

# DESIGN

## Adaptive by

Adaptive trial designs have the potential to speed development and reduce overall costs — that is, if sponsors invest in up-front planning and can implement these designs correctly.

*Interest in adaptive designs has risen in recent years. These types of studies involve a broad class of methods and can have a positive impact on any program across the different stages of development. Experts say the flexibility of an adaptive design allows sponsors to make course corrections during a trial based on interim data. But experts stress these changes should be pre-planned decisions based on simulations and well-thought out, up-front planning.*

### The Potential

*Our experts discuss how adaptive designs address the challenge of getting new products to the market faster and with greater efficiency.*

**COLLINS.** ARIS GLOBAL Adaptive designs, when implemented fully and successfully, will make clinical development faster. They will reduce development costs, and patients will not be exposed unnecessarily to unsafe drugs or drugs that are not efficacious. If done right, adaptive designs can be profound.

**BLAKE-MICHAELS.** CLEARTRIAL There is a realization that adaptive designs can be a more efficient way of gaining information about a drug. Adaptive designs increase the likelihood that a compound that actually works will make it to market. They can also be used to identify drugs

DR. JENNIFER DUDINAK / Roche



“ Adaptive trials should not be a substitute for poor planning.”



“ A communication plan is needed to manage the adaptation and to mitigate the potential for operational bias.”

What is an Adaptive Design?  
Adaptive trial design refers to a clinical trial methodology that allows trial design modifications to be made after patients have been enrolled in a study, without compromising the scientific method. In order to maintain the integrity of the trial, these modifications should be clearly defined in the protocol.



OLGA MARCHENKO / i3 Statprobe



“Adaptive designs, relative to fixed designs, are on the order of 20% of total studies.”

that don't work earlier; this is an enormous advantage, as determining if a drug doesn't work can take a considerable amount of time.

**JOHNSON.** PHARMANET. Stopping trials early or reducing treatment group sizes save both time and money. We can also check study design assumptions earlier. If the assumptions were wrong, we can modify the ongoing study instead of wastefully abandoning it. Adaptive designs have the potential to accelerate almost every phase of drug development. They are most commonly used during the early exploration of drug dose effects, in Phase I. But adaptive designs have even greater potential value in

later-phase trials, where they make it possible to adjust treatment group sizes, terminate one or more treatment groups, drop ineffective doses, select the best dose for future studies, prepare early for regulatory filing, or terminate the study of an ineffective or dangerous drug.

**SIETSEMA.** KENDLE. Adaptive trials can result in speedier, more efficient trials. A good example of that is the seamless move between Phase II and Phase III; the dosing range can be determined in Phase II and the product moved into a Phase III program without having to do an extensive analysis of the Phase II results before

proceeding. This can save at least six months or more during development.

**BOYD.** INC RESEARCH. An adaptive design is not a shortcut nor is it a mechanism for avoiding the requirements for adequate and well-controlled trials. Adaptive trials do, however, have several potential advantages, including the ability to check design assumptions for future studies and transition from one phase to the next with a higher chance of success. Key to this process is ensuring that there is a factor of trust with the FDA. Clear documentation of the process for unblinding and any modifications must be provided to ensure the validity and integrity of the trial.

**LUCE.** UBC. An adaptive design creates a continuous learning process that allows the clinical team to be much more flexible in determining what works best. The experience to date is that adaptive designs have led to a more efficient means for making decisions. An adaptive design means that the dosing, the types of patients, or treatment settings can be adjusted during the course of the trial as evidence accumulates, as long as the midcourse decision rules were pre-specified.

**BOYD.** INC RESEARCH. If properly designed, any number of adaptations can be made to increase efficiency. Examples include sample size re-estimation to maintain power, adjusting eligibility criteria, dropping ineffective treatment

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“Improved trial technology is part of the reason adaptive designs are becoming more common.”



