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An important measure of success of any clinical supply chain strategy is whether or not clinical sites have the necessary study medications at the ready when needed to avoid delays in new patient starts or continuance of therapy. The complex nature of some clinical trials can create challenges which can place considerable stress on the supply chain. The difficulty in ensuring the continuity of supply increases as variables are introduced into the mix. These variables can include blinded studies, those with multiple arms or dynamic designs such as adaptive studies, fluctuations in patient recruitment, insufficient or interrupted supply of the IMP or comparator drugs, and more.

Forecasting and demand simulations are useful for anticipating when and where stock is likely to be needed to formulate a kit production and
distribution strategy. Additional stock over and above the forecasted amount needed is commonly added to create a generous buffer inventory to help manage any deviations and hopefully avoid supply disruptions or shortages. However, even with forecasting and building out a sizeable buffer inventory, clinical sites may still not always have the appropriate kits on hand to dispense to patients. Why?

The answer is surprisingly simple. Nearly all clinical supply models in use today are linear and rely upon the advance production of finished or partially-finished patient kits prior to the study start. Depending upon the supply strategy employed, large initial lots of finished kits and periodic resupply shipments may be sent to clinical sites based upon anticipated demand or partially-finished kits may receive final labeling and be shipped to clinical sites on an as-needed basis. In either scenario, drug product must be committed (e.g., packed into) a patient kit before it is actually needed. And therein lies the crux of the problem – a linear supply chain lacks the flexibility to effectively address unforeseen inconsistencies between supply and demand.

In order to create a supply chain that is flexible and responsive, it must first be broken. By splitting the supply chain into two independent stages the root cause of supply delays and shortages can be eliminated instead of just managed and the focus can shift from managing inventory to managing demand. By using a demand led approach the supply chain becomes much more flexible and responsive and requires a significantly smaller buffer stock.

Stage 1: Advance Preparation of Bright Stock
Prior to the start of the study the investigational medical product and any comparator drugs are processed up to the point of primary packaging. These primary packaged drugs are uniquely numbered but remain unlabeled. And because the drugs are not packaged into patient kits at this stage, they can be pooled for use across multiple protocols if applicable. Once released by Quality, they are tracked in a central inventory management system as bright stock, but are physically distributed to regional GMP clinical packaging facilities closer to the clinical sites.

Stage 2: Secondary Packaging and Distribution
Once clinical sites indicate the need for a small supply of seed stock or there is an actual patient demand, the appropriate regional packaging facility picks the required bright stock from its inventory and performs secondary packaging and
labeling to produce only the type and quantity of patient kits requested. The finished kits are released, packed and shipped out to the clinical site in a matter of days.

Not only does the demand led approach mean that clinical sites receive the kits they need quickly, it greatly reduces the risk of treatment delays due to insufficient inventory. In addition, slower recruiting clinical sites are not faced with the challenge of storing an overabundance of inventory or potentially returning or updating the labeling on expiring inventory. Delayed commitment of the study drugs greatly reduces the amount of buffer stock needed from upwards of 200% or more common in today’s linear supply models to less than 20%.

By interrupting the traditionally linear supply chain at the primary packaging stage instead of the secondary packaging stage, the supply chain under a demand led approach is transformed into one that is flexible, efficient and most importantly, able to get study drugs to clinical sites quickly.

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ADOPTION OF ADAPTIVE TRIAL DESIGNS POISED TO ACCELERATE

Adaptive trial designs have the potential to transform success rates, but require new operating strategies and practices.

By Kenneth A. Getz

Risk-based monitoring, patient centricity, and investigative site management reform (e.g., selection, training, and accreditation) are widely cited today as critical areas that will transform drug development performance, cost, and inefficiency. Adaptive trial designs are one area that has received scant attention but that holds the near-term potential to have a far more transformational impact.

Adaptive trial designs are preplanned, typically through the use of trial simulations and scenario planning where one or more specified clinical trial design elements are modified and adjusted—while the trial is underway—based on an analysis of interim data. Most transformational approaches receiving attention today aspire to reduce cost and development duration. Adaptive trial designs could potentially improve success rate. With less than 20% of drugs that enter clinical testing ultimately receiving regulatory approval, modest...
increases in success rates have been a coveted yet elusive goal.

Current adoption low and later stage In late 2012, the Tufts Center for the Study of Drug Development (Tufts CSDD) conducted a study among 12 major pharmaceutical companies. Based on in-depth interviews, Tufts CSDD probed current adoption rates and their impact on drug development study economics and durations. As a follow-up to the in-depth interviews, in February 2013, Tufts CSDD hosted and facilitated a roundtable in Boston to gather a more comprehensive assessment of industry-wide adaptive trial design practices and perspectives. Forty senior executives representing 31 companies participated in the roundtable. Executives represented cross-functional viewpoints from clinical research and development, biostatistics, project management, and clinical operations. Perspectives from the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) were also represented in the roundtable meeting. This study was funded by an unrestricted grant from Aptiv Solutions.

