

# Advancing clinical development through innovative trial design

The application of platform, enrichment and adaptive designs can deliver innovative therapies to patients, faster and more efficiently.

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As part of their initiative, according to an October 2022 update, FDA had accepted five meeting requests for participation in their pilot program.<sup>5</sup> FDA is now planning a follow-up public meeting on Advancing the Use of Complex Innovative Designs in Clinical Trials: “From Pilot to Practice” to be held on March 5, 2024.

### **The European Commission, the Heads of Medicines Agencies, and the European Medicines Agency (EMA)**


The European Commission, the Heads of Medicines Agencies, and the European Medicines Agency (EMA) have also introduced an initiative referred to as Accelerating Clinical Trials in the EU (ACT EU). This project aims to transform how clinical trials are initiated, designed, and run in Europe, bringing together regulators and other stakeholders (patients, academia, Health Technology Assessment bodies and payers). The plan for 2023 includes establishing a process to support academic sponsors in enabling large multinational clinical trials, setting up systems for dialogues between key stakeholders, revision of guidelines, and facilitating innovation in clinical trial methods by publishing guidance and roadmaps.<sup>6</sup>

### **Intense and intelligent planning**

Intensive and intelligent planning as well as close interaction with the regulatory agencies is essential in the design and successful execution of complex innovative trials; defined by FDA as those that “have rarely or never been used to date to provide substantial evidence of effectiveness in new drug or biologics license applications” and that “represent a deviation from the traditional clinical design”.<sup>5</sup> Innovative trials in focus for this paper include platform, enrichment, and adaptive designs with examples of their application. Use of Real-World Data and External Control Arms represent other important approaches to drug development and will be discussed in separate articles.

## **>>> Platform trials**

Platform trials or master protocols include the investigation of multiple products or different patient populations within a single trial and can also allow for new treatment arms to be added over time. Platform trials played a key role in rapidly identifying effective therapies for treating COVID-19.<sup>7</sup> Between 2001 and 2019, only sixteen platform trials were initiated globally, whereas in just over a year, between January 2020 and May 2021, 58 COVID-19 platform trials were globally registered. An adaptive platform trial known as RECOVERY studied different treatments in parallel in hospitalized COVID-19 patients and identified four treatments (dexamethasone, tocilizumab, baricitinib and a monoclonal antibody combination) that were effective for severe COVID-19. The trial has recruited close to 50,000 patients to date and is currently testing COVID-19 patients requiring mechanical ventilation. It has expanded to include oseltamivir, baloxavir and low-dose corticosteroids in treating influenza.<sup>8</sup>



Platform trials have also been applied in oncology, but not yet for registration purposes. Our growing understanding of biology has created new opportunities for endpoint selection. In cancer, what was believed to be one tumor type has fragmented into multiple types bearing different combinations of mutations. Conversely, what were considered different tumor types may contain the same target mutation. This has given rise to new approaches of umbrella and basket designs.

### **Basket trials**

Basket trials are a type of platform trial that assesses drugs targeting a common pan-cancer gene defect, regardless of tissue origin. Basket trials have been, or are being adopted for dozens of products.<sup>9,10,11,12</sup> Pembrolizumab was the first product to gain tumor-agnostic FDA approval, this was in mismatch repair deficiency/microsatellite instability-high (dMMR/MSI-H) tumors and was based on five single-arm trials.<sup>13</sup> Other examples include larotrectinib based on three trials (LOXO-TRK-14001, SCOUT, and NAVIGATE)<sup>14</sup> and entrectinib<sup>15</sup> in tumors harboring NTRK. Limitations of basket trials include identifying the target mutation, resistance to targeted therapies, and recruiting adequate patients, particularly for rare tumor types.

### **Umbrella trials**


Umbrella trials evaluate multiple treatments in different genomic/biomarker subsets for a single histology. The umbrella design requires development of multiple assays to identify patients for the appropriate treatment arm. Successfully conducted umbrella trials include the Lung Cancer Master Protocol (Lung-MAP) which applied a 200-gene molecular profiling assay to match patients to sub-studies. Treatments were added or removed depending on performance.<sup>16</sup> Other examples are the Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial (ALCHEMIST)<sup>17</sup>, and I-SPY-2<sup>18</sup> and plasmaMATCH, both in patients with breast cancer.<sup>19,20</sup> Umbrella and basket approaches have unexplored utility outside oncology. For example, the effect of an immunosuppressive agent could be evaluated across multiple autoimmune diseases in a single study or an anti-infective trialed against multiple infectious organisms that generate a similar disease profile e.g., urinary tract or respiratory tract infections where treatment may need to commence before the infectious agent is identified.

