WHITE PAPER: ADAPTIVE CLINICAL TRIALS

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The Adaptive Concept

The clinical development of drugs and devices is a challenging task, and more so than product development activity in most other industries. The technical challenges are huge because understanding of the biological systems involved is usually incomplete. The complexity is significant because patients vary significantly from one another and are unpredictable in their responses. Additionally, every sponsor has to contend with the need for speed because of competition and the existence of budgetary pressures arising from the need to get a good return on investment in clinical development. The result is well known: success rates overall are low, New Drug Applications are too few, and the return on investment is abysmal. See Exhibit 1 for data on problems in clinical development.

Exhibit 1. Problems in clinical development

- The biopharmaceutical industry worldwide spends $100 Billion per year on the clinical development of drugs, up from $33 Billion in 1999 [**1**].
- The number of NCEs and New BLAs approved by the FDA was 35 in 1999 and 20 in 2008 [**2**].
- 50% of phase trials are failures [**3**].
- 45% of phase 3 industry trials have the wrong dose [**4**].
- Obtaining accurate estimates of variance in patient response data can reduce sample size by as much as 50% [**5**].
- Wasted medical supplies in typical conventional trials are 30% to 60% of the optimum. In an adaptive dose-finding trial, conventional planning methods can yield overages of 300% to 500% [**6**]. In some oncology trials, the cost of medical supplies can be as much as $100,000 per patient per year.
- 10% to 30% of clinical sites never recruit a patient, but nevertheless incur a set-up cost of around $70,000 per site. Data are not analyzed during the implementation stage of a trial to identify these sites [**7**].
- The largest single cost in clinical trials is site monitoring—as much as 30% of the total. However, real-time data are not available to optimize visit schedules, leading to large amounts of money wasted [**8**].

An effective approach to re-thinking how clinical development is done is adaptive clinical trials. What is it? In a conventional or “fixed” trial, all of the important details of the trial are decided before the trial starts, and are then not changed. The trial is completed, the data is analyzed, and if the results are positive, an NDA is submitted to the regulatory authorities. Unfortunately, in a large percentage of Phase 3 or “confirmatory” trials, the results are not positive, the trial is a failure, and the investment is unproductive. With adaptive trials, in contrast, it is possible to look at the accruing data from patients at one or more times (called “interim looks” at the data) as the trial is on-going, and adjust certain parameters of the trial in order to increase the probability of success when the trial comes ends.

Exhibit 2: some of the adaptations now being tried

Exhibit 2. Adaptive designs currently in use

Continual Reassessment Method and modified CRM designs (Phase 1)
Simon 2-stage designs and modifications thereof (Screening)
Two Stage Phase 1 / 2 designs (Dose-toxicity and early Proof-of-Concept)
Adaptive designs for drug combination therapies
Response-adaptive designs (for Proof-of-Concept and dose-ranging)
Frequentist dose-response modeling
Bayesian dose-response modeling
Group sequential designs with early stopping for efficacy, harm or futility
Sample size adjustments (Phase 3)
Two Stage Phase 2b/3 designs (dose-selection plus confirmatory)
Dropping doses (Phase 3)
Population enrichment (Phase 3)
Information-based trials (Phase 3)

Benefits of Adaptive Trials

The benefits of adaptive trials fall into three categories: commercial, ethical, and budgetary.

The commercial benefit is that much better information is obtained on the drug and its dosage, resulting in a much greater chance that the phase III confirmatory trials will be successful, with a reduced probability that the phase III dose will either be toxic or show inadequate efficacy. Exhibit 3 illustrates the potential for better information to reduce the rate of failure in Phase 3.

Exhibit 3. Why drugs fail in phase 3

Reason for attrition	Category	Phase 3 %		Questions
Efficacy uncompetitive	Economic reasons	18	42	Could we stop earlier? Was the dose right? Was the population right?
Safety uncompetitive		11		Were Phase 1 and Phase 2 thorough?
Lacks "strategic fit"		3		Why is the decision so late?
Market too small		8		Efficacy too low? Was the dose right? Was the population right?
Mfg cost too high		2		
Inadequate efficacy for FDA Approval	Approvability reasons	18	45	Was the dose right? Was the sample size right? Was the population right?
Inadequate safety for FDA approval		13		Was the dose right? Was the population right? Were Phase 1 and Phase 2 thorough?
PK/bioavailability issues		3		Was Pk/Pd work thorough?
Compound was backup		8		
Chemistry/control issue		3		
Other		13	13	

Source: Cytel Analysis of Boston Consulting Group data

Another commercial benefit is that the time-to-market for a drug can be reduced by combining proof-of-concept trials (to show that the drug works) with dose-finding trials (to pick the right dose) or by combining dose-finding trials with confirmatory trials. This eliminates the “lost” time (also known as “white space”) between the end of one trial and the startup of the next. Being faster to market increases the Net Present Value (NPV) of the product.

