

# Adaptive Design:

## Addressing Pharma's Productivity Crisis

WHITE PAPER

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# Introduction

Over the last decade, pharmaceutical development productivity has dropped remarkably even in the face of rapidly escalating investments. Today, it costs more than fifteen times as much to develop a new product as it did ten years ago. A leading cause of the industry's disappointing productivity is the traditional approach to development: a linear, sequential series of steps punctuated by substantial pauses and a high risk of failure that is discovered only after substantial expenditures.

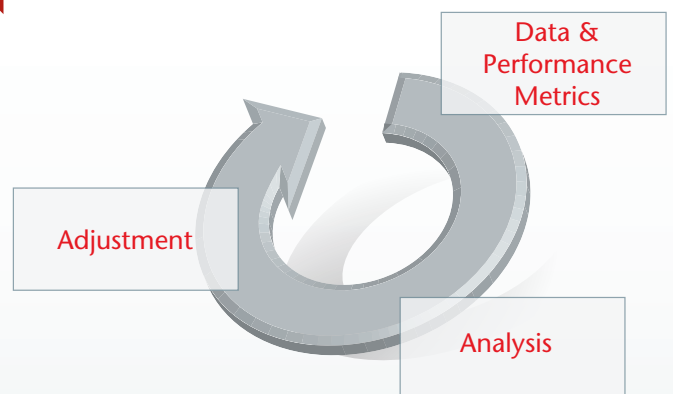
Adaptive methods provide greater flexibility in program planning and study design. The ability to focus resources where they are most productive substantially reduces development timelines and costs as well as reducing the risk of failure because of multiple checkpoints during each study. The result is faster achievement of milestones with fewer patients and less wasted resources. Rather than following a plan rigidly to the end, and only then discovering whether the plan was on target, adaptive techniques enable mid-course adjustments to both study design and operations based on results observed during the study.

# The Heart of Adaptive Design

Several adaptive design techniques involve continuous adjustments based on evolving data, especially in early dose finding. Other techniques provide great value by utilizing interim looks and an analysis of study data to adjust a design element such as sample size.

Whether designated parties examine and analyze data continuously or at intervals, and whether the adaptive design provides for continuous adjustments or a single change in accordance with predefined criteria and rules, the principle is the same: collect timely data, analyze it and make adjustments to keep the study on track.