## »»» Enrichment designs

Enrichment trials apply selection criteria to maximize the probability of success; they can take a standard approach or an adaptive approach, as discussed in the next section. In fact, all trials apply some degree of enrichment as part of their selection criteria. An enrichment study takes this concept a step further by applying more stringent criteria in patient selection to maximize the probability of success with a limited sample size. The main drawback with the use of enrichment strategies relates to the generalizability and applicability of the study results. If the criteria applied are too restrictive, this may translate into a more restrictive label.

FDA have published a guideline on enrichment designs<sup>21</sup> which outlines three broad approaches in which enrichment strategies might be applied. The first approach focuses on decreasing variability by either using baseline assessments within a narrow range, biomarkers as inclusion criteria, or eliminating placebo responders during a run-in phase. The second approach utilizes the patient's history to inform the prognosis or frequency of prior events or exacerbations to maximize the placebo event rate or symptom severity. The third approach is to apply predictive markers to select patients most likely to require therapy or to respond to that therapy, which is now common in oncology and requires the availability of a companion diagnostic. Variability can also be controlled by requiring consistent baseline values (e.g., for blood pressure measurements, treadmill exercise tests, pulmonary function tests, or patient-reported outcome measures) during the run-in period.

**Application of an adaptive design can provide flexibility and a faster path for new therapeutic agents to reach patients and allow for better dose optimization, better definition of the target population while also having ethical appeal, as they can minimize the number of participants exposed to ineffective or toxic doses.**



An interesting early enrichment approach used to maximize compliance was applied in the Veterans Administration Cooperative hypertension studies started at the end of the 1960s. During the run-in period, patients were given placebo tablets containing riboflavin and the trial randomized only patients whose urine tested positive for riboflavin on two consecutive visits.<sup>22</sup>

Enrichment can also occur according to set rules, post-randomization. This approach is prominent in selecting patients who benefit most from therapy, e.g., PD-L1 positive vs all comers or a subgroup meeting specific criteria to define positivity. Antibacterial drugs need to be evaluated in patients infected with an organism sensitive to the test treatment. It often takes several days to identify the pathogen, but it is important to commence therapy immediately. Consequently, patients are randomized before the diagnostic laboratory results are available, but the primary data set includes only patients testing positive for the sensitive organism.

## »»» Adaptive trials<sup>23</sup>

FDA guidance defines an adaptive trial as one that allows for prospectively planned modifications to one or more aspects of the design based on accumulating data from patients in the trial.<sup>2</sup> Application of an adaptive design can provide flexibility and a faster path for new therapeutic agents to reach patients and allow for better dose optimization, better definition of the target population while also having ethical appeal, as they can minimize the number of participants exposed to ineffective or toxic doses.

Adaptive designs can be applied across all phases of clinical research. During early development, they have great utility in dose ranging and selection. Group-sequential designs with stopping rules for futility or early efficacy demonstration have been accepted for decades in pivotal studies, while the more radical adaptive designs are currently mostly accepted only for early phase proof of concept trials; however regulatory agencies may accept these designs if satisfied that adequate safeguards are in place to account for potential bias and ensure safety of patients throughout.

### **Designing an adaptive trial**

The pace of uptake of adaptive designs in clinical research has remained limited, despite their advantages. This is mainly because regulators often remain reluctant to accept them, concerned that in some cases, knowledge of accumulating data can affect the course and conduct of a trial, and the behavior of its sponsor, investigators, and participants, in ways that are difficult to predict and impossible to adjust for. Careful consideration is needed in the design and conduct of adaptive trials to limit the potential for erroneous conclusions.

Guarding against bias is of key importance, particularly when data are unblinded during the study. Unblinding data for interim analyses requires a blinded and unblinded team separated by a firewall, with an unblinded Independent Data Monitoring Committee (IDMC) reviewing unblinded interim analysis results and making recommendations for trial adaptations to the sponsor. Also, regulators will need to be convinced, (e.g., by separate analysis of data obtained before and after an adaptation has been implemented) that any mid-trial adaptations do not introduce biases that impact the trial outcome.

For complex adaptive designs, simulations may be needed to ensure that planned adaptations do not introduce bias. In addition, detailed planning is required with respect to trial supply logistics, maintenance of blinding, avoidance of confounding influences and reacting to advice from the unblinded IDMC. These plans should describe the processes intended to control access to information and to document access throughout the trial and be discussed and agreed with the regulatory agencies.