MOLLY BLAKE-MICHAELS / ClearTrial

arms, and stopping the trial early because of futility or efficacy. The goal is clearly to make good decisions more quickly, without assuming too much risk. This needs to be a joint effort among clinical, regulatory, and statistical colleagues.

## The FDA Draft Guidance

*The FDA released a draft guidance in February 2010 for pharmaceutical and biologics developers on adaptive design clinical trials. The guidance covers the clinical, statistical, and regulatory aspects of adaptive design clinical studies. (For more on the draft guidance, see the digital edition of PharmaVOICE.)*

an adaptive design is sorely needed because of the cost of the confirmatory trials.

**JOHNSON.** PHARMANET. The FDA's draft guidance distinguishes between adaptive designs that are less risky and are already commonly used in Phase III trials for example group-sequential studies, internal pilot studies with blinded interim analyses to verify assumptions, conditional power calculations to predict trial success, and designs whose properties are not as well understood, such as Bayesian techniques, sample size re-estimation, and response-adaptive methods.

**MARCHENKO.** STATPROBE. We have one concern about the guidance. Regulators separated adaptive designs into two big types of designs: well-understood adaptive designs and less well-understood designs. They are concerned about confidentiality and integrity of the trials, especially when less well-understood adaptive methods are used. There are several examples of successful less well-understood adaptive designs used in pivotal trials that improved and accelerated the drug development. Bigger companies are willing to take a risk to make these designs well-understood ones, while smaller companies may not be able to afford to take such a risk. I think we need to hear that regulators are open to considering various kinds of adaptive designs including less well-understood designs in adequate and well-controlled studies when the designs are planned and implemented properly.

## The Challenges

*Our experts discuss the importance of addressing issues, such as ensuring integrity of the study and controlling against bias.*

**SIETSEMA.** KENDLE. In many adaptive designs, the data have to be unblinded in some way so that decisions can be made on how to proceed with the trial. The unblinding of the data creates a potential for bias in how the rest of the study is conducted or how the data are processed or interpreted. If bias is introduced, this can reduce the credibility of the study.

**QUINLAN.** CYTEL. From a practical aspect, there are more complex logistical issues that need to be addressed. For example, one such issue is the timely availability of data for the interim analysis. Additionally, for adaptive dose ranging studies, we can't predict at the start of the trial what will be needed, so more thought needs to be given to how to manage drug supply and distribution during the course of the trial.

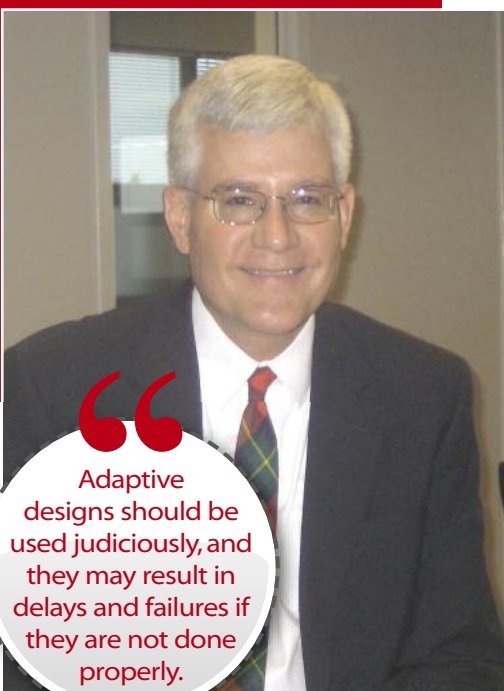
**LUCE.** UBC. Another challenge is that most trial-

**GAYDOS.** LILLY. The guidance provides a path forward, a blueprint to successfully implement these new methods. Regulators have taken the tack of covering the full range of adaptations at a principle level instead of focusing on specific methodology. This is going to enable the guidance to be relevant over time since new methods will continue to be developed. This also enables sponsors to determine where the opportunities may be and, once determined, how to engage the regulators to implement successfully.

