Cytel

Shaping the Future
of Drug Development

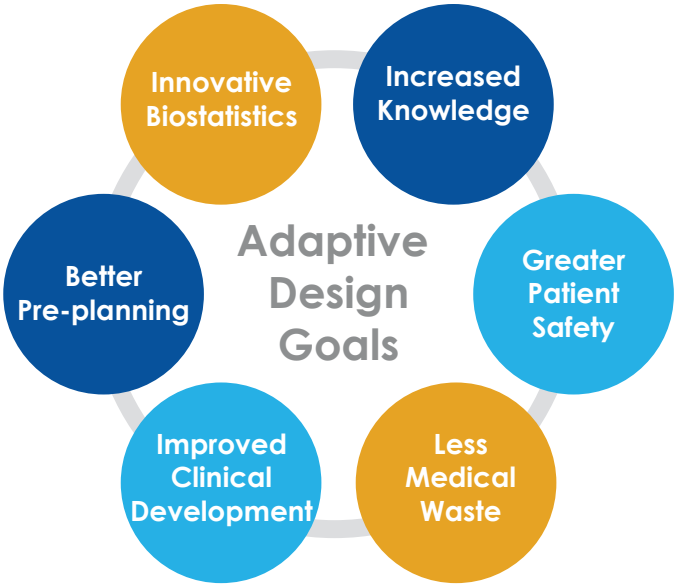
Adaptive Trials at the Mainstream of Drug Development

The Cytel Strategic Consulting Team

INTRODUCTION

The appointment of Scott Gottlieb as FDA Commissioner brought increased optimism toward the potential benefits of adaptive trials[1]. Traditionally associated with more efficient trials and better prospects for patients while maintaining statistical rigor, a more holistic approach to the role of adaptive trials within the industry is making room for a transformative, arguably revolutionary, change to drug development for human impact.

Although biostatistics remain important, adaptive trials are now also aligned with the overarching goals of improved clinical development, better pre-planning, greater patient safety, less medical waste, and/or increased knowledge. These features of clinical trials balance against one another; therefore, the overall aim is to improve one or more of these features, while maintaining the others. 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 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.

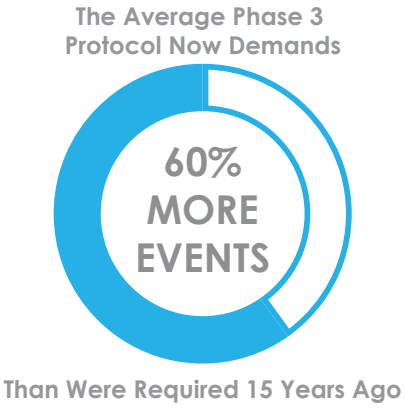
According to the FDA, an adaptive design is any "study that includes a prospectively planned opportunity for modification," where prospective refers to an adaptation that was determined with "details specified" prior to the unblinding of data[2] and preferably at the initial protocol-design stage. Such 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, or a study that has failed to confirm effectiveness by only a small margin. Further, new information that is obtained during a trial can drive new routes of inquiry that are critical for both drug development and patient safety. Adaptive trials are inherently more flexible than traditional trials, and allow trial sponsors to use the accumulating data to take advantage of new routes of inquiry without sacrificing statistical rigor or patient safety.

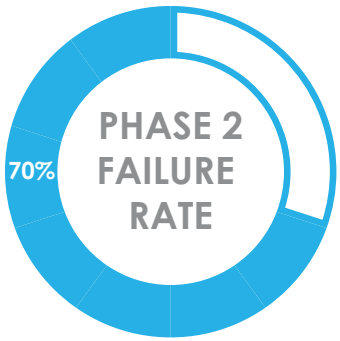


In early phases, adaptive designs can facilitate the collection of data that informs go/no-go decision-making, dose-response modeling, and other critical decision points in trial development. Adaptive designs can empower trial sponsors to make the most of the information collected during the trial.

In later phases, adaptive 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.[3] 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.

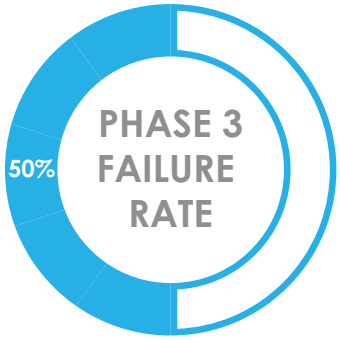
Financial: Adaptive Trials Manage Uncertainty and Scale New Knowledge

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 estimated to fail.[4]



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).[5] Prospectively planned adaptations can yield strategic advantages while also being safe.

