

## CONFERENCE REPORT

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“The next generation of trial design innovation conference had invited several industry experts, and the focus was to explore strategies, methods and logistical considerations for flexible trial designs at the study, product and portfolio level.”

## The next generation of trial design innovation: strategies, methods and logistical considerations for flexible trial designs

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The US FDA's critical path initiative is a national strategy to drive innovation in the scientific processes, through which medical products are developed, evaluated and manufactured. Launched in 2004, and followed in 2006 by the Critical Path Opportunities List, it lists several areas where technology and systems could improve the accuracy of tests that predict the safety and efficacy of potential medical products. Adaptive clinical trial design is one of the major components of the critical path, and in 2010, the FDA issued its draft Guidelines. The Next Generation of Trial Design Innovation Conference had invited several industry experts, and the focus was to explore strategies, methods and logistical considerations for flexible trial designs at the study, product and portfolio level.

The conference was preceded by a 3-hour workshop attended by approximately half of the conference participants. Terry Katz (Merck Animal Health, NJ, USA) examined several types of commonly used adaptive designs, with an emphasis on operational considerations in efficient execution of adaptive designs. Prospective adaptive trials that most fully meet the critical path by including all adaptive elements in the protocol at the time of trial initiation, were operationally easiest to implement. Katz demonstrated that findings from external sources or interim analyses can result in the need for concurrent adaptations, with a higher complexity to implement, especially if the amended protocol now excludes patients who were enrolled and treated. Retrospective adaptations will not change the study conduct, and are not considered 'adaptive' under the US FDA guideline [101], but can narrow the label claim to target a responding subset if the all-comers study was positive, and the retrospective analysis was prospectively planned under stringent FDA criteria [1]. These principles were carried into an interactive session with ten adaptive case studies covering pneumonia, mastitis and cancer. Five operational considerations were evaluated for each case study:

- What needs to change to implement the adaption (e.g., protocol, Case Report Form, drug supply);
- What costs (increase or decrease) results from the adaption;
- Who needs to approve these adaptations (e.g., internal management, external Institutional Review Board/EC, Independent Data Monitoring Committee, regulatory authorities);
- What advantages are gained for the trial or compounded by implementing the adaptations;

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- What barriers stand in the way of implementation (with time delay as the most common issue).

The attendees proposed solutions on how to convert a conventional design into adaptive for each scenario, and using these five factors, gained the operational perspective that is rarely included as part of the scientific disclosure.

### FDA draft guidance review & impact on the industry

Three waves of government guidance take place after the infancy of adaptive regulation, according to Quin Liu (Janssen R&D [NJ, USA], Johnson and Johnson [NJ, USA]). Early FDA regulation [102] required an agreement between government and sponsor on trial design and size, which is not changed unless “*a substantial scientific issue essential to determining the safety or effectiveness of the drug has been identified after the testing has begun.*” In the mid 1990s, the Code of Federal Regulations was clearer on use of prospective adaptive designs: “*A protocol for a Phase II or III investigation should be designed in such a way that, if the sponsor anticipates that some deviation from the study design may become necessary as the investigation progresses, alternatives or contingencies to provide such deviation are built into the protocols at the outset*” [103]. This induced the first wave of adaptive designs, which included two-stage designs with sample size adjustments and group sequential designs. The second wave, based on theoretical and methodological research, expanded the options, and had support and guidance from the Pharmaceutical Research and Manufacturers of America (Washington, DC, USA) working group, the Committee for Medicinal Products for Human Use (London, UK), and the FDA. Methods, such as adaptive, doubly randomized enrichment designs, dynamic randomization, adaptive error spending functions and adaptive designs with changing populations, were adopted. Frequentist and Bayesian statistical foundations were challenged however, and grass root approaches to innovation pushed for academic, industry and government consensus. As an illustration, Liu quoted a 2004 critique by DR Cox of reluctance by frequentists to accept an error spending rate since they are “*more than just hypothetical concepts used for calibrating measures of uncertainty against performance in idealized situations...In principle it is hard to see an argument at a completely fundamental level*” [2]. Liu concluded that the third wave will occur after 2015, based on a new evidential paradigm.