Alongside efficacy, clinical trials also need to address safety. When stopping a trial early for efficacy following interim analysis, it is important to ensure that adequate safety data are also available. The Rotavirus Efficacy and Safety Trial (REST) was a group sequential trial designed specifically to evaluate safety in terms of the risk of intussusception, a serious gastrointestinal condition. Up to 100,000 infants were planned to be recruited, of whom only a subset was used for efficacy evaluation. Following interim analysis, the primary endpoint was met at about 70,000 infants and the trial was stopped, making it one of the largest vaccine trials ever conducted.<sup>24</sup>

### **Blinded sample size re-estimation**

The simplest adaptation approach involves blinded sample size re-estimation, based on checking that the actual interim variability aligns with the initially assumed variability used for power calculation, and increasing the sample size to maintain the desired power if variability is higher than anticipated. This approach does not impact sample size and is a valuable mechanism against under powering a study.

### **Group sequential designs**

Group sequential designs are the most well-accepted unblinded approach. Here adjustment can be made based on the results of interim analyses. The simplest designs allow for termination due to futility or sample size re-estimation if the underlying event rate or observed effect size differ from the initial assumptions. Such adaptations, if implemented correctly, do not impact the type-I-error (false-positive) rate. However, if early stopping for efficacy is allowed, there needs to be an adjustment of alpha both at interim and final analysis by an alpha-spending function; typically, a higher bar (smaller nominal alpha) is set for early stopping as compared to the final analysis. Such an approach was applied in the development of the Pfizer COVID-19 vaccine<sup>25</sup> and we frequently recommend this approach, even for late-stage trials.

## Dose selection

Dose selection is an important objective of phase 1 studies, and adaptive model-based designs are gaining in acceptance by both industry and regulators alike. In model-based designs, dose-escalation is guided by modelling the dose-toxicity relationship. Toxicity data from all explored doses including data from previous trials (if available) are fed into the model to estimate the toxicity rate at each dose-level. In model-based designs, the recommended phase 2 dose (RP2D) is defined as the dose that induces toxicity at the pre-defined target toxicity rate (mostly set to 10-33 %). Simulations have shown that model-based designs perform better, faster and are safer to establish the RP2D than rule-based designs. Van Brummelen EM et. al. reviewed 172 trials that had been published over the previous two years and showed a non-significant but clinically relevant reduction in trial duration and the need to treat, fewer patients at dose-levels below the RP2D (31 % versus 40 %;  $p = 0.73$ ) while safety was preserved (13 % DLTs versus 14 % DLTs).<sup>26</sup>

## Other types of adaptation

Further types of adaptation include dropping a treatment arm or changing the randomization ratio against less effective or more poorly tolerated treatments or doses, or less responsive patient groups selected by phenotype or biomarker. Such an approach was taken by the SLEek phase 2 study. Three hundred and forty-one (341) patients undergoing standard lupus therapy were randomized to receive one of four treatments or placebo. After a planned interim analysis when 50 percent of patients reached week 24 or withdrew, 205 patients continued to week 48. Based on the results, upadacitinib 30mg is advancing to phase 3.<sup>27</sup>

## More complex designs

A more complex dose ranging approach was discussed with FDA as part of their 2018 initiative and has been published in anonymized form. This phase 2 study, also in systemic lupus erythematosus (SLE) was similar in intent to the SLEek study but includes additional innovative features such as an adaptive rule to allow for the possibility of changing the primary endpoint and the pooling of data from different dose groups. The study also applied Bayesian and response adaptive randomization methods to modify randomization dose allocation probabilities while retaining fixed randomization to the placebo arm. The sponsor conducted simulations to assess the operating characteristics of the proposed model under different true dose-response relationships and under a multidimensional range of plausible values for the nuisance parameters. To facilitate evaluation the number of adaptations was reduced by dropping primary endpoint adaptation and by fixing the lag time between data cut-off and the time of adaptation.<sup>28</sup>




## Multi-arm multi-stage design

The multi-arm multi-stage design is an approach that can be used to explore multiple treatments, doses, durations or combinations with options to ‘drop losers’ or ‘select winners’ early. Generally, this approach introduces selection bias into a standard final analysis. A workaround is to use a non-related endpoint for selection during the interim analyses and a clinically relevant endpoint for the confirmatory analyses. An example might be a pharmacodynamic response used for dose selection and symptomatic disease incidence as the confirmatory endpoint. Such an approach was used and accepted by FDA in the development of a vaccine against human papilloma virus where different endpoints were used in phase 3 following interim analyses at end of phase 2; this allowed for adding the phase 2 patients to the phase 3 population.<sup>29</sup>