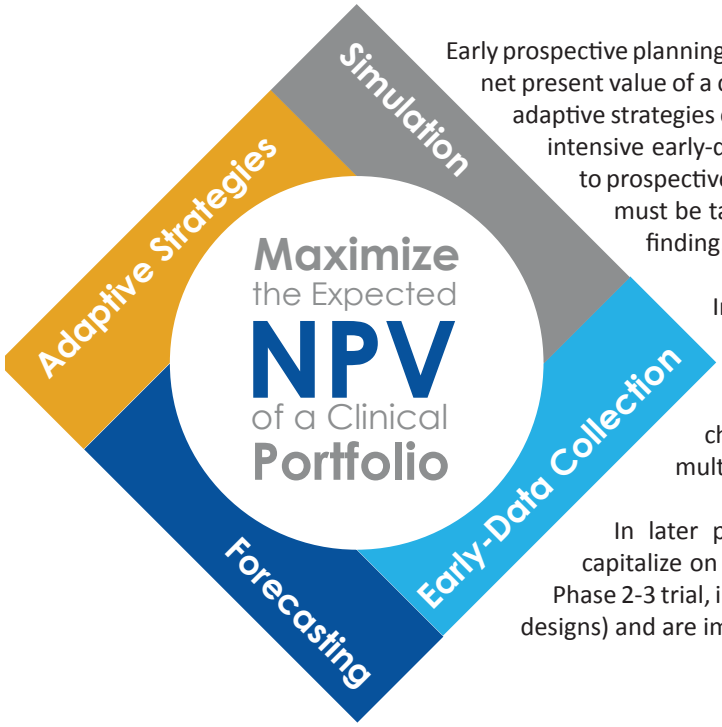
Adaptive strategies can constrain or increase sample size, allow for changes in dosage, and enable other modifications that allow sponsors to preserve the validity of a trial that would otherwise fail. Trial risks are mitigated through the use of adaptive strategies, while ensuring optimization of resources.



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

Strategic: Adaptive Trials Allow for Holistic Program & Portfolio Development

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 could 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.

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) and are important tools for mitigating Phase 3 risk.

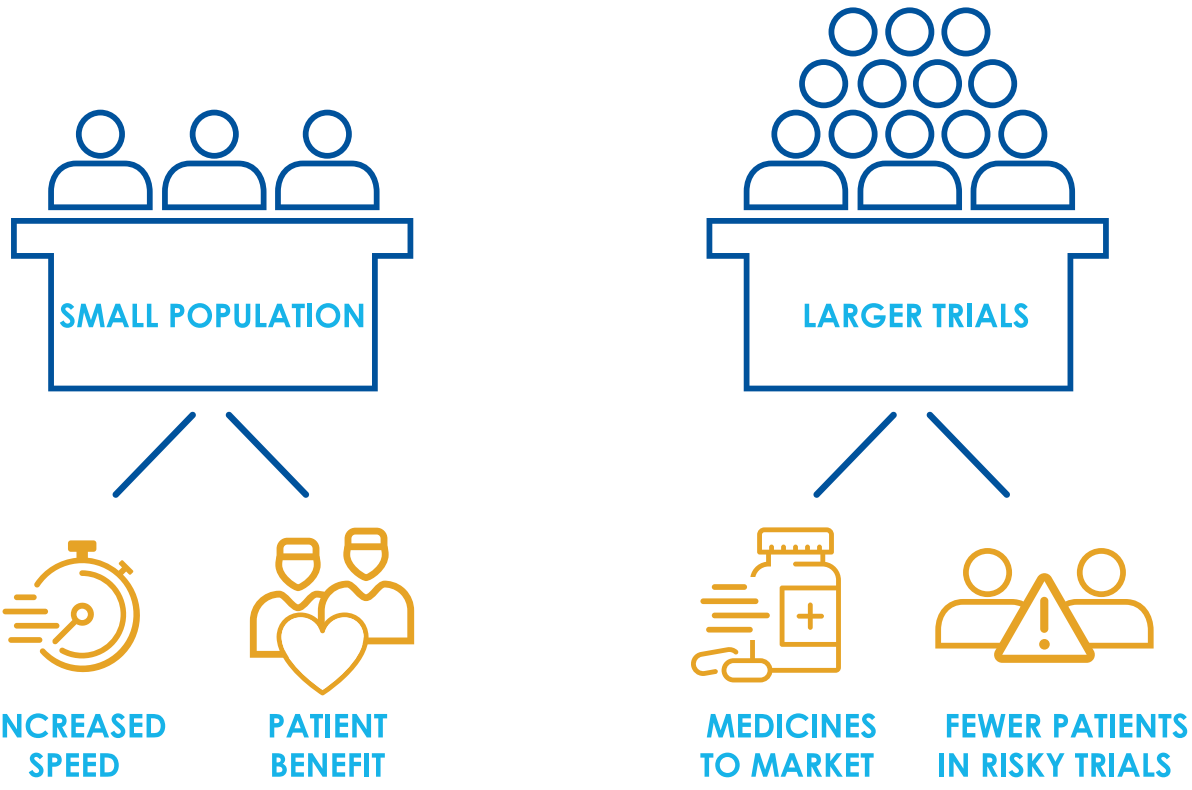
Ethical: Adaptive Trials May Benefit Patients