The results of this study suggest that overall, simple adaptive designs are being used on approximately one out of five (20%) later stage Phase III clinical trials. Sponsor companies report, however, that they expect the adoption of adaptive trial designs in earlier exploratory phase clinical trials to increase significantly over the next several years.

“Study terminations due to futility” is the most common simple adaptive design used and it is becoming widely adopted throughout the industry. Sponsor companies unanimously agreed that early terminations due to futility are relatively easy to implement and should become standard practice in Phase II and Phase III studies, across all therapy areas. Although companies view sample size re-estimation as a relatively simple adaptive design, the adoption of this approach appears to be well below that of futility stopping.

The adoption rate of more sophisticated adaptive design approaches—dose-finding and seamless Phase II/III studies—appears low at less than 10% of clinical trials. Despite the fact that sophisticated adaptive designs during exploratory phase clinical trials could have the greatest impact on improving later phase success rates, Tufts CSDD found low use of adaptive dose finding and extremely low use of seamless Phase II/III studies.

Areas of resistance
Although the concept of adaptive trial designs has been discussed and explored by pharmaceutical and biotechnology companies for decades, adoption has been slow for a variety of reasons. Tufts CSDD interviews revealed that internal
organizational resistance appears to be the primary factor limiting more widespread adoption. Regulatory agency receptivity to the use of adaptive trial designs does not appear to be a barrier to adoption. Agency clarity to sponsor companies on its position regarding the use of adaptive designs appears to be lacking.

Clinical teams and operating functions perceive enrollment and logistical factors—specifically delays and disruptions in trial execution, patient participation, and distribution of clinical supplies—as major barriers to adoption. Sponsor companies express concerns around how to monitor data without introducing bias; the lack of adaptive trial design experience among both internal development teams and external contract research organizations; gaps in infrastructure and technology to implement more sophisticated adaptive designs; and the limited capacity of independent data monitoring committees.

Senior pharmaceutical company executives perceive that regulatory affairs functions are risk averse to adopting sophisticated adaptive design approaches due to their belief that more clarity from regulatory agencies is needed.

Regulatory agencies, in contrast, appear highly receptive to exploratory phase adaptive trial designs to challenge and inform clinical teams prior to committing to pivotal late-phase studies. The agencies are concerned that early development approaches are not efficiently detecting failures prior to Phase III or that decisions taken in exploratory development are sub-optimal leading to unnecessary Phase III failure. Using adaptive trial designs to perform Phase II dose response assessments, for example, could dramatically improve dose selection in Phase III clinical trials.

Reported and estimated impact
In theory, adaptive trial designs may help to reduce the number of protocol amendments. In a 2012 study conducted by Tufts CSDD, we found that sponsor organizations spend approximately half-a-million dollars in direct costs and an additional 60 days to implement each protocol amendment. In our interviews on adaptive trial design adoption, however, several sponsors have indicated that not all amendments will go away since certain country-specific health authorities will still require protocol modifications after pre-planned adaptations have been approved.

Early study terminations due to futility and sample size re-estimation could save up to a hundred million dollars in direct and indirect costs annually for a sponsor company depending on clinical trial scope, when the trial is actually terminated, and on the sponsor’s overall
implementation of this adaptive approach across the development portfolio.

A global top 20 drug development company that has been applying simple adaptive trial designs to Phase II and Phase III studies across its portfolio for five years reported saving more than $70 million each year through the adoption of simple adaptive dose-finding studies in Phase II and sample size adjustments and futility stopping in Phase III.

Sponsor companies recognize that the greatest potential value created by adaptive trial designs will come from improvements in late-stage success rates. Even modest improvements in success rates for new molecular entities (NME) and new biologic entities (BME) represent billions of dollars in increased revenue potential for research sponsors.

In the immediate term, adaptive trial designs are already offering cross-functional teams direct insights into study design through scenario planning and trial simulation prior to finalizing the protocol. Rigorous upfront planning is forcing organizations to challenge protocol feasibility prior to placing the protocol in the clinic.

**Ramping up adoption**

In most sponsor organizations, awareness and knowledge about the usage and the potential impact of adaptive trial designs has been limited to statistical functions. Cross-functional education and support, aided by senior management encouragement, will go far in increasing general awareness and stimulating usage. Sponsor organizations that have established strong proponents among therapy area heads, medical experts, and clinical operations professionals in addition to their statistical functions—have been far more effective in promoting successful adoption.

Sponsor organizations higher up the adoption curve did so by starting with simple and straightforward adaptations (e.g., sample size re-estimation and futility analyses). Simple designs applied across the portfolio appear to ease the company into implementing adaptive designs and to facilitate a smoother transition to sophisticated approaches. Companies that have applied sophisticated and complicated adaptive designs to a few select studies early in the organization’s adoption process have had a lot of difficulty promoting more widespread usage.