Changing the randomization ratio allows more patients to receive the effective treatment or a more optimal dose. This has been used to identify promising treatments applying a platform approach or for dose selection and may apply conventional or Bayesian statistics. Kaizer et al. proposed a platform design with adaptive randomization and information borrowing through Bayesian hierarchical modeling with a multi-source exchangeability method and illustrated their design using the PREVAIL II Ebola trial.<sup>30</sup> The PREVAIL II master protocol allowed for the rapid evaluation of multiple candidate treatments with a “Barely Bayesian” design. Within a segment, PREVAIL II used frequent interim monitoring in the Bayesian paradigm to allow early termination when a treatment provided a substantial survival benefit over the standard of care. The authors proposed that power could be improved by as much as 51% with limited type-I error inflation and allow for more patients to be randomized to the experimental regimens by incorporating non-contemporaneous standard of care control data from prior segments into the analyses.

The I-SPY-2 (Therapeutic Response with Imaging and Molecular Analysis) trial is an example that includes multiple treatment arms concurrently evaluating the efficacy of standard neoadjuvant chemotherapies in combination with innovative drugs compared to standard treatment alone. Ineffective treatments were dropped, and new investigational arms were added as new data became available. Pembrolizumab was one of the products added to the treatment of patients with triple-negative breast cancer and resulted in a 3-fold increase in pathologic complete response rates (60% vs. 22%) compared to standard therapy alone.<sup>31</sup> This approach therefore has great utility in bringing novel therapies to patients early.

Adaptive trials have also proved extremely important in identifying treatments for COVID-19. Vanderbeek et al.<sup>7</sup> identified COVID-19 platform trials globally registered between January 2020 and May 2021. Forty-nine trials (84%) explicitly report adaptive features like sample size re-estimation, and 21 trials (36%) state Bayesian methods.



It is also feasible to apply an adaptive strategy to select the primary endpoint, which can be achieved in many ways. In some cases, it may not be clear which represents the most responsive endpoint to therapy, and this can be addressed in a seamless adaptive trial where several key secondary endpoints are included alongside an initially preferred primary endpoint. Following interim analysis, the primary endpoint could be switched to one of the key secondary endpoints, although the sample size would then need to be increased to include only patients recruited after the endpoint was changed or to accommodate a higher level of confidence. An alternative may be a hierarchical approach involving for example applying requirements first for partial recovery, and if met for full recovery.

In general, the same principles apply to Bayesian adaptive designs as to adaptive designs without Bayesian features. One common feature of many Bayesian adaptive designs is the use of simulations to estimate trial operating characteristics like rate of false-positive or rate of true-positive conclusions. Because many Bayesian methods themselves rely on extensive computations (Markov chain Monte Carlo (MCMC) methods and other techniques), trial simulations can be particularly resource-intensive for Bayesian adaptive designs.

It should also be noted that adaptive designs impact analysis of secondary endpoints, as most secondary endpoints correlate with the primary endpoint. Without adjustment, secondary endpoint results must be interpreted cautiously. For group sequential approaches, methods exist to adjust secondary endpoint analyses for adaptation.<sup>32</sup>

## »»» Conclusion

Complex clinical trials offer opportunities for innovative approaches to accelerate delivery of novel treatments to patients, but to date have had limited application. Intensive and intelligent planning as well as close interaction with the regulatory agencies offer greater potential for their adoption.

Platform trials have proved highly successful, particularly during the COVID-19 pandemic but have far wider application if an infrastructure to support multi-sponsored trials were further developed. Umbrella and basket trials are used in oncology, albeit not yet to support regulatory approvals. They have potential in other therapeutic areas as well, across multiple autoimmune diseases or for an anti-infective trial against multiple infectious organisms, for example.

Enrichment trials, although not a novel concept, also have an important role in accelerating drug development by applying narrow, well-considered selection criteria to maximize the probability of success.

**Other applications**

Adaptive clinical trials represent an important mechanism for optimizing drug development. They are particularly useful in early development and in optimizing dose levels. With meticulous planning and discussion with regulators, adaptive trials could benefit late phase clinical development too. To apply complex adaptive trials in late phase, it is essential to present a thoroughly researched position to the regulators addressing all potential concerns while highlighting the benefits from an operational and ethical perspective.

Complex and innovative trials have played a key but limited role in medical research. They represent an important approach to meet the challenges of drug development in a changing landscape, with the promise of more receptive regulatory thinking coupled with increasing experience in the application of adaptive approaches. With careful planning and well-researched justification, innovative trials could become more widely accepted, bringing therapies to patients faster and more efficiently.

**Adaptive clinical trials represent an important mechanism for optimizing drug development.**



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