ADAPTIVE DESIGNS AND ORPHAN DISEASES: BUILDING A BRIDGE OF INNOVATION

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Adaptive Designs: The Moment is Now

Adaptive study designs (ASD) are increasingly vetted for use across a wide range of therapeutic indications, particularly for orphan disease indications. The resurgence of interest in innovative trial methodology is born from the need for efficient and informed program development suitable for investigation of unique products, in unique indications, in which benefits associated with traditional trial methodology are not applicable.

Many orphan diseases have pathways that result in diverse expressions of pathology, requiring multiple assessments for comprehensive evaluation of interventional products targeting orphan disease pathology. For example, dose response relationships are often uncertain; differences in genetic and phenotypic expression must be accounted for in small patient samples; and unlike many traditional indications, there is little opportunity to replicate study results, given the small populations of patients that are frequently affected. Additionally, these diseases often impact children, many times with devastating consequences. Thus, efficient and informed product evaluation, which nevertheless adheres to good standards of methodological rigor, becomes a mandatory asset.

Herein lies the promise of ASDs, which allow for greater flexibility in product evaluation and shorter overall program development timelines, while still achieving the highest scientific integrity under a sanctioned regulatory umbrella. Representative ASDs are depicted in the sidebar. Furthermore, as interest has increased in ASDs so too has knowledge of how to execute these programs, which by definition are frequently associated with operational complexity because of the many adaptations that ensue.

Combining Adaptive Design Models Represents Next Frontier in Clinical Trial Design Innovation

For example, the 2010 FDA guidance on ASDs classified designs into "generally well-understood adaptive designs with valid approaches to implementation" or "adaptive study designs whose properties are less well-understood" (see notes in sidebar). This demarcation reflected uncertainty within the biostatistical and regulatory community regarding methods of analysis and interpretation, but in many respects, it also mimicked the operational challenges attendant to many of these designs. However, though not yet reflected in updated regulatory guidance, these design permutations were discussed at the Adaptive Clinical Trial Symposium, March 22-23, 2018, in Philadelphia, with attendees noting that most are now considered "well-understood" by the field, including biostatistical reviewers at the FDA, and that the challenge now is how best to combine these models for even greater innovation in ASD designs.

WELL-UNDERSTOOD ADAPTIVE DESIGNS

- Adaptation of Study Eligibility Criteria Based on Analyses of Pretreatment (Baseline) Data
- Adaptations to Maintain Study Power Based on Blinded Interim Analyses of Aggregate Data
- Adaptations Based on Interim Results of an Outcome Unrelated to Efficacy
- Adaptations Using Group Sequential Methods and Unblinded Analyses for Early Study
- Termination Because of Either Lack of Benefit or Demonstrated Efficacy
- Adaptations in the Data Analysis Plan Not Dependent on Within-Study, Between-Group Outcome Differences

LESS WELL-UNDERSTOOD ADAPTIVE DESIGNS

- 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 End Point Selection Based on Interim Estimate of Treatment
- Adaptation of Multiple-Study Design Features in a Single Study
- Adaptations in Non-Inferiority Studies

Note: Adaptive study designs described as "Well-Understood" or "Less Well-Understood" in the 2010 FDA Draft Guidance (Guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics. (DRAFT GUIDANCE). February 2010).

Case Studies: ASD Development in Orphan Disease Program

Within the last 12 months, Worldwide has been instrumental in the design of five ASDs, which all have a two-stage component permitting adaptation in dose (dropping uninformative dosages) or eligibility criteria (shaping eligibility criteria to enhance inclusion of more patients with likely response). These designs have occurred in orphan indications within central nervous system disorders, hematological disorders, and rheumatologic conditions. Notably, none of the studies were in oncology, a therapeutic area that has pioneered the use of these designs, an observation reflecting the breakthrough occurring across therapeutic areas that now routinely exploit these approaches.

"Building the Bridge Slowly to Cross it Quickly"

For all programs, both traditional (phase I, II, and III studies) and adaptive design (seamless phase II/III designs) were vetted for feasibility, highlighting costs, timelines, impact on patient recruitment and retention, sensitivity of proximal and distal end points, and corporate goals. These factors required extensive discussion between various stakeholders (sponsor, trial feasibility specialists, KOLs, operation specialists, statistical experts) to develop an extensive "pro" and "con" assessment for each program, highlighted in the list below.

Although there are many permutations, all designs that have been utilized by Worldwide have used a two-stage, inferentially or operationally seamless phase II/III approach. The two-stage design optimizes the treatment dose selection process, as well as allows for determination of clinical efficacy within one protocol (Stage 1 - dose optimization/safety; Stage 2 - determination of efficacy/safety), thus addressing the requirement for dose selection and efficacy in a small sample of patients. Additionally, as uninformative doses are discontinued early during the trial based upon accruing efficacy and safety data, more patients are exposed to a potentially optimal dose compared to alternative approaches.

Academic, Sponsor, CRO Collaboration

Because of its complexity, the ASD process includes team members who must be familiar with the pharmacological attributes of the investigational agent (sponsors); biostatistical staff (implications of using an inferentially seamless vs. operationally seamless design); scientific and medical input (identification of interim biomarkers/end points with KOL interface); operations team (trial execution, organization of stages); clinical assessment technologies (identification of relevant end points); and members from bids and proposals (budgets, timelines). Although team composition is constant, leadership within each ASD process will change contingent upon the phase of development and study objectives. Thus, the process of ASD development is ultimately one of adjudication in which the needs of different stakeholders merge into a coherent concept, ideally suited to orphan indications and the innovative technology to treat them.

ADVANTAGES

- Program efficiency
- Stages can be different lengths, different measures
- Interim informative (business, clinical, statistical)
- Dose selected based on interim data
- More patients on optimal dose
- Fewer total patients
- Dose Exposure Response descriptively addressed
- Gated exposure; minimizes risk
- Potentially pivotal

DISADVANTAGES

- Less precedent
- Requires FDA regulatory vetting as not traditional
- Trial simulations and conduct before implementation
- Interim based upon clinical > biostatistical contrasts
- Limited formal dose ranging information
- Operationally more complex (but seamless to centers)