**SIETSEMA.** KENDLE. The draft guidance provides clarity; up until now there was confusion. When people hear the term adaptive designs, they heard faster and cheaper. But the improper use of adaptive designs can introduce bias within a clinical study and can result in making incorrect conclusions and that's a major concern for regulatory agencies. The adaptive design guidance does a nice job of explaining the permissible limits under which adaptive designs can be used; the factors that cause concern when introducing bias; and how to organize the data to be acceptable to regulatory agencies.

**BLAKE-MICHAELS.** CLEARTRIAL. The agency's concern is to make sure that they still receive adequate characterization of the dose response and safety profile of the drug in the marketing application. We really needed this guidance. A lot of companies that would have liked to start using adaptive designs in their drug development programs have been waiting for the guidance because there is risk involved in trying a new approach.

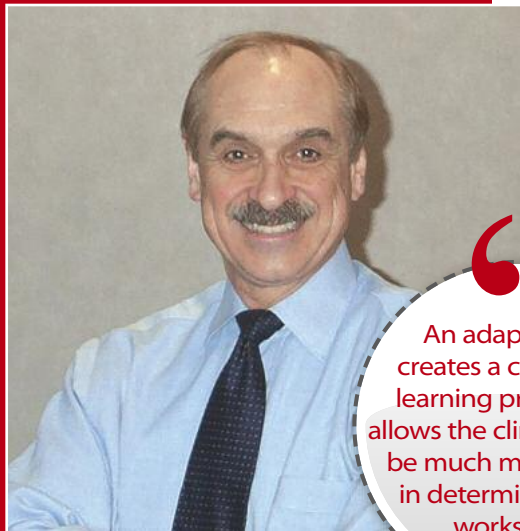
**ANDERSON.** PPD. The guidance has really been needed. It sets high standards for rigor. It may have an impact of slowing the adoption of adaptive designs in adequate and well-controlled studies, but there are going to be instances where



DR. MICHAEL BOYD / INC Research

“Adaptive designs should be used judiciously, and they may result in delays and failures if they are not done properly.”

DR. BRYAN LUCE / United BioSource



“An adaptive trial creates a continuous learning process that allows the clinical team to be much more flexible in determining what works best.”

ists and most biostatisticians are not trained to do this type of work. The traditional double-blind frequentist hypothesis testing randomized controlled trial is a tried-and-true method that people are very comfortable with and many people are not ready to accept a new paradigm, even when there is good evidence that it may lead to a more efficient process. There is a lot of inertia because of that. The challenges come when we get beyond Phase II and into Phase III or Phase IV. On the face of it, Phase IV trials would seem to be particularly well-suited for adaptive designs. The concept of adapting a comparative trial or registry for the real world in a systematic way just makes sense, but this really hasn't happened yet.

### Best Practices

*Our experts discuss the important factors to consider when planning an adaptive study.*

**BLAKE-MICHAELS.** CLEARTRIAL Adaptive trials involve a lot of up-front planning. It can take twice as long to plan an adaptive trial as a traditional trial. Simulations are required not only for patient outcomes, such as efficacy, but also to understand the drug supply, head count, and budget requirements. This really represents a paradigm shift in planning. Teams need to think in terms of ranges of possible outcomes and plan a variety of different scenarios to make sure they understand the impact each would have on the program. A lot of the benefits of this type of study — such as time savings or earlier identification of doses — can be lost if adequate long-term planning doesn't occur up front.

**JOHNSON.** PHARMANET. The adaptive methodology to be used and the modifications to be made must be specified at the outset of a trial, not devised ad hoc during the course of the trial. Similarly, interim analysis procedures, group-sequential stopping boundaries, risk/benefit determinations, and criteria for maintaining the blind should be specified at the outset. In a Phase III trial, it's best to plan for just one modification during the study, not several. The FDA is very clear in urging drug sponsors to interact with the agency during the early planning of adaptive designs and gain agreement on the methodology before launching any studies. These include methods for controlling bias, maintaining blinding, and providing documentation of statistical procedures, including simulations or other calculations necessary to support study results.