The ethical benefit is that in both early-stage and late-stage trials, more patients will receive doses that work because doses with inadequate efficacy are adapted out. This benefit is both immediate (early stage) and deferred (late stage).

The budgetary benefit is that, frequently, the number of patients required in a Phase 2 trial can be reduced. See Exhibit 4 for an illustrative example from Eli Lilly.

Exhibit 4. Sample size reduction with adaptive designs

	Sample sizes	
Treatment group	**Real trial**	**Retrospective adaptive design**
Haloperidol IM	126	60
Olanzapine IM	131	66*
Placebo IM	54	30

Trial stopped: criteria met to declare olanzapine IM superior to placebo and non-inferior to haloperidol IM
*note: max value based on prior sensitivity analysis (min=62)

Source: Stacy Lindborg, Eli Lilly, presentation to FDA/Industry workshop,

At its core, the idea behind adaptive trials is simple and compelling. Reduce the uncertainty in clinical development that leads to flawed trial designs by getting additional information (beyond what one had at the beginning of the trial) from the ongoing trial. Additional information is always better, leading to better decisions about what to do during the course of clinical development. Gaining more opportunities to refine decisions is also a benefit, as illustrated below.

Fig.3 Old Drug Development Paradigm

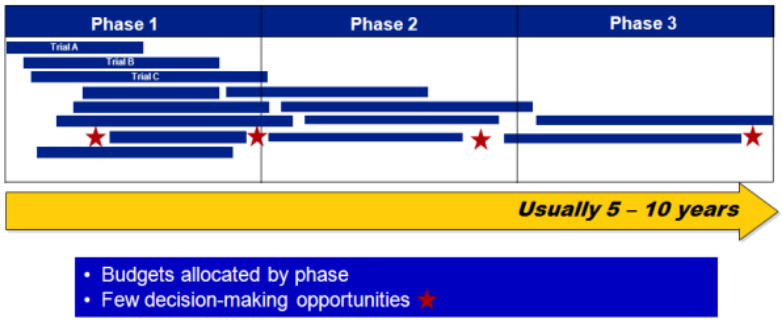
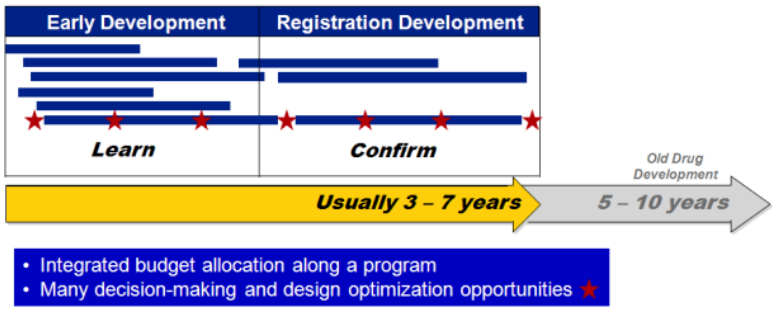


Fig. 4 New Drug Development Paradigm



In practice, however, adaptive designs have attendant challenges so that the adaptive route may not be the right one for every trial. A thorough evaluation is needed to determine in any given instance the best choice of design, whether adaptive or not.

Adaptive or Not?

It is useful to think of the decision on whether to make a trial adaptive or not as passing through three gates with gatekeepers who may not let you through.

The first gate is owned by regulatory agencies. One needs to show them the logic for doing an adaptive design and, if they accept the logic, that the statistics have been done correctly ("show me that you have controlled the Type I error"), and if they accept that, that the possibility of bias and manipulation of the trial have been minimized. See Exhibit 7 for a summary of regulatory concerns.