The adoption of more sophisticated adaptive designs in exploratory development may necessitate the use of new technology solutions and operating practices and will require organizations to re-evaluate their existing clinical operating processes.

Clinical operations teams will need to focus particular attention on obtaining
expertise in planning and forecasting logistics and resource requirements under more flexible study designs. At this time, most sponsors have set very rigid performance and cost variance thresholds making it challenging for operating staff to entertain more variable capacity and resource planning practices. Clinical teams will also need to work more closely with investigative site personnel to ensure that patient safety and expectations are maintained under more adaptive clinical trial conditions.

Active and careful measurement of cost savings from the use of adaptive designs (e.g., futility analysis) is an essential ingredient in convincing organizations—particularly senior management—to continue to support and extend adoption. Companies that have led successful implementations have been particularly adept at publicizing quantitative measures of the impact of adaptive trial design use.

Adaptive trial designs represent a critical opportunity for pharmaceutical and biotechnology companies to transform drug development performance, efficiency and—most importantly—success rates. Beyond building awareness, as always, the challenge will be implementing successful adoption of simple adaptive designs leading to more sophisticated approaches.

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Flexible, scalable, full-service clinical supply services to take your study from Phase I to Phase IV.
Our innovative solutions leverage our comprehensive services and expertise to create tailored clinical supply solutions that meet your needs, regardless of trial size or complexity. With 8 GMP facilities and 50+ strategically located depots worldwide, we have the local expertise to help speed your molecule to clinic and the global scale to handle virtually any clinical supply need.
Today’s rich oncology pipeline—accounting for nearly 25% of agents in clinical development—promises much needed advances in cancer therapy. That promise dims in the face of other discouraging statistics: only 7% of oncology agents entering Phase I clinical trials gain marketing approval while only 34% of Phase III oncology trials achieved statistical significance in primary endpoints.

The cost, time, and numbers of patients required to conduct conventional oncology clinical trials continue to escalate. The complex demands of evaluating new targeted therapies add to this burden. Novel methodologies are available that make trials more efficient and informative so that precious resources of patients, time, and money are invested in studies with the greatest chances of success.

Adaptive trial design offers opportunities for improvement by shortening the time needed to
answer key research questions, reducing the number of patients needed for evaluation, and improving the quality of decision-making to increase overall success rates. The use of adaptive designs also raised scientific and regulatory questions that slowed adoption by the biopharmaceutical industry. A growing body of experience culminated in the U.S. Food and Drug Administration’s (FDA) 2010 draft guidance, Adaptive Design Clinical Trials for Drugs and Biologics, which details adaptive approaches and encourages their use.4

FDA defines an adaptive study as one that “includes a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (usually interim data) from subjects in the study.” Five adaptive designs—including blinded sample size re-estimation and halting early for lack of utility—are cited as “well-understood.” FDA encourages drug developers to use these approaches for all studies. Seven “less well-understood” designs—including unblinded applications that use interim estimates of treatment effect for endpoint selection and sample size re-estimation—should be reserved for exploratory studies while more experience is gained.

This regulatory underpinning supports wide application of adaptive design in oncology drug development. Its positive impact can be seen in the groundbreaking I-SPY 2 breast cancer trial, which uses adaptive design to streamline identification of active drugs and predictive biomarkers.5 I-SPY 2 (“Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis”) suggests a model for new, adaptive design-based approaches to advance the oncology drug development process.

Traditional Design: Poor information leads to poor performance

Traditional designs contribute to high failure rates and escalating costs because answers to pivotal research questions are obtained only at the end of the trial. Trials using fixed designs rely on assumptions that may be found to be incorrect at the end of the study. Faulty assumptions used in underpowered Phase I and Phase II trials yield poor information on which to base decisions about Phase III designs where the impact of failure is greatest due to the large number of patients and time involved. The cumulative effects of the traditional approach are low overall success rates and high costs (Table 1).

Advancing oncology drug evaluation depends on: 1) selecting the best drug candidates; 2) identifying and eliminating failures as early as possible; and 3) designing trials to identify the right dose,
Adaptive trial designs are especially well suited to this purpose. For the right disease, in the right patients as early as possible. With thousands of potential drugs awaiting development—and with relatively few of these likely to demonstrate efficacy—earlier information and better-focused evaluation are critical to improving success rates. Adaptive trial designs are especially well suited to this purpose.

### Incremental decision-making improves research outcomes

Adaptive designs leverage accumulating data to modify trials as they progress, making better decisions at each sequential step. Adaptive approaches use early findings to improve the next phase in a flexible process that can accelerate timelines, reduce costs, and generate the most knowledge from the smallest number of patients.