## Iterative Process, Continuous Refinement

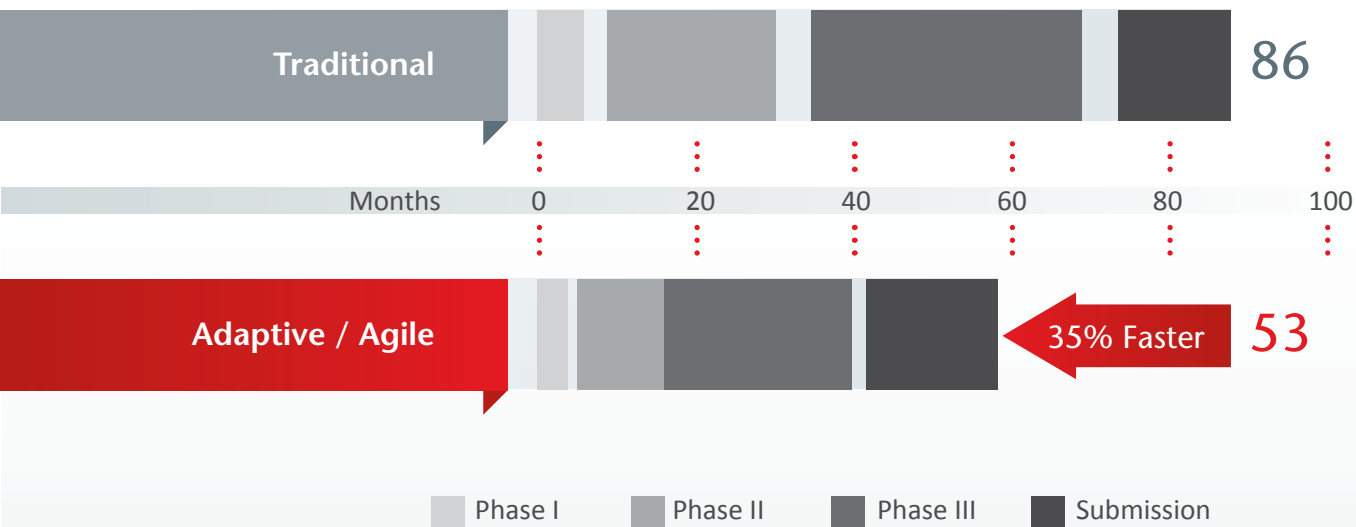


# The Goal of Adaptive Design

Adaptive design refers to protocol-level techniques that increase efficiency through a combination of eliminating waste on less-promising elements (such as dosing arms) and reducing timelines by focusing resources where they are most needed. The success of an adaptive technique is reflected in the improvement it provides to a traditional study design, whether by completing a study successfully with less wasted time and resources, failing a poor product earlier or eliminating the chance of failure for products that do work well.

Adaptive design techniques reduce or eliminate between-phase gaps, as well as reducing the time and expense involved in completing work in each separate phase, shortening development by a minimum of 20% over traditional designs. As shown below, a traditional program consists of separate studies for phases I, II and III, and development time averages 86 months. An adaptive approach reduces the duration of each phase and eliminates between-phase gaps, on average reducing the timeline by 35 percent. Full-blown adaptive programs can go even further, blurring traditional distinctions through the ability to execute in one study several techniques that would traditionally be executed in separate studies and in different phases within the same program.

## Adaptive Goals: Faster & Shorter



# Ten Adaptive Design Techniques

- 1. Sample-size reestimation (SSRE).** SSRE adjusts the initially planned sample size based on actual study data for key parameters such as the size of the treatment difference.
- 2. Seamless combined-phase studies (phases I-II, II-III, I-II-III).** This technique eliminates between-study gaps to accelerate development programs.
- 3. Dose pruning.** Continuous or intermittent assessment allows stopping clearly inferior dosing arms early, allowing resources to be focused on more promising doses.
- 4. Flexible randomization.** More promising arms are weighted more heavily so that patients are selectively randomized to more promising dosing arms. This process is continuous throughout the trial.
- 5. Interim analysis to confirm that a study is on track or terminate for futility.** A mid-course check allows failing a clearly unsuccessful product early, rather than wasting resources on a doomed effort.
- 6. Interim analysis to refine endpoints, biomarkers and surrogate markers.** Sometimes an interim analysis shows a highly favorable response on some endpoints and a poorer response on others, and some surrogates (including biomarkers) may either singly or in combination require validation against an endpoint. Execution of these assessments may in some cases take place continuously during a study.

## **7. Refocusing on a responsive subpopulation.**

Sometimes averaging patient response across a general population may conceal a substantial benefit for a subpopulation. Rather than risking study failure, thus preventing responsive patients from receiving the benefit, refocusing a study on the responsive subpopulation allows collecting data that leads to approval of the drug for treatment of that group.

The first three adaptive design techniques listed are the most commonly used and provide a substantial portion of the benefit to be derived.

## **8. Pursuing approval based on noninferiority while continuing a study to establish superiority.**

This tiered analytic approach may enable a quicker path to market and a powerful risk reduction strategy. An analytic analysis can allow marketing approval based on noninferiority to an established product while the study continues in order to secure a superiority claim.

### 9. The Continuous Reassessment Method (CRM).

In early safety studies, especially where patient response is relatively quick, this method reduces the number of cycles over the standard 3+3 ascending dose study.

**10. Bayesian approaches.** Bayesian modeling can predict study outcomes early on, enabling faster decisions and shorter study timelines. Bayesian statistics also have other applications, especially in devices. Bayesian approaches have certain

advantages over traditional frequentist statistics in enabling the sizing of studies with exactly the minimum number of subjects necessary to achieve a specified goal, with continuous indication of progress towards that goal.

The first three adaptive design techniques described are the most useful and provide a substantial portion of the benefit to be derived. The remainder of this paper will focus on these three techniques, comparing each to a traditional approach.