**GAYDOS.** LILLY. It is important to have clarity on the rationale for doing an adaptive design

over a conventional design. These aren't something to do because they are neat or new. In addition, more up-front planning is required. A team needs to appropriately adjust its project management plan. A lot of clarity on the data flow is needed to implement these trials; they need to run efficiently. Teams need to ensure they have good firewalls to protect data integrity.

**QUINLAN.** CYTEL. Not every trial has to be an adaptive trial. Like any trial it has to make sense within the clinical development plan and it has to add value. Unfortunately because adaptive trials have become a buzz term, there are a lot of people who say they can do adaptive trials. So it's very important to make sure the right people are working on these trials. These should be people who have experience and know the planning and execution issues involved.

**DUDINAK.** ROCHE. Adaptive trials should be evaluated in the scope of all other trial designs. Companies should consider how this approach fits into the overall development program and life cycle of the product. Team discussions and the strategic evaluation should be initiated as early as possible. There are times when an adaptation may not be appropriate. There isn't a one-size-fits-all approach as it relates to adaptive designs. Generally, a very quick enrollment rate isn't advantageous to an adaptive design. Companies need to look at adaptive studies from a cross-functional perspective. There are multiple stakeholders that need to be involved: clinical, regulatory, operations, technical, safety, biostatistics, and data monitoring. It also requires support from trial simulation to justify the design and control for a type 1 error.

**MARCHENKO.** STATPROBE. Implementation of adaptive designs involves integration of data capture, drug supply management, data analysis, and interactive communication systems. A key operational aspect for resources means more planning is needed up front if additional resources and monetary investment might be needed for such trials. Clean data are definitely desirable, but quality needs to be balanced against timelines. If the decision is made during the interim analysis on primary endpoints only, then primary endpoints should be clean.

**BORNSTEIN.** ECLINICAL SOLUTIONS. A key practice is to use technology to have cleaner data sooner. Leveraging electronic data capture and having the data in a central repository are important. It's key to interact with the data ongoing and have a proactive data management plan. In an adaptive design or in any clinical trial, the data are vital. Updating SOPs

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To make quick and reliable decisions during an ongoing study, we need real-time access to clean data for interim analysis,  
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DR. MARY JOHNSON / PharmaNet

DR. BRENDA GAYDOS / Lilly

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An adaptive trial design should never be done unless it can demonstrate a benefit over a conventional method.  
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DR. BILL SIETSEMA / Kendle

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The improper use of adaptive designs can introduce bias within a clinical study and can result in making incorrect conclusions.  
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When using adaptive designs, sponsors have to think strategically, not tactically.”

up front is one best practice that needs to occur to incorporate adaptive trial design into the process; for example this would allow for the protection of the study blinding and eliminate the introduction of bias.

**COLLINS.** ARIS GLOBAL. Management and leadership are key. Hundreds of people have to do things more quickly than they would normally be accustomed. They are not doing more work, but they have to do it faster and in an environment with a lot of pressure and a lot of visibility from higher levels. EDC and standards provide the brains to be fast. Management is the spine. If the sponsors are going to seek approval based on trials that involve multiple looks at the data, they must show efficacy with greater statistical certainty. If sponsors are not fast, what happens is that they would have done a less efficient conventional study that is burdened by a statistical penalty. Even if the database is locked fast and the analysis completed faster, there is one more thing that is needed: a sponsor has to act on the information quickly. If it takes weeks to make a decision on how to change the course of the study, nothing much was really accom-

plished. In fact, one might pay a penalty for the multiple looks at the data.