Traditional designs use a probabilistic statistical approach. Decisions regarding dosage, randomization, and sample size are made in advance and usually do not change throughout the trial. Instead of making pivotal decisions with limited information before a trial, adaptive designs use accruing information to obtain relevant data that inform and improve critical decisions. Data are analyzed continuously or at designated interim points, and results are used to shape future design parameters such as doses, disease indications, or populations being studied. Using this flexible approach, the trial becomes a learning tool that applies evolving knowledge to drive subsequent decisions.

#### Roles of Bayesian statistics, simulation, and biomarkers

Adaptive designs can incorporate more than one adaptation in a trial and may address a number of research questions simultaneously. A single trial can be designed to evaluate multiple dose regimens, indications, drug combinations, and even multiple drugs.

For example, a seamless phase II-III breast cancer trial might include adaptive approaches to stop early for futility, assess dose response, drop or add arms, change the proportion of patients randomized to each arm, and enrich the patient population with subjects most likely to respond. Table 2 lists eight adaptive settings commonly used in drug development and particularly relevant for oncology trials.6
Bayesian statistics in adaptive design. Adaptive designs often use Bayesian statistical methodology to model complex scenarios. In Bayesian approaches, statistical models require the formulation of a set of prior distributions for any unknown parameters, in addition to the parts of the model based on the traditional probability distribution of observations. Multiple sources of information are combined to make inferences, allowing researchers to test assumptions based on both direct observations and additional information on neighboring doses, different populations, similar compounds, preclinical modeling, genetic targeting, and historical data. Repeated analyses can be conducted within a study—and even across studies—using sequential analysis techniques. Results can be used to inform the design of the current trial.

Simulation informs optimal design. While fixed designs depend on theoretical justification of trial behavior, adaptive designs are more complex and depend heavily on simulations to understand trial behavior, efficiencies, and risks as inputs to inform and optimize trial design. Depending on the phase and design, regulators may require submission of simulation results to justify the scientific credibility of an adaptive trial, particularly if the data is intended to support a regulatory approval. Specialized simulation software, such as FACTS, is available to assess key performance characteristics including power, Type 1 error, bias, and average sample size.

Biomarkers provide early information. Biomarkers are important in adaptive designs to provide early measures of efficacy. Since early data may be used to modify a trial as it progresses, the traditional long-term oncology endpoints of survival and progression-free survival are of less benefit. To satisfy this purpose, biomarkers do not need to be validated surrogates. Berry notes that early findings based on “auxiliary markers (that) might be correlated with, and predictive for, the primary end point … may be incorporated into the trial design to help guide the adaptive aspect of the design.” Useful markers might include early clinical outcomes (such as imaging, response, and progression), serum markers, or molecular markers.
from tumors via biopsies. In a provocative article, Verweij suggests that functional target pharmacology studies followed by proof-of-concept studies could replace traditional Phase I, II, and III trials, given that early tumor shrinkage—as measured by Response Evaluation Criteria in Solid Tumors—still appears to be the most reliable biomarker.8

### Improves Phase I dose determination

The primary goal in Phase I is to determine maximum tolerated dose (MTD) for the experimental agent. Over- and under-estimation of the true MTD is a common problem in oncology trials, most of which identify MTD using the “3+3” method. An emerging adaptive approach, called the Continual Reassessment Method (CRM), yields more precise MTD determination and increases the likelihood that the true MTD is used in Phase II.

#### Traditional 3+3 method.

In the 3+3 method, dose escalation steps are defined prior to the trial. A cohort of three subjects receives the drug at a starting dose based on preclinical data. If no toxicity is observed, another cohort of three subjects is added and the dose is escalated to the next level. If one of three subjects experiences dose-limiting toxicity, another three-patient cohort is added at the same dose, and dose escalation continues. If any additional toxicity is observed, the lower dose is declared to be the MTD.

A 1999 analysis reported that when using the 3+3 method, “the probability of recommending the (correct) MTD at the end of the trial … never exceeds 44% and is most often closer to 30%.”9 Poor MTD identification is attributable to the tendency to select larger incremental “jumps” in order to observe toxicity more quickly in fewer steps. The true MTD often resides in a smaller incremental dose and is not observed.

#### Adaptive CRM design.

The Continual Reassessment Method pinpoints the true MTD more precisely by efficiently evaluating more dose levels. CRM models the probability of the MTD as a function of dose at each dosage level and continuouslyRefines it. The 3+3 method bases the next dose allocation (and, therefore, the level that will eventually be declared the MTD) on the last cohort of subjects, while ignoring the data from the previous cohorts. CRM uses all the data to update the estimation of the MTD and to allocate the next patients, either in cohorts or continuously. The model is frequently updated and improves with accruing data.