### Biomarkers & adaptive designs for personalized medicine

Personalized medicine has the goal of selecting the right treatment at the right dose, for the right patient at the

right time, for the right outcome. Prognostic biomarkers are associated with a clinical outcome regardless of treatment received, whereas predictive biomarkers are associated with a clinical outcome in response to a particular treatment. Sandeep Menon (Pfizer Biotherapeutics Research and Boston University, MA, USA) equated individual response to a pharmaceutical to the adage: ‘One man’s food, another man’s poison’ since some patients will benefit without side effects while others will have drug toxicity with no clinical benefit. With personalized medicine, scientific breakthroughs increase our understanding of how each person’s unique molecular and genetic profile makes them susceptible to certain diseases. Using the example of cetuximab and panitumumab, survival benefits were seen in treating late stage colorectal cancer for those patients positive for EGFR (65% of the population was EGFR positive based on immunohistochemistry). When that population was further limited by a second biomarker, KRAS wild-type, an improved clinical outcome occurred. The promise of personalized medicine, according to Menon, is greater therapeutic effect in selected patient populations, decreased development costs, fewer patients treated with ineffective drugs, potentially favorable pricing/reimbursement, larger market share and longer treatment durations. Challenges include defining the selection criteria early in the development, co-development of companion diagnostics, limited prevalence of the targeted population and the complexity of implementing a targeted therapy approach from preclinical to Phase III development. To aid development, Menon presented biomarker-enrichment designs, marker-by-treatment-interaction designs, biomarker-strategy designs, adaptive-threshold designs, adaptive-signature designs and bayesian-adaptive designs.

Stan Kachnowski (Indian Institute of Technology [New Dehli, India]; Healthcare Innovation & Technology Lab, Columbia University [NY, USA], and Royal Society of Medicine, [London, UK]) also emphasized biomarkers in a diffusion segmentation model, but warned that whole genomic mapping yields too many false positives. He advocates broad data access to connect sponsors and regulators to patient electronic health records and academic testing laboratories. This would provide relevant biomarkers for adapting treatment and research, but different platforms and standards adds a sizable challenge to streamlining the process.

R Stephen Porter (VDDI Pharmaceuticals [TN, USA] and Dragon Bio-Consultants [Hong Kong, P.R. China]) referenced Frueh (2008) [3] by reporting that approximately a quarter of all patients, processed by Medco, had been prescribed at least one drug with pharmacogenomic information on the label. He cautioned, however, that not every biomarker that can be

measured is of importance, and not all biomarkers of importance can be measured. Porter looked at traditional sequential development as 'Prescription Roulette' whereas the modern biomarker-based targeted therapy uses diagnostic testing to save money, time and reduce illness. Global regulators, including the State Food and Drug Administration (Beijing, China), as well as FDA and European Medicines Agency, are increasingly receptive to adaptive trials. Traditional Chinese medicine was based on individualized therapies, and the concept of using a scientific marker to parallel traditional medicine, is resulting in rapid uptake of these techniques. Porter also summarized the BATTLE and ISPY screening platforms to study marker signatures and tailor therapeutics.

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### **Designing an adaptive strategy at the portfolio level**

While most adaptive strategies are focused on an individual trial, expanding the concept to the portfolio level could further streamline the development process. Benefits would be to access more opportunities by focusing on responding patients and assessing more assets concurrently, rather than consecutively. This enables one drug, in a preplanned adaptive manner, to be explored over multiple potential indications or multiple drugs over a single indication or multiple drugs over multiple sub-populations. Vlad Dragalin and Sarah Arbe-Barnes (Aptiv Solutions, VA, USA) proposed a model-based drug development to use internal and external sources to inform strategy, trial design and decision making. Capitalizing on simulations, models are built to simultaneously look at the effects of patient, disease, therapeutics and design to make portfolio go/no-go decisions to select a drug or indication. Case studies were shown for a pick-the-winner strategy among multiple indications for a single compound, based on likelihood of success and size of market, and multiple drugs for a single indication based on the ability to apply adaptive trials with a clear end point and gaining of marketing authorization. A multiple-compound example was shown for an Alzheimer's indication using an iterative drop-the-loser-arm adaption during interim analyses of a multicenter study using a single common comparator.