**BOYD.** INC RESEARCH. The FDA's major concern is bias. It is imperative, therefore, to have clear documentation about SOPs and firewalls to protect against bias. It is also important to recognize that this is a new process and each adaptive design is different. It cannot be stressed too much that early communication with the agency is vital. The FDA will need to review and understand any proposed design. ♦

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## Sound Bites From The Field

### PHARMAVOICE ASKED INDUSTRY EXPERTS HOW PHARMA/BIOTECH COMPANIES CAN USE ADAPTIVE DESIGNS FOR MORE EFFICIENT DRUG DEVELOPMENT.



**MELISSA HAMMOND** is Managing Director of Snowfish, which provides insights to healthcare, life-sciences, and biotechnology companies. For more information, visit [snowfish.net](http://snowfish.net).

“From a marketing perspective, adaptive trial design appears to make excellent sense, particularly with respect to large trials with extended follow-up. Ideally, analysis of the overall clinical data and practice landscape for an area is ongoing, even while a large-scale study is being conducted. Such analysis may indicate subtle changes in the clinical and marketing landscapes, which if not addressed, can pose major marketing barriers moving forward.

An adaptive approach can therefore allow for appropriate modification of the trial in order to proactively address key issues, thereby obviating a need for multiple post-hoc analyses (which many times are poorly powered) and additional follow-up studies.”

**ANDREA PERRONE, M.D.**, is VP, Clinical



Operations and Medical Director at BioClinica Inc., a global provider of integrated, technology-enhanced clinical trial management services. For more information, visit [bioclinica.com](http://bioclinica.com).

“In February 2010, the FDA, CDER, and CBER released a draft guidance on adaptive design in clinical trials for drugs and biologics. Their mission is to provide further clarity on how trials can be designed more efficiently and to maximize the knowledge accumulated. The metrics for efficiency can be monetized by the pharma and biotech industry in three main areas: by decreasing the number of patients needed to reach statistical significance; decreasing the length of the study; and potentially expanding the data gathered based on dose and response.

Specific modifications that may occur throughout an adaptive trial and are defined a priority include study eligibility, randomization, treatment regimens, concomitant treatment, schedule of assessments, primary endpoint, including outcome assessments, order of secondary endpoints and/or analytic methods to evaluate endpoints. A critical factor to the success of an adaptive design is the prospective

nature of the modifications that are proposed before any unblinding of the data.”

**JASON ROCK** is Chief Technical Officer at GlobalSubmit, a developer of software designed exclusively for the review and validation of electronic common technical document (eCTD) global submissions. For more information, visit [globalsubmit.com](http://globalsubmit.com).

“The main reason why drug development is so costly is the time needed for clinical trials. Even when a drug is not working, standard trial design forces sponsors to run a trial to the end. If trial data were made available earlier, sponsors would know that the trial will be ineffective earlier. Accordingly, the cost of bringing drugs to the market would drop significantly. Adaptive trials will greatly reduce the cost of drug development by allowing a sponsor to quickly learn that a drug is not working and stop the trial.

The real sticking point between the FDA and industry with adaptive trials is around how well the protocol needs to define recruitment. Clearly allowing the sponsor to unblind the study and add one patient at a time is not sound but waiting until the trial is complete is too costly.”

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BY DENISE MYSHKO

# TECHNOLOGY

## Makes Adaptive Designs Possible



DR. BRENDA GAYDOS / Lilly

Simulations help provide quantitative information on whether or not an adaptive trial really provides an improvement over the conventional approach. My clinical trial optimization team consulted with at least 34 teams in the first quarter. We're moving toward having 90% of all trials simulated.

tistical groups at pharmaceutical companies and CROs need to develop statisticians and programmers with the background necessary to implement the statistical procedures requisite for adaptive designs. In some cases, this requires the purchase of specialty software or in-house program development."

Randy Anderson, Ph.D., VP, global product development, at PPD, agrees that technology is critical for managing the logistical demands of adaptive trials.