In the majority of cases, CRM yields better estimation of the MTD and can allow for more rapid progression through early dosing levels depending on the
operating characteristics and rules that are established in the design. Although the CRM approach is more complex and requires high levels of modeling and simulation, experience has proved its value in identifying true MTD with a higher level of confidence. As shown in Figure 1 adapted from Parke, CRM is better than 3+3 at identifying the correct dose level in nine of the 10 scenarios presented. In Scenarios 1, 3, 4, and 6, CRM was substantially better, providing a 10% higher probability of identifying the MTD than the 3+3 method. In Scenario 2, the CRM and 3+3 approaches yielded very similar results.10

Additional CRM benefits. Parke cites additional advantages of CRM: “Unlike the 3+3, its operating characteristics can be easily optimized in light of the current circumstances, different levels of toxicity can be targeted, different cohort sizes used and different levels of accuracy required before stopping, offering better determination of the MTD at the cost of greater sample size.”10 Seamless Phase I-II trials can be designed to allocate subjects based on continuing information on both tolerability and efficacy, an approach that shortens timelines. Another benefit is that patients involved in dose determination may continue to participate in activity evaluation—an important advantage from an ethical point of view.

Slow adoption of CRM. Despite current literature demonstrating the superiority of CRM in determining the MTD, most Phase I and Phase I-II oncology trials continue to use the 3+3 method, likely based on sponsor and investigator level of familiarity. Our search using the key words “adaptive,” “Bayesian,” “CRM,” “3+3” and “escalation” found a total of 12 Phase I and Phase I-II dose escalation trials published in The Oncologist (four trials) and the Journal of Clinical Oncology (eight trials) from August 2012 through August 2013. All 12 trials used the 3+3 design, confirming the 2013 review by Ji and coworkers, which reported “… more than 95% of Phase I studies have been based on the 3+3 design.”10
Adaptive approaches in Phase II improve Phase III trials

**Improving dose-response evaluation.** Adaptive designs can be used to efficiently evaluate several active doses in Phase II without necessarily increasing the sample size. Evaluation of more active doses provides a better understanding of the dose-response relationship, reducing the likelihood of failures due to suboptimal dose selection in Phase III. Ineffective or unsafe dose levels can be discontinued early, and the majority of patients can be allocated to the dose levels most likely to be active.

**Improving identification of target populations.** Increasing genomic knowledge of cancer subtypes is driving the need for efficient drug evaluation in targeted patient populations. The milestone genetics study of breast tumors published in 2012, for example, identified four distinct subtypes of breast cancer, suggesting targets for new drugs and better uses of existing drugs.11 As noted by Esserman and Woodcock, “The inability (or lack of explicit effort) to identify and incorporate specific disease subtypes into trial design inhibits the development of more cost-effective drugs that target specific populations,” a dilemma that demands new clinical trial designs that can address disease heterogeneity and complexity.5

Adaptive Phase II designs can be instrumental in identifying the appropriate patient population for Phase III evaluation. Identification of the right subpopulation can have a dramatic impact on the number of patients required in Phase III trials to demonstrate efficacy. For example, suppose one half of subjects with non-Hodgkin lymphoma respond well to a drug, as measured by a 60% hazard ratio; the other half benefit by only 10%. To show superiority in a Phase III trial with all patients enrolled at 90% power, 530 events would be required. But in a trial with the subpopulation of more positive responders, only 210 events would be needed.

**Halting for futility.** Preplanned futility analysis based on interim data can be used to stop a study that is unlikely to meet its primary endpoint. Interim futility analysis also can allow developers to continue a study with greater confidence of success in Phase III. For example, a simple preplanned futility analysis was conducted in a Phase III multicenter study comparing a new therapy to standard of care in patients with progressive and/or recurrent non-resectable glioblastoma multiforme. The target sample size was 323 randomized patients. Recruitment was difficult; after three years, only 137 patients were randomized. An unblinded interim futility analysis indicated that
the therapy was unlikely to demonstrate efficacy. Based on the analysis, the independent data monitoring committee recommended halting the trial. Early termination avoided unnecessary exposure for approximately 180 subjects. Halting early avoids Phase III failures that contribute significantly to the low productivity and exorbitant cost of drug development, widely estimated at $1.8 billion per approved drug. A 2013 Forbes analysis suggests that for large biopharma companies—those that earn approval for eight to 10 new drugs over a decade—the greater number of failures experienced in managing a large pipeline result in an average cost of $5 billion per approval.12

Re-estimating sample size. Sample size is fixed in traditional designs, with size based on initial assumptions about primary efficacy measures and the rate and timing of patient withdrawal from the study. This approach often results in under powering or over powering. In the first case, the study fails to show definitive results. In the second, the trial requires more subjects and time than necessary. Adaptive designs use interim data to re-estimate sample size as the trial proceeds, so sample size can be increased to ensure adequate powering.