## Sample-Size Reestimation

The worst thing that can happen to a pivotal study is to have it fall just short of producing statistically significant results. Nevertheless, such an outcome is anything but rare. Pivotal studies typically have large sample sizes and high costs. When a pivotal study fails to produce results that can determine a difference between the test product and the comparator, the sponsor has wasted substantial resources without answering the question that motivated the study. To guard against such an unwelcome and costly failure, planners “overbuild” studies—usually providing a buffer against uncertainty by including a sample

size 20% greater than what they really estimate is necessary. One planning parameter involved in calculating the necessary sample size is the magnitude of the treatment difference.

In the example of a \$50 M pivotal study shown on the next page, calculations based on estimates for such key parameters indicated that a sample size of 400 subjects would suffice. The 20% buffer increased sample size to 480. This example will walk through 4 scenarios in both a traditional study and a study utilizing SSRE.

Adaptive Design: SSRE

Assumption: \$50M study, 400 subjects + 20% buffer\*

Traditional vs Adaptive

	# of Subjects		Timeline	Cost	Outcome
Drug/device fails	480	T1		\$50M	Fail
		A1		\$25M	Fail
$\delta$ is lower than planned	480	T2		\$50M	Fail
<i>Study has too few subjects</i>	528	A2		\$55M	Success
$\delta$ is as planned	480	T3		\$50M	Success
<i>Study has too many subjects</i>	384	A3		\$44M	Success
$\delta$ is greater than planned	480	T4		\$50M	Success
<i>Study has far too many subjects</i>	288	A4		\$38M	Success

SSRE

\* Planning convention recognizing uncertainty of  $\delta$

Traditional Scenarios T1-T4

- T1.** If the drug or medical device fails, the sponsor finds out after the study is completed. The sponsor has risked and lost \$50 M.
- T2.** If the drug has a lower treatment effect than initially estimated, the study will again run full term. But this time, the study will likely fail to achieve statistical significance. Once again, the sponsor has lost \$50 M and came away with nothing. The only difference on these two scenarios is that in the first case the sponsor has established that the product failed on the merits while in the second the sponsor still does not know whether the product might have succeeded if planners had set a larger sample size and the study had produced significant results.
- T3.** If the planning estimate of the treatment effect proves accurate and the drug works, the study will run full term. The sponsor will spend \$50 M

and get statistically meaningful results. However, in retrospect, the sponsor will realize that the study tested excess subjects—the 80 patients added as a buffer. The sponsor wasted research funds and opportunity costs because of an unnecessary buffer.

- T4.** If it turns out that the treatment effect exceeds the planning estimate, the sponsor will discover at the end that the results are favorable and statistically significant. However, the study will have wasted substantial funds testing a large excess of subjects—not only the 20% buffer, but also a substantial number of subjects above that. The study will have wasted some of the sponsor’s \$50 M testing subjects that were not necessary to obtain the results.

If the same study utilized SSRE, an interim look at data halfway through the study would determine the

actual treatment effect. Based on this determination, designated parties (such as an independent data management committee) would recalculate the sample size required. In each of the successful scenarios (T3 and T4), an even stronger factor is the opportunity costs from the lost time the product would have been on the market.

### Adaptive Scenarios A1-A4

Four adaptive scenarios (scenarios A1-A4) corresponding to the traditional scenarios above would produce different and superior results.

**A1.** If, at the interim look, the efficacy data was extremely disappointing, the sponsor might decide to pull the plug on the study. The drug would still fail as with the traditional approach, but stopping early would reduce the investment loss from \$50 M to \$25 M. The sponsor would understand the situation earlier and could make more informed decisions about the allocation of resources going forward. **The adaptive difference:** Saves \$25 M over scenario T1.

**A2.** As on scenario T2 above, the treatment effect is less than planners estimated. Rather than completing a study that failed to produce statistically significant results, the study could expand sample size to ensure significant results. That would increase costs—in this case, by 10%, to \$55 M. However, the additional \$5 M would transform a failed study into a success. **The adaptive difference:** By spending an additional 10%, the sponsor converts a failed study to a successful study.