Exhibit 7. Regulatory concerns – a summary

Rationale for adaptive – is it a cover for sloppiness in design or is there a provable need and benefit?
Control of Type I error. "Show me."
Adaptations defined in advance
Protocol for interim monitoring known in advance, proves that potential for bias is virtually eliminated
After-the-fact proof that the protocol and interim monitoring procedures were followed (audit capability)

The clinical operations team owns the second gate. They will want to know whether all of the operational challenges of an adaptive trial have been dealt with. These range from the need to make accurate get data available on time for interim analyses, to the need to ensure there is adequate medical supply at all sites (but not too much, for overages could be very expensive), and to the need to put in place an interim monitoring body such as a Data Monitoring Committee and make sure that the "unblinded" data they see are not seen by those who should not.

The finance staff owns the third gate. They will want to know if the adaptive trial is going to cost more or less than a conventional trial and, if it is potentially more, why the added cost is justified.

We find it useful to take these three gates and convert them into ten questions to answer in deciding "Adaptive Or Not".

1. First, and most importantly, what is the timing of observation of the key endpoint upon which to base adaptation and what is the expected enrollment rate? More specifically, is there sufficient time between the observation of a sufficient number of patients' endpoints and the enrollment of the last patient to afford opportunity for adaptation? Cytel can assist you in making this assessment.

2. If answer to 1 is "no", is there a sufficiently reliable surrogate or biomarker that is observable early enough upon which adaptation could be based?

3. Are there any regulatory concerns / reservations which would prohibit use of an Adaptive Design (AD)? To answer this question, consultation with regulatory affairs personnel, and/or those experienced in dealing with regulatory agencies, may be required. Cytel can help you in making this assessment.

4. Will sufficient safety data be available at filing if Adaptive Design is used? That is, will the number of patients required by regulatory agencies to support the safety of the candidate product be available at expected time of filing? If the adaptive design provides fewer patients than required for completion of the required safety database, the sample size may need to be increased beyond that necessary for the adaptive design.

5. Is there sufficient drug supply (for all potential doses & durations) to support all possible adaptations? Cytel has the technology to help you to make this assessment.

6. Can the needed drug supply be made available at the sites when needed to support all possible adaptations? How can one do this without either the risk of stockouts or the cost of massive overage and waste?

7. Is data acquisition to inform on the planned adaptations rapid enough so the required analyses to inform the adaptation can be completed in time? Cytel can help you make this assessment.

8. Is there sufficient statistical expertise to support the evaluation of design options so that the Adaptive Design can be properly evaluated and implemented? Cytel can provide this expertise if a sponsor does not possess it.

9. Is the software necessary for evaluation and implementation of Adaptive Design options available?

> Adaptive design performance characteristics must be thoroughly summarized prior to protocol approval. Software for closed form calculations and/or simulations is necessary to document these characteristics, and must be available in time to support the protocol development, and then to execute the necessary adaptive design calculations during the trial. Cytel's East, Compass and SiZ software are industry standards for both adaptive and non-adaptive designs. In addition, Cytel has a large suite of validated proprietary software that can be applied to unusual situations where the standard software is not adequate.
>
> Software is needed that facilitates the interim monitoring process while satisfying regulatory concerns about bias. Software is also needed to make the adaptive changes happen – communicating what the changes

are to the IVRS system, and making sure that the necessary doses are available at every site where they may be needed.

Cytel's ACES is our best-in-class system for adaptive trial implementation by securely managing communications with independent trial recommendation committees (DMCs / DSMBs).

10. Does the use of Adaptive Design in comparison to a classical alternative non-Adaptive Design afford sufficient improvement on cost, time to complete, and/or quantity / quality of information favor the use of Adaptive Design? In order to answer this question, one should have a full evaluation of the costs, the time to complete, and the quantity and quality of information expected from the candidate adaptive design and the non-adaptive-design alternative. With this information, a design can be chosen to balance among these aspects of each of the design candidates. Cytel can help you in making this comparison.

Given the potential benefits of adaptive designs, we believe it makes sense for a sponsor to evaluate the adaptive alternative for their clinical trial to determine whether the benefits offered are significant and are worth the additional regulatory and operational complexity. Cytel has the experience and the tools to make this assessment. We will help you make the correct choice.

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Learn more about our adaptive trial design software and expert consultancy at cytel.com