"For example, technology can be used to speed subject accrual with outbound call centers, Web-based trial registries, and mass notifications to preregistrants who match inclusion/exclusion criteria," he says. "By speeding subject accrual, trialists address one of the major time elements that determine whether an adaptive design will work logistically. Also, highly automated phone or Web-based randomization and study drug supply management are essential elements for accurate and time-efficient implementation of adaptive design changes."

Dr. Anderson says also critical is electronic data accrual immediately after a patient visit, with well-automated edit checks at entry, relational queries running automatically near the time of entry, and automation support for remote and onsite monitoring.

"Many results come from lab assays, so those results also need to be incorporated into an analysis database soon after those assay results are available," he says. "Once the team

### The FDA Draft Guidance

The Food and Drug Administration released draft guidance on Feb. 25, 2010, for pharmaceutical and biologics developers on adaptive design clinical trials. The 50-page guidance covers the clinical, statistical, and regulatory aspects of adaptive design clinical studies and focuses on adaptive designs that are not well-understood.

Designs that are not well-understood include: adaptations for dose selection studies; adaptive randomization based on relative treatment group responses; adaptation of sample size based on interim-effect size estimates; adaptation of patient population based on treatment-effect estimates; adaptation for endpoint selection based on interim estimate of treatment effect; adaptation of multiple-study design features in a single study; and adaptations in noninferiority studies.

The guidance also covers the statistical concerns for less well-understood adaptive designs, the safety considerations for all adaptive designs, the content of an adaptive design protocol, interactions with the FDA, and documentation needed to protect study blinding and information sharing for adaptive designs.

The guidance noted that standard operating procedures (SOPs) for an adaptive design study with unblinded interim analyses are likely to be more complex than SOPs for non-adaptive studies to ensure that there is no possibility of bias introduction.

FDA officials say the written documentation should include identification of the personnel who will perform the interim analyses; who will have access to the interim results; how that access will be controlled and verified; how the interim analyses will be performed, including how any potential irregularities in the data, such as withdrawals or missing values, will be managed; and how adaptation decisions will be made.

To view the draft guidance, please click <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201790.pdf>

*Technology advances have increased the opportunities for adaptive studies, becoming a facilitator for these more flexible designs that allow for an interim analysis of data. Our experts discuss EDC, simulations, centralized data repositories, and how they can be leveraged for improved efficiency and efficacy.*

Industry experts agree that the implementation of adaptive trials would be difficult without the help of technology.

To make quick and reliable decisions during an ongoing study, we need real-time access to clean data for interim analysis, says Mary Johnson, Ph.D., executive VP, biostatistics, at PharmaNet Development Group.

"Adaptive designs allow us to leverage our use of new technologies that accelerate data-based decisions, such as electronic data capture and centralized systems for randomization and dose distribution," she says. "In addition, sta-

has an analysis database, then highly automated real-time analysis needs to be in place.”

The foundation of an adaptive design is speed, says Sylva Collins, Ph.D., VP, e-clinical solutions at Aris Global.

“Adaptive designs need an effective EDC system,” she says. “EDC systems, effectively used, can lock a database in days rather than weeks or months.”

According to Susan Bornstein, executive VP at eClinical Solutions, an adaptive trial design is about capturing cleaner, high-quality data sooner to have the ability to interact and trend data to make go/no go decisions.

In addition, Ms. Bornstein says having a central repository for the data is critical.

“With more complex trials, data are coming from multiple labs,” she says. “There could be pharmacogenomics data, biomarker data, ePRO data, IVRS data, etc., which then need to be standardized and leveraged. We use an interactive data visualization tool, which allows a dashboard with multiple windows to track trends and look for outliers in the data, as well as what was defined up front in the analysis plan and protocol.”

### Trial Simulation

Experts say it takes twice as long to plan an adaptive trial than a conventional trial. To help with that planning, simulations are recommended to determine a range of outcomes for planning drug supply, resource needs, and budgets.