**A3.** When the planners' initial estimate of the treatment effect proves to be on target, the interim analysis shows that the 20% buffer is unnecessary. Sample size is reduced by 80 subjects, saving \$5 M. Furthermore, completion of the study with fewer subjects would not take as long. The drug might get to market six months ahead of schedule. **The adaptive difference:** Scenario A3 saves \$5 M and 6 months of development time, resulting in generation of revenue 6 months earlier than expected and potentially generating greater revenue due to a longer period under patent protection.

**A4.** When an interim analysis of data reveals that the observed treatment effect is markedly greater than the planners' estimate, the designated parties reviewing the data recommend a reduction of the sample size from 480 subjects to 288— by 192 subjects. This reduces study costs by \$12 M and reduces timelines by approximately 40 percent. **The adaptive difference:** Scenario A4 saves \$12 M and almost one year of development time. With an average drug generating \$350 M in its first year, earlier generation of revenue can materially improve a company's financial position.

Thus, the use of an adaptive design technique enabled informed decisions based on an interim analysis of data that increased the success rate from 50% on the four scenarios to 75%, saved \$15 M in the event of a failed drug, and, on the more favorable scenarios with a stronger treatment effect, saved from \$5 M-\$12 M in development costs and six months to a year of development time. The sponsor wins on all four adaptive scenarios over their traditional counterparts.

## Adaptive Treatment/Dose Pruning

The adaptive technique of dose pruning examines data during a study to select treatments for testing in a pivotal study. The treatment might involve therapeutic devices such as arterial stents or transcutaneous electrical nerve stimulators, combination products such as stents coated with different doses of a drug, or different doses of a drug administered on different schedules. Rather than running every arm for the full duration of the study, the goal of this technique is to prune the least safe and clearly inferior arms when identified as such.

In the example below, run the traditional way, this study would take about 400 patients, 16 months and cost \$6 M. For simplicity, assume that the test product is a drug and each treatment arm tests a different dose. The study tests four doses plus a comparator and continues all five treatment arms for 16 months.

With adaptive dose pruning, the study would prune the least promising arms as soon as an interim

analysis justified it. On the scenario shown in the figure below, a safety issue requires terminating one treatment arm after only two weeks. The inferiority of a second arm is apparent by week 10 and that arm is terminated. Terminating these two arms allows assigning the newly enrolled patients to the three most promising arms at an accelerated rate. Because enrollment accelerates, the study identifies the most promising doses in 12 months instead of 16, by testing 300 patients instead of 400, at a cost of \$4.5 M instead of \$6 M. In addition, the study exposes 70 fewer patients to the problematic treatment arm. Had the data not been examined early, the safety issue with the dose in arm 1 might have escaped notice until the end of the study. **The adaptive difference:** Saved four months and \$1.5 M while exposing 100 fewer subjects to the experimental treatment. The 25% savings is typical of this kind of dose pruning approach.

### Traditional

Time (mo)	2	4	6	8	10	12	14	16	
1	10	10	10	10	10	10	10	10	80
Am 2	10	10	10	10	10	10	10	10	80
3	10	10	10	10	10	10	10	10	80
4	10	10	10	10	10	10	10	10	80
Comparator	10	10	10	10	10	10	10	10	80
<b>Total Enrolled</b>	<b>50</b>	<b>50</b>	<b>50</b>	<b>50</b>	<b>50</b>	<b>50</b>	<b>50</b>	<b>50</b>	<b>400</b>
#/arm/mo	10	10	10	10	10	10	10	10	

TOTAL **\$6,000,000**

### Adaptive

Time (mo)	2	4	6	8	10	12	14	16	
Am 1	10								10
2	10	12.5	12.5	12.5					48
3	10	12.5	12.5	12.5	16.7	16.7			81
4	10	12.5	12.5	12.5	16.7	16.7			81
Comparator	12.5	12.5	12.5	12.5	16.7	16.7			81
<b>Total Enrolled</b>	<b>50</b>	<b>50</b>	<b>50</b>	<b>50</b>	<b>50</b>	<b>50</b>			<b>300</b>
#/arm/mo	10	12.5	12.5	12.5	16.7	16.7			

TOTAL **\$4,500,000**

## Seamless Combined-Phase Study

The third most commonly used adaptive design technique combines two traditionally separate studies into a single study that spans two phases. In this case, the studies combined are a phase II dose-pruning study, like the previous example, and a phase III pivotal study. The goal of the phase II portion of the combined-phase study is to select the optimal dose