The 2010 FDA draft guidance makes a distinction between blinded and unblinded adaptations to maintain study power. Blinded approaches, which FDA characterizes as generally well-understood, compare interim findings to assumptions used in the planning of the study. For example, in studies that use an event outcome such as response rate for the endpoint, a blinded examination of the overall event rate can be compared to assumptions used in study planning. If the comparison shows that actual event rate is well below the assumption, sample size can be increased. Such blinded approaches also can be used in studies using time-to-event analysis and continuous outcome measures. Since blinded approaches do not introduce statistical bias or require statistical adjustments, they maintain Type 1 error control. FDA recommends that they “should generally be considered for most studies.”4

Unblinded approaches use interim analyses to estimate treatment effects. Unblinded approaches allow initial sample size to be increased if the size of the treatment effect is seen to be smaller than anticipated, but is still clinically relevant. In some cases, adaptations that address other elements of study design—such as dose, population or study endpoint—could alter the study power and require re-estimation of sample size. Changes in sample size based on unblinded data analysis may cause an
increase in the Type 1 error rate, and a statistical adjustment is necessary for the final study analysis.

FDA considers unblinded approaches to be less well-understood and cautions researchers to be conservative when making changes based on early estimates of treatment effect, which can be misleadingly large or small. Due to concerns about Type 1 error and operational bias, FDA suggests that unblinded approaches be used primarily for studies in which the primary objectives cannot be achieved using blinded designs. Drug developers exploring these designs must show adequate control of Type 1 error.

**Seamless adaptive designs improve trial efficiencies**

Seamless designs use adaptations and interim data to combine phases into a single study, reducing timelines and the number of patients required. These designs are especially useful in oncology studies because adaptations can address a wide variety of questions in the early (Phase II) stage to improve the later confirmatory stage. Seamless designs allow the long-term clinical endpoints from subjects enrolled in an early phase to be included in overall trial results. **Seamless Phase I-II designs.** Seamless designs can answer Phase I toxicity questions and early Phase II efficacy questions in the same study. A simulated Phase I-II oncology study designed by Huang and coworkers demonstrates the efficiencies that can be gained using seamless approaches.13

The authors designed a parallel Phase I-II study that combined dose determination with efficacy assessment for two oncology agents when administered in combination, and when administered concurrently versus sequentially. The trial begins with an initial period of dose escalation. Then patients are randomly assigned to admissible dose levels that are compared with each other. Bayesian probabilities are used to adaptively assign more patients to doses with higher activity levels. Combination doses with intolerable toxicity are eliminated, while those with lower efficacy are temporarily closed. The trial would be halted if the posterior probability of safety, efficacy, or futility crosses a pre-specified boundary.

**Seamless Phase II-III Trial**

![Seamless Phase II-III Trial](source: The National Academy of Sciences)

**Figure 2.** A seamless Phase II-III trial to evaluate two drugs alone and in combination.
Applying this design to a combination chemotherapy trial for leukemia, the authors used simulations to compare the seamless Phase I-II approach to a conventional design with separate Phase I and Phase II trials. Results showed that the Phase I-II design reduced sample size was better powered and was more efficient in assigning more patients to doses with higher efficacy levels.14

Seamless Phase II-III designs. Larger Phase II studies can increase the probability of success in Phase III but also increase research timelines and costs. In many cases, Phase III success rates can be improved and overall timelines reduced using a seamless Phase II-III design that combines the learning-and-confirming phases into a single study. The first stage generates information to guide the confirmatory stage regarding decisions such as: whether to stop for futility; what dose, regimen, endpoint, and responding subpopulation to study; and whether to evaluate the experimental drug alone or in combination with another therapy.

Figure 2 shows a seamless Phase II-III design for a trial to evaluate two experimental drugs, alone and in combination, as adapted by Berry from “A National Cancer Clinical Trials System for the 21st Century.”7 In this example, the single agent, Drug B, is selected in Phase II and continues into Phase III. The number of patients and randomization in Phase II are chosen adaptively. Phase II results determine sample size in Phase III. Phase III may use interim analyses to halt early for either futility or expected success. Berry notes that the Drug B-versus-control element during Phase II may be counted in the Phase III comparison (i.e., inferentially seamless), or it may not be counted (i.e., operationally seamless). The entire trial must be simulated to control the Type 1 error rate.

Like the use of CRM in dose determination, the adoption of seamless designs in oncology studies is slow. When we broadened our key word search of The Oncologist and the Journal of Clinical Oncology to include all trials at any phase of development, we found only three published studies (all in Journal of Clinical Oncology) that used adaptive designs between August 2012 and August 2013: two used adaptive randomization strategies, while one was a seamless Phase II-III trial.14,15,16

A 2012 survey conducted by the DIA Adaptive Design Scientific Working Group17 suggests a considerable increase in the use of adaptive design, particularly compared to a previous survey conducted in 2008 (i.e., before the publication of the draft FDA guidance). The survey of 16 biopharma companies and CROs showed more enthusiasm overall for adaptive design within industry and academia, and
in particular an increase in the number of trials using designs described as less well understood in the draft FDA guidance (i.e., typically more complex adaptive designs). The Tufts Center for the Study of Drug Development also showed that, based on a roundtable discussion held in 2013 with 40 senior executives, across the industry simple adaptive designs (such as early stopping due to futility and sample size re-estimations) are used on approximately 20% of clinical trials and that the adoption of adaptive design in the exploratory drug development phase is expected to increase significantly over the next several years.