Alternatively, simulations of the portfolio can be based on the financial value of a product or portfolio. Using expected net present value, which considers cost, revenues and risk, Zoran Antonijevic (Cytel, MA, USA) presented case examples to maximize profit at the portfolio level. Factors included in the simulations included proof-of-concept criteria, optimal sample size for Phase II and III, and futility boundaries in Phase III. One illustration used multiple compounds/trials with their respective sample size and probability of success,

and trial selection was based on maximized expected net present value, within a predefined budget. This was contrasted to an innovative simulation, where all trials started with no patients allocated, and the incremental benefit was calculated for each patient added to each trial, and repeated until the portfolio budget was consumed, resulting in funding for the best trial(s).

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### **Strategies for medical device flexible trial designs**

Adaptive designs are not limited to pharmaceuticals and biologicals, and can equally be applied to clinical trials for medical devices. Roseann White (Abbott, IL, USA) stated that the Center for Devices and Radiological Health (CDRH) is comfortable with Bayesian adaptive trials, although they can be labor intensive for the FDA, as well as the sponsor. CDRH is typically satisfied with a single confirmatory study while the Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research prefer two studies. Sample sizes are typically smaller than pharmaceutical trials, and while masked studies are used, sham controls are rare. Instead of Phase I, II and III monikers, device trials are typically labeled as first-in-man, feasibility, and pivotal. Investigational device exemption is the device equivalent to an investigational new drug application, and noninferiority trials are common. White presented Abbott's successful 2004 randomized clinical trial of drug-eluting stents versus an active control, allowing two lesions to be simultaneously treated in one patient, and using two co-primary end points with tight non-inferiority margins. When the trial's surrogate end point was questioned, Abbott moved into an adaptive sample size re-estimation to ensure the primary end point could stand alone. Since the enrollment would be complete before the first patient reached the end point, the FDA asked for a registry, but Abbott proposed expanding the clinical trial with only one stratum fully meeting a widened inclusion/exclusion criteria. The interim analysis and adaption was conducted by an independent third party, who found no additional patients were needed to maintain the 80% conditional power, and the results were ultimately statistically significant in favor of noninferiority.

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### **Utilizing Bayesian statistics in clinical development**

Bayesian statistics hold great promise in clinical trials, with a higher efficiency than frequentist designs based on incorporating prior study information. After data are collected, the parameter distributions are updated and credible intervals are calculated. A key benefit to adaptive Bayesian studies, as discussed by Jeff Palmer (Genzyme, MA, USA), is that inference is not affected

by interim analysis, whereas inference adjustment (alpha spending) is required with frequentist methods. Using Bayesian methods, response-adaptive randomization, enrichment and stopping rules can be added to the trial design. Use of predictive probabilities to forecast future trial outcome(s) is particularly useful for trial monitoring purposes. Bayesian methods are still not mainstream, and regulatory agencies including the Center for Drug Evaluation and Research, and Center for Biologics Evaluation and Research are slow to uptake for confirmatory trials. The CDRH, however, has issued a guideline that supports Bayesian application to medical device trials where there exists prior evidence for a control arm. A critical assumption of Bayesian is that the use of prior information assumes that historical subjects are exchangeable with subjects in the current trial. Palmer presented a simulation of a binomial variable using a Frequentist sample size calculation, and the corresponding smaller sample size of the same trial using Bayesian, with futility bounds recalculated after each cohort, under a variety of true response rates. This lead to a response adaptive randomization where one modifies the randomization probabilities for subsequent cohorts based on posterior (predictive) probability that one treatment is better than the other. In a two-stage Phase I oncology example, Palmer showed how the maximum tolerated dose defined in stage 1 could be revised in stage 2 by continuing to monitor dose limiting toxicities, and then

dose-escalate/de-escalate as the toxicity data become available according to a predefined Bayesian decision criteria look-up table. He cautioned that this approach was strong for safety, but not for efficacy dose selection.

## Conclusion

The next generation of trial design innovation brought together experts supporting pharmaceutical and medical device clinical trials in the USA and globally, with a drive to reduce development costs and time by efficiently using adaptive trial methods. Many of the presentations combined adaptive methods with other developing techniques, such as genomic biomarkers and Bayesian statistical methods, to better determine the right product for the right patient for the right condition. Defining the population most likely to respond during development improves the likelihood of a positive outcome by the general population, when they are prescribed the product.

## Financial & competing interests disclosure

*The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.*

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