According to a 2015 study,[6] 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.

> **"BETTER USE OF SAMPLE SIZE AND INCREASED SPEED OF TRIALS, WITHOUT SACRIFICING STATISTICAL RIGOR"**

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.



OPERATIONAL CONSIDERATIONS

When deciding whether or not 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.[7]

Scott Gottlieb, the FDA Commissioner, has shown specific commitment to supporting adaptive trials as a strategy for developing better medicines within shorter time frames. In a speech delivered in September 2017, Gottlieb described the benefits of the adaptive approach:

"[W]e're seeing wider use of adaptive approaches, which allow scientists to enrich trials for patient characteristics that correlate with benefits, or that help predict which patients are least likely to suffer a certain side effect.

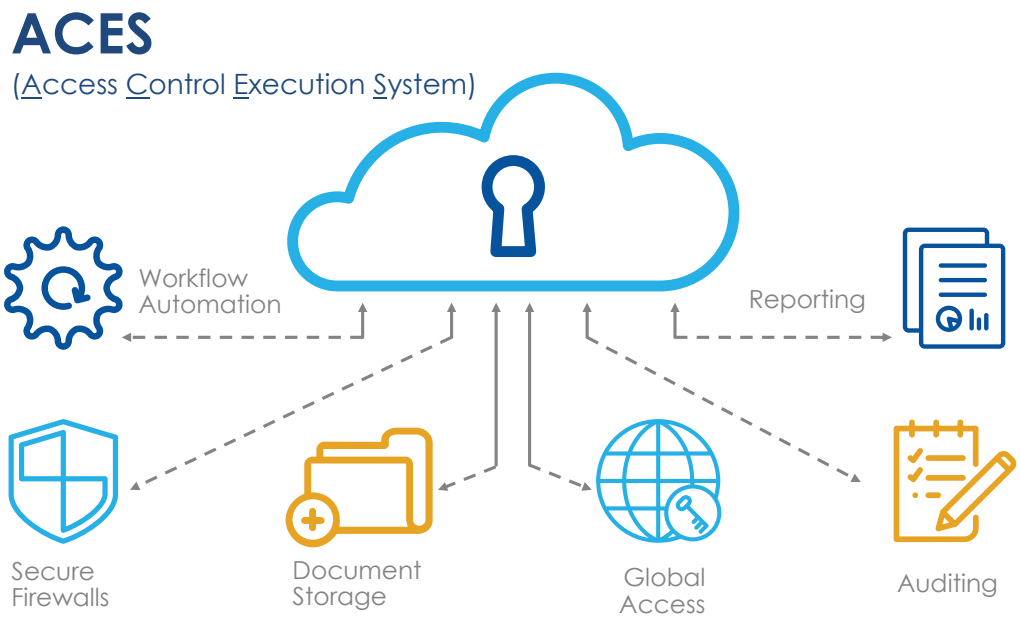
This predictive information is valuable. It can be incorporated in a new drug's label and help inform more careful prescribing.

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."[8] On August 29th 2018, the FDA announced that it would be establishing a Complex Innovative Trial Design (CID) Pilot Meeting Program. The stated goals of CID program are to facilitate and advance the use of complex adaptive, Bayesian, and other novel clinical trial designs in late-stage drug development, and further innovation by allowing the FDA to publicly discuss those trial designs that are being considered through the pilot program.

"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.



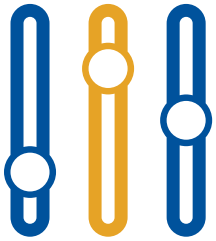
The very existence of interim analyses requires adaptations to the trial process. First, all interim analyses should theoretically implement a "soft lock" in which the data management team ensures that all data is entered and monitored, without additional enrollments being included in the interim analysis 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.[9] 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.