**Adaptive I-SPY 2 trial models a better research approach**

The potential of adaptive design to advance oncology drug development is evident in the groundbreaking I-SPY 2 screening trial, a collaborative Phase II research platform sponsored by the FDA and used by multiple industry and academic researchers. I-SPY 2 is designed to identify active experimental drugs for breast cancer, together with predictive biomarkers.

I-SPY 2 uses an adaptive design to simultaneously screen Phase II anticancer agents in women with stage 2 or 3 breast cancer at risk for recurrence. Drugs are evaluated by class, using standard and emerging biomarkers to measure their impact on pathologic complete response (pCR), a predictor of disease-free survival. Drugs considered successful in the screening trial are predicted to have an 85 percent likelihood of success in a confirmatory, randomized trial of 300 patients with tumors that have the drug’s identified biomarker signature. The ultimate goal is to evolve a new model to streamline clinical evaluation and accelerate regulatory approval pathways.

The first two “graduates” from the I-SPY 2 trial are veliparib in combination with carboplatin and standard neoadjuvant chemotherapy in the triple-negative breast cancer subset, and neratinib in combination with standard neoadjuvant chemotherapy in HER2+/HR-breast cancer. Details of the clinical results and predictive probability of success are shown in Tables 3 and 4.

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*Source: Reitsma et al.*

**Table 3.** The graduating arm is triple-negative (HER2/HR-) subset with a 93% Bayesian probability of success in a 300-patient Phase III trial.

The graduating arm is triple negative (HER2-/HR-) subset with a 93% Bayesian probability of success in a 300 patient Phase III trial.
The graduating arm is the HER2+/HR- subset with a 78% Bayesian probability of success in a 300 patient Phase III trial. (Reprinted by permission from the American Association for Cancer Research.20)

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<td>92%</td>
<td>44%</td>
</tr>
<tr>
<td>HR+</td>
<td>81%</td>
<td>40%</td>
</tr>
<tr>
<td>HR-</td>
<td>89%</td>
<td>53%</td>
</tr>
<tr>
<td>HER2+</td>
<td>95%</td>
<td>73%</td>
</tr>
<tr>
<td>HER2-</td>
<td>63%</td>
<td>20%</td>
</tr>
<tr>
<td>MP+*</td>
<td>91%</td>
<td>66%</td>
</tr>
<tr>
<td>HR-/HER2-</td>
<td>72%</td>
<td>34%</td>
</tr>
<tr>
<td>HR-/HER2+</td>
<td>94%</td>
<td>78%</td>
</tr>
<tr>
<td>HR+/HER2+</td>
<td>91%</td>
<td>65%</td>
</tr>
<tr>
<td>HR+/HER2-</td>
<td>39%</td>
<td>12%</td>
</tr>
</tbody>
</table>

Source: American Association for Cancer Research20

Table 4. The graduating arm is the HER2+/HR- subset with a 78% Bayesian probability of success in a 300-patient Phase III trial.

Each drug’s Bayesian predictive probability of success is calculated for each unique patient subset until the threshold of 85 percent is met within any given subset. When 85 percent probability of success is reached, the accrual is stopped within this subpopulation and the drug graduates to a separate Phase III trial within the defined subpopulation. While the published probability of Phase III success is greater than 85 percent for veliparib in the triple-negative breast cancer subset, neratinib’s predictive probability of success was 78 percent at the time of publication.

The benefits of the I-SPY 2 trial are illustrated with the graduation of both neratinib and veliparib. Development has been accelerated and focused on the patient population with the greatest probable benefit from treatment with the selected drugs, which leads to the greatest likelihood of success in a pivotal Phase III trial. Interestingly, without participating in this collaborative trial, these agents may have been in competition following traditional drug development pathways with a lower probability of success for each compound in a broader population. Having graduated in unique patient subsets, the compounds are no longer competing for the same patient population. This property of the I-SPY 2 trial enhances the development of multiple novel agents in breast cancer, which is increasingly recognized as consisting of many distinct sup-types of disease.

