there are model-based methods like Bayesian logistic regression models and the continual reassessment method, which depend on models for precise dose-selection and other biological and chemical knowledge about new therapeutic assets.²³

Seamless Phase 2-3 Designs:

A prominent trial design involves combining Phases 2 and 3 of a clinical program into one “seamless” clinical trial. In such designs, what is traditionally viewed as Phase 2 is converted into the first part (pre-interim look) of an adaptive trial. When safety and efficacy conditions are satisfied, the trial continues after the interim look as a Phase 3 trial, enabling all the information collected during Phase 2 to also be used for the final analysis. If dose-selection is a part of Phase 2, the trial is set up as an adaptive multi-arm trial, where all arms except the ones with target responses are dropped after an interim look if the trial needs to proceed. One example of such a trial is the Cytel-designed INHANCE trial.²⁴

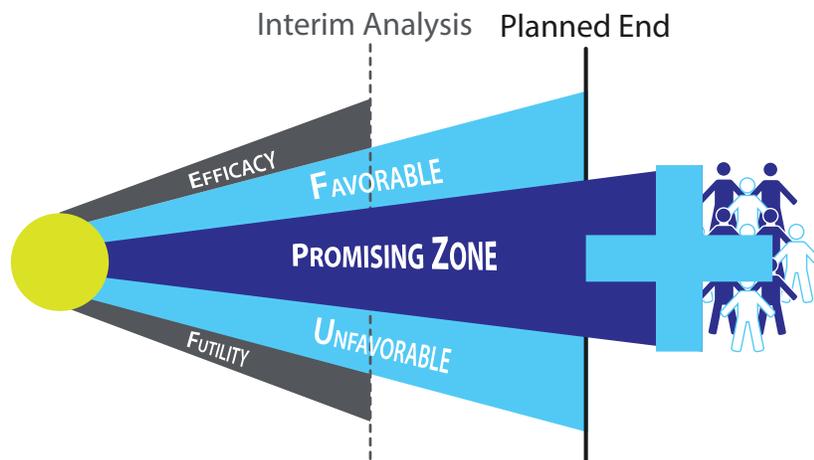
SEAMLESS PHASE 2/3

SAVE TIME AND PATIENT RESOURCES



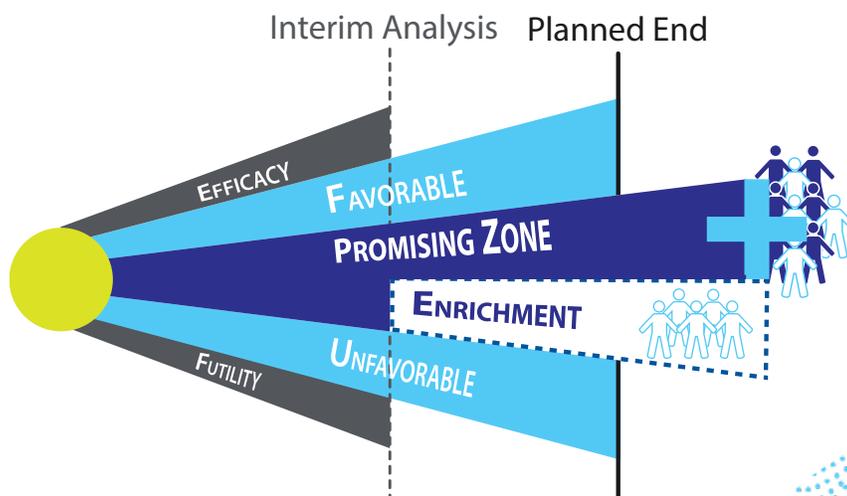
Promising Zone:

In traditional adaptive designs, one purpose of an interim analysis is to determine whether to stop for efficacy or futility. Given that sample size re-estimation is also possible at this time, a promising zone design offers clarity on which alternative sample size can be chosen. A promising zone design can be considered as one that offers a set of decision rules based on what the data monitoring committee learns during an interim analysis. In addition to stopping for efficacy, stopping for futility, and continuing as planned, the design offers the additional possibility of increasing sample size to strengthen statistical precision and then proceeding with a longer trial. This latter possibility occurred during the Cytel-designed CHAMPION PHOENIX trial; during interim analysis in this trial, after 70% enrollment, observed differences in the relative risk between trial arms resulted in an increase from the original planned sample size.



Promising Zone with Enrichment:

Promising zones can also be used in enrichment designs. In an enrichment design, at least two different populations are tested in the early part of the trial: typically, the full population and a specific sub-population that might have a particularly beneficial response to a new therapy. In an interim analysis, the data monitoring committee must decide whether to continue the trial with the full population or only a sub-population. If a sub-population is chosen, the next question is whether sample size re-estimation is necessary, focusing specifically on increasing a sample relative to that sub-population.



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