Finance

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, and/or the start of other parts of the drug development process like beginning carcinogenicity and/or formulation evaluation studies. The financing of an adaptive trial can also benefit from strategic resource allocation and enrollment techniques.

TO ADAPT OR NOT TO ADAPT?

Here is a 9-point decision framework that can help you decide whether your next trial should be adaptive:



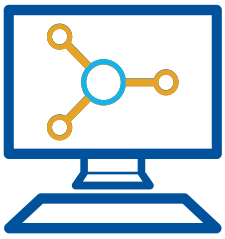
Are there any regulatory concerns or complexities? In order to answer this question, it is advisable to approach regulators early to receive statistical guidance and advice on protocol. There is growing evidence that adaptive trials that have received regulatory guidance in the design of protocol are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

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.[11]

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.

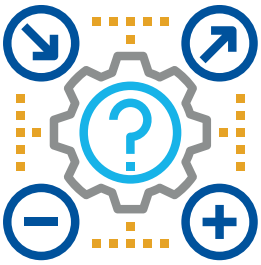
Can the data monitoring committee receive and evaluate data in a timely manner? Otherwise, an interim look might hold up the trial for longer than expected. In general, ensure that clinical operations can keep up with the needs of your trial. can be used to ensure that this does not occur.

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.



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.

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



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.

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

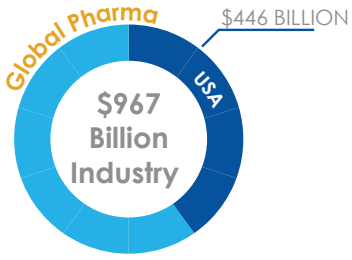
The Future

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 executing 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”**

EXHIBIT 1:

INDUSTRY SIZE



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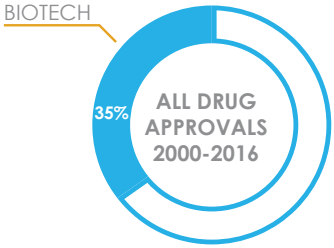
APPROVAL RATE



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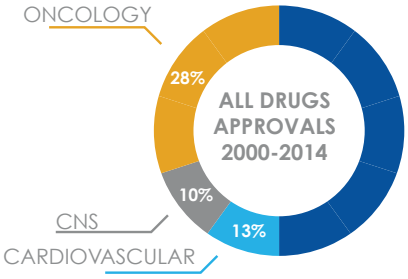