Conclusion

Regulatory guidance recognizes the value of adaptive design, and emerging research models like I-SPY 2 demonstrate its great value in advancing oncology drug development. It remains for the biopharma industry to implement and advance adaptive design as a fundamental clinical research methodology.
References

With the introduction of mobile health (mHealth) technologies in the field of healthcare, Sponsors and CROs are looking into mHealth to design patient centric clinical trials in order to reduce study visit costs and trial participation burden on patients. Nonetheless, with mHealth at its infancy, Sponsors and CROs at The Partnerships in Clinical Trials Conference expressed their encounters and challenges with the concept and execution of patient centered clinical trials. This article will evaluate concerns with patient centricity, and conceptualize how site-centered clinical trials may address these concerns, particularly with more complex studies.

Patient Centered Clinical Trials: Works for Some, but, Not All
The concept of patient centric clinical trials (also
dubbed siteless trials, remote trials and virtual trials), involves designing study visits in combination with mHealth and telehealth technological capabilities to allow patients to conduct study visits from the convenience of their homes. Subsequently, this convenience can offer benefits to Sponsors, such as reducing study visit costs, and minimizing subject dropout rates.

During a round-table session on this topic led by Kamyar Farahi, Clinical Trials Lead at Janssen, the discussion favored that with the help of telemedicine and virtual technologies, one can potentially reduce the trial visit costs, travel burden to the patient, and potentially improve patient and investigator interactions during the course of a clinical trial.

While this model may work for less complex trials, such as vaccine studies, or trials that require self-administered exams (i.e., mobile blood pressure, mail in blood test kits, urine exams, etc.), the siteless model poses limitations to more complex trials, such as those that require more complex study visit procedures, or study visit procedures that can only be conducted by trained specialists with specialized equipment.

Patient Centric Model: Concerns with Investigators
While siteless models offer benefits towards Sponsors and CROs, study sites are expressing concerns with the model, as principal investigators (PIs) feel they do not have much control over the patient, and they are specifically concerned with accountability (i.e., if a patient is harmed, the PI is ultimately accountable for the patient’s safety). Additionally, with clinical trials being a financially restraining engagement at study sites, siteless models impact study sites, as sites generate less revenue from missing in-person study visits.

The round-table discussion with Farahi also touched on this topic and the consensus was that one of the limitations of site-less clinical trial models could be the impact on the business model of the investigators, but with limited interactions between the patient and the investigator the patients could be less satisfied with his/her participation.

**Breakthroughs in Telemedicine Clinical Research**
In the field of healthcare, advances in telemedicine are reaching new heights with telerobotics, where highly trained specialists are experimenting with conducting complex medical procedures remotely. Dr. Partho Sengupta of The Icahn School of Medicine at Mount Sinai in New York in collaboration with Rush University Medical Center in Chicago recently initiated a breakthrough clinical trial to evaluate remote telerobotic
ultrasound examinations over the Internet. Through his computer in New York, Dr. Sengupta is able to control a robotic ultrasound arm to obtain cardiac echoimages of patients in Chicago.

This capability can be particularly useful in implementing site centric clinical trial models to distribute specialist access to study sites globally. “Launching long-distance, tele-robotic ultrasound exams between two major hospitals in two large cities is a sign that we may be able to make waves in accelerating access to specialists to support global clinical trial site centric models,” said Sengupta.

What’s the Difference between Patient Centricity and Site Centricity?
Patient centricity involves conducting clinical trial study visits and providing study measurements directly from the patient and by the patient in the comfort of their own homes and lives. Telehealth and mobile health (i.e., Fitbit, Apple Watch, Scanadu, etc.) technologies enable patients to report their outcomes directly to study sites and Sponsors.

Site centricity involves the process of engaging patients and conducting study visits in local neighborhood clinics or medical centers and allowing physicians to remotely monitor the patients and collect data via telehealth. For example, Novartis partnered with Walgreens to run a 10,000 patient clinical trial pilot, where Walgreens acted as the study site.

Walgreens recently unveiled its patient recruitment services at the Partnerships in Clinical Trials Conference, and may progress towards acting as remote study sites in clinical trials, especially with its specialty pharmacy division, that wields specialized facilities to handle a wide range of disease indications including oncology, cystic fibrosis, multiple sclerosis, rheumatoid arthritis, transplants, and much more.

Is Site Centricity a More Compatible Model than Patient Centricity?
Patient centric models tend to work best with less complex clinical trials and relatively easy data collection methods. However, this model includes limitations for more complex study procedures that require specialized equipment, and expert medical specialists. Moreover, this model may introduce risks with data quality, as patients may not adhere to study regimens, or required data collection methodologies (i.e., giving up on taking their blood pressure if the device malfunctions on the first round, or if there are too many procedures).

With site centric models, although can be more costly than patient centric models, study teams can rely on local trained healthcare professionals to collect required data according to
study procedures (which may contribute towards enhancing data quality compared to patient centered models), and with the advances of telehealth and telerobotics, study teams can deploy hub and spoke models to execute global studies with fewer PIs/specialists. This method can be less costly and more efficient compared to selecting/initiating numerous academic medical centers/involving several PIs, and might be more acceptable by PIs compared to patient centric models.
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