“Simulations help provide quantitative information on whether or not an adaptive trial really provides an improvement over the conventional approach,” says Brenda Gaydos, Ph.D., senior research advisor at Eli Lilly and Co. “When we optimize a trial design, we want to understand the risk in the design and try to mitigate that risk. We typically start with a conventional clinical plan and then we brainstorm different clinical trial alternatives that may improve a particular molecule. My clinical trial optimization team consulted with at least 34 teams in the first quarter. We’re moving toward having 90% of all trials simulated.”

Dr. Gaydos says trial simulations are necessary to design and assess an adaptive trial because of their complexity.

“Without the proper software tools to do these complex simulations, adaptive studies can be very resource intensive,” she says. “In the future, I believe all clinical trials will be simulated prior to implementation. One of the benefits of doing simulations is that they improve all trial designs, regardless of whether the study has adaptive elements or not.” ♦

### The Adaptive Process

**OUR INDUSTRY EXPERTS DISCUSS HOW ADAPTIVE DESIGNS ARE CURRENTLY BEING USED AND THEIR APPLICABILITY TO FUTURE DEVELOPMENT.**



**DR. RANDY ANDERSON.** PPD. Adaptive designs relative to fixed designs are about 5% to 10% of our total studies. The majority of the adaptive designs we conduct are group sequential designs.

Interestingly, the simplest group sequential design is a two-stage design with a single interim analysis and a final analysis. The technical capabilities to do truly sequential designs are now available. Although they have been around since the 1940s, only recently have truly sequential designs been technically feasible for trial applications, with the availability of dramatic computing power and the rapid, secure flow of information over the Internet.



**MOLLY BLAKE-MICHAELS.** CLEARTRIAL. The term adaptive study means one in which data obtained during the study are used to modify one or more features of the study in some way, and

it aren’t specific to a certain phase of study. Adaptive designs can be used in any phase study, although based on the recent FDA guidance, it seems likely that the most common use will be in Phase II.



**DR. SYLVA COLLINS.** ARIS GLOBAL. An adaptive trial is one in which the data from the ongoing study are used to change the course of the trial, using a predefined decision tree and without jeopardizing

the statistical validity, scientific validity, and the integrity of the study.



**DR. JENNIFER DUDINAK.** ROCHE. There are various levels of adaptation. This is a quite common approach on the exploratory side of development. There are newer frontiers in using adapting design

in pivotal registration trials. It will be very exciting to see the full spectrum of the use of adaptive trials that result in a registration and approval.

**DR. BRENDA GAYDOS.** LILLY. I lead the clinical trial optimization team. We have been working very



actively to identify new approaches and have assessed broad aspects of the drug development process from drug supply to data management and statistics, as well as regulatory

issues, to help optimize processes. In general, the decision to use an adaptive design, depends on the disease state as well as on the molecule that’s being investigated and the particular clinical questions the team is asking.



**DR. BRYAN LUCE.** UBC. Adaptive designs are becoming more common. Although the medical device industry (and CDRH/FDA) have much broader experience and comfort in these methods,

within drug development, they have been applied most commonly in Phase II dose ranging trials. As such, they provide a much more efficient process to hone in on the doses that are the most therapeutically viable with the best side-effects profile.



**OLGA MARCHENKO.** I3 STAT-PROBE. Adaptive designs can play a huge role in confirmatory trials as well in exploratory trials. Adaptive designs have potential to improve the efficiency of drug

development at each stage, but we need to be very careful in terms of statistical transparency, how to control for type 1 errors, and how to preserve confidentiality and the integrity of the trial. Sponsors are worried they might spend more money because, while the average adaptive design saves time, it could cost more in the end because of its complexity and in some cases increased sample size.



**DR. BILL SIETSEMA.** KENDLE. Almost every company is executing some type of adaptive design as part of its programs. The protocol title doesn’t always say it is an adaptive design. I wouldn’t be

surprised to find that greater than half of the studies have some element of an adaptive design.