15, 16, 17

AVERAGE NUMBER OF PHASE 3 TRIAL PROCEDURES REQUIRED

15 years ago

67 — 60% Increase

Today

167

MAKING CONFIRMATORY TRIALS MUCH LONGER

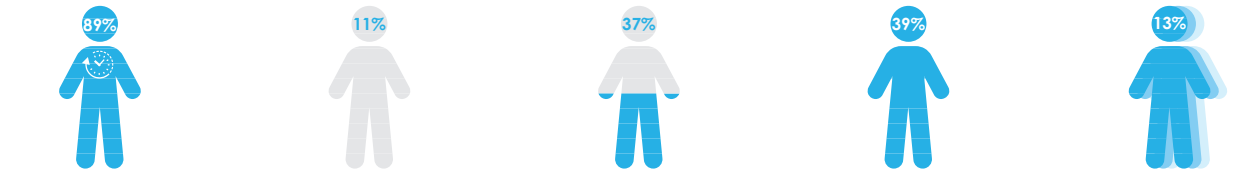
23

AVERAGE COST OF NEW DRUGS

$2.6 BILLION & 15 YEARS

13, 14

TRIALS ENROLLING PATIENTS



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DRUG APPROVAL RATES

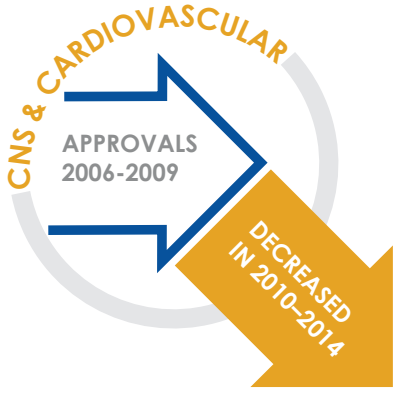

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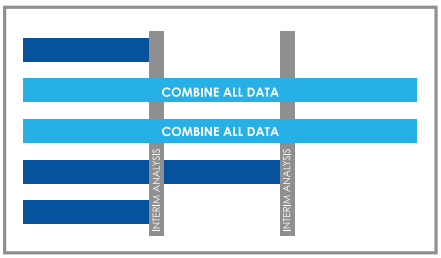
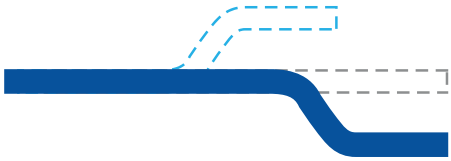
EXHIBIT 2: TYPES OF ADAPTIVE DESIGNS

SEAMLESS PHASE 2/3

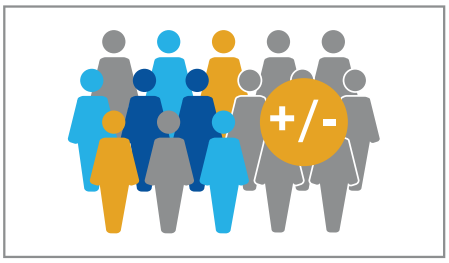


ARM DROPPING AND DROP-THE-LOSER DESIGNS

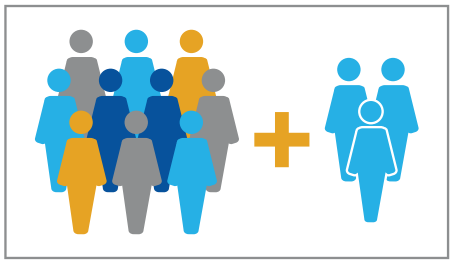
CHANGE OF PRIMARY ENDPOINT



SAMPLE SIZE RE-ESTIMATION

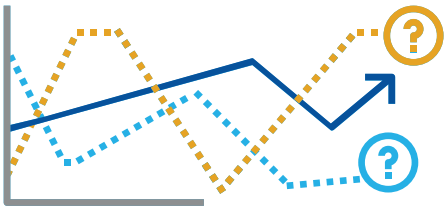


POPULATION ENRICHMENT

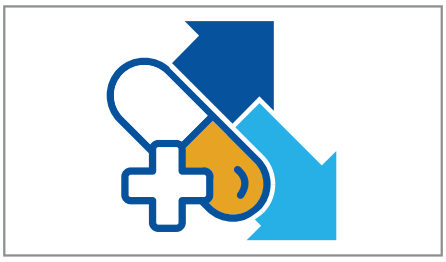


ADAPTIVE DOSE-FINDING

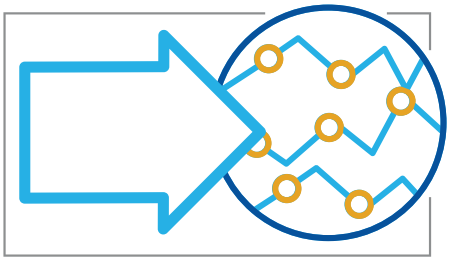
MULTIPLE ADAPTATIONS REQUIRING SIMULATIONS AND FORECASTING



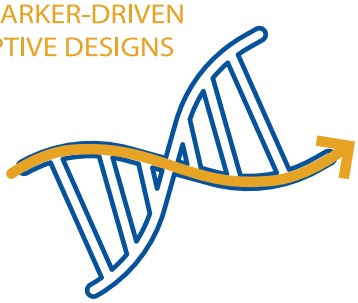
CHANGE IN DOSAGE OR EXPOSURE



BAYESIAN PREDICTIVE PROBABILITY



BIOMARKER-DRIVEN ADAPTIVE DESIGNS



Design Examples

Early Phase Dose-finding Trials:

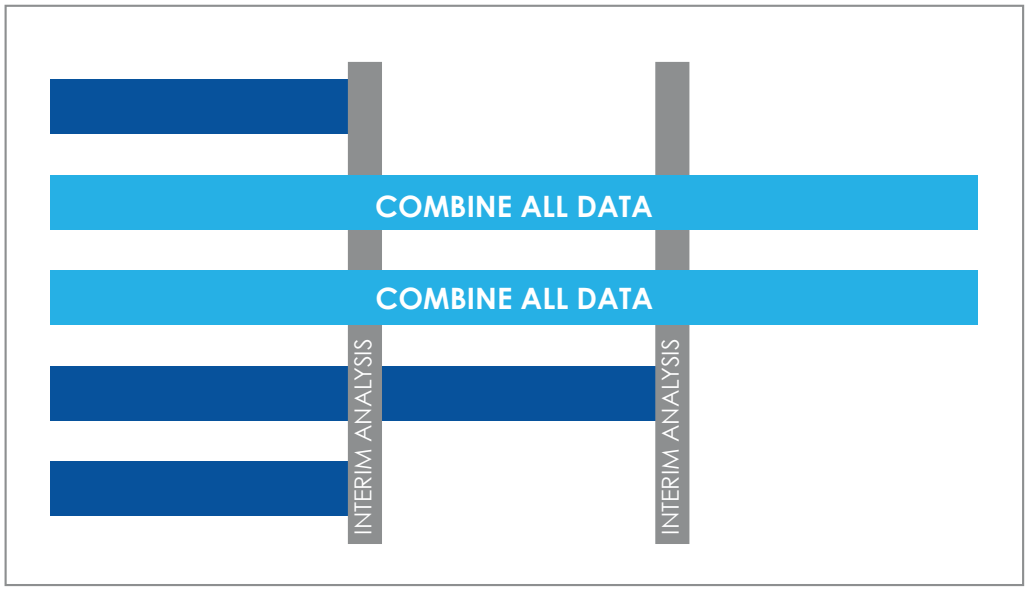
One of the challenges identified in the 2010 guidance on adaptive clinical trials was the possible use of adaptive strategies for clinical development in the early phases. In particular, the guidance identified dose-finding trials as particular beneficiaries of strategies, even while labeling the specific 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.[24] 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.[25]

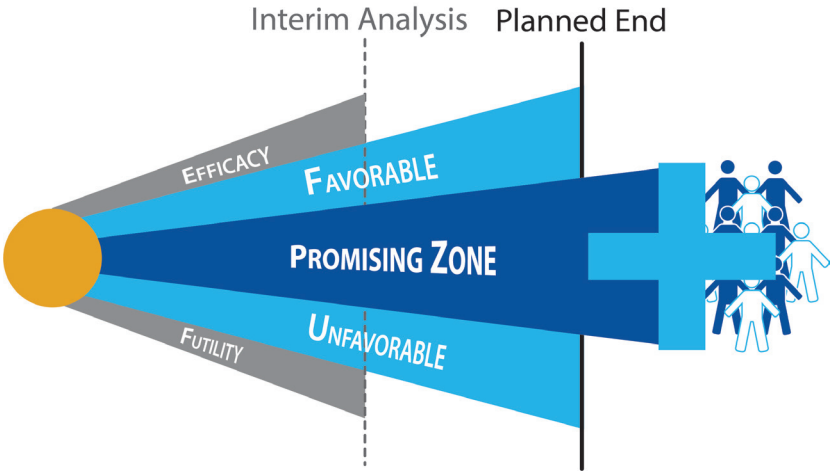
Seamless Phase 2-3 Designs:

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.[25]



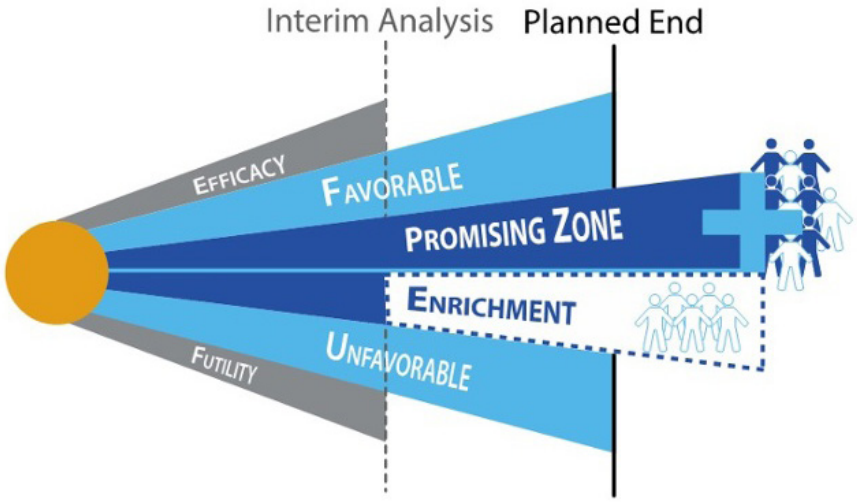
Promising Zone:

In traditional adaptive designs, one purpose of an interim analysis is to determine whether or not 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. See, for example, this cardiovascular trial case study.



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