The adaptive difference from a combined-phase study: likely on the order of one third savings against both timelines and budget compared with timelines and budgets for separate phase II and phase III studies.

or doses for the phase III portion. Instead of stopping after phase II, the study will continue the most promising doses directly into phase III testing, expanding enrollment to meet the goals of the pivotal study. To conduct a combined-phase study that involves phase III, the study must be treated as a registration study

from the beginning of the dose pruning portion of the study. This means that regulators will provide less latitude about degree of blinding and data access than in a typical standalone phase II study. However, the benefits of combining phases, both financial and time savings, can be substantial.

Since a combined-phase study eliminates the pause between phases to analyze data from a phase II study and then design the separate, follow-on phase III study, planners must take greater than usual care at the outset in planning the combined phase study and set conditions for continuing into phase III testing.

As described in the previous dose-pruning example, the study would prune the least promising treatment arms as soon as data justified the step. The combined-phase study would identify the most promising arm or arms, expand enrollment, and continue directly into phase III. **The adaptive difference:** likely on the order of one third savings against both timelines and budget compared with timelines and budgets for separate phase II and phase III studies.

# Benefits and Caveats of Adaptive Design

## Benefits

The first three benefits address the shortcomings that have plagued clinical studies in recent years—long development cycles that eat into patent protection and thus future revenues; high direct costs, especially in late phases; and a failure rate so high that it threatens the industry's business model. The top benefits of adaptive design techniques include:

- Shorten timelines
- Reduce operational costs
- Reduce risk of failure
- Ensure the right sample size
- Enable continuous development
- “Look ahead” capabilities allow an early start on next steps
- Enable development in parallel
- Add checkpoints and facilitate decision-making
- Fail products earlier, potentially saving millions in development costs
- Improve investment returns

## Caveats

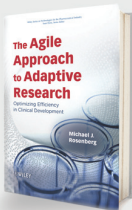
Adaptive design is truly a different approach, not an isolated feature added to a traditional study design. The difference becomes apparent from the greater demands involved in planning an adaptive study. The top caveats that should be understood before incorporating adaptive design techniques into a protocol are:

- Adaptive design is not a single technique, and may include many
- Adaptive design demands meticulous planning
- Planning is iterative because decisions often have a ripple effect
- Planning must involve identifying and thinking through scenarios with multiple “what-ifs”
- Each adaptive study involves a negotiation with regulators
- Executing an adaptive design requires timely, accurate, actionable study information
- Adaptive design is a fundamental process change, not a window dressing

## Regulatory Considerations

One of the most important factors in planning and executing adaptive techniques is establishing a dialogue with regulators, indicating the intention to take rigorous steps to preserve study integrity and demonstrating thorough preparation. Regulators often wish to see simulations of different scenarios and sponsor plans to address the issues that might arise with each scenario. It is important to keep the following considerations in mind:

- As noted under "Caveats," every trial involves a negotiation so talk to regulators early and often
- Study integrity is paramount
- There are no shortcuts; firewalls are very important
- It is important to prepare thoroughly, demonstrate knowledge of the techniques involved and make modest requests
- There is no harm in asking and no need to establish prior use by others
- The FDA seems to be the preferable lead regulator for adaptive studies at this stage (over EMA and ROW)



### Additional Resources

Health Decisions' CEO Dr. Michael Rosenberg's book:

[The Agile Approach to Clinical Development: Optimizing Research Efficiency, by Wiley.](#)

[Buy now on Amazon](#)

### About Health Decisions

Health Decisions is the leading contract research organization (CRO) in Adaptive Clinical Trials committed to shortening development timelines and maximizing pipeline value for pharmaceutical, biotech and medical device companies. Through Agile Clinical Development—a strategic three-pronged approach that combines adaptive design, adaptive operations and proprietary technology—Health Decisions delivers real-time performance metrics that enable sponsors to make the most of competitive market opportunities. Health Decisions is headquartered in Durham, NC, with over twenty years of experience helping sponsors exceed development goals in Phase I-IV clinical trials across all major therapeutic areas.

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