Overview of Adaptive Design Methodology

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Adaptive Design: Definition

Adaptive Design is defined as a *multistage* study design that uses *accumulating data* to decide how to modify aspects of the study without undermining the *validity* and *integrity* of the trial.

### Validity
- Providing correct statistical inference:
  - Adjusted p-values, estimates, confidence intervals
- Providing convincing results to a broader scientific community
- Minimizing statistical bias

### Integrity
- Preplanning based on intended adaptations
- Maintaining confidentiality of data
- Assuring consistency between different stages of the study
- Minimizing operational bias

Aspects of the Study to be Modified

- Number of Subjects
- Study Duration
- Endpoint Selection
- Treatment Duration
- Patient Population
- Number of Treatments
- Randomization Ratio
- Number of Interim Analyses
- Hypotheses

- Combining Conventional Phases in a Single Trial
  - Seamless Phase I/II
  - MAD and POC
  - POC and ADRS (Adaptive Dose Ranging Studies)
  - Seamless Phase II/III
  - Population finder
  - Indication Finder
  - Compound Finder
Drivers for Conducting ACTs

- To make earlier go--no go decisions: 43% (single top reason) 74% (top reason)
- Faster to market/commercialization: 14% 45%
- More focused resources on trial arms that demonstrate efficacy: 10% 40%
- Higher likelihood of candidate success: 9% 38%
- Shorter trials, time savings in general: 8% 45%
- Avoid underpowered/overpowered studies: 6% 28%
- Lower overall development costs: 5% 42%
- Smaller trials in general: 2% 32%
- To provide better clinical care, fewer patients, fewer adverse events: 2% 19%
- Integral to personalized medicine approach: 2% 18%

Source: Industry Standard Research, 2012
Benefits of Adaptive Design

• Opportunity to calibrate initial assumptions used at trial design stage by undertaking an interim analysis and implementing one or more pre-planned adaptations

• Improved efficiency vs. conventional (non-adaptive) designs
  – Faster and less expensive (sometimes)
  – More information for same investment (always)

• Improved understanding of treatment effect
  – Dose-response
  – End-points
  – Subgroup effects

• Increased likelihood of success or reliable early termination

• Smarter product development decision-making

• Ethical Imperative – Adaptive Trials Put Patients First
Perceptions vs Reality

- **Adaptive designs**
  - will **NOT** make drugs/medical devices work, which don’t work
  - are **NOT** a panacea for everything
  - can early on redirect our attention to promising assets
  - can increase the “**information value**” per **$$ invested**
    (in a resource constrained environment)
  - are an “enabler” for
    - team-building and integrating processes (discovery, clinical, biostatistics, IT, regulatory, project management, clinical operations, marketing)
    - earlier and better planning, decision-making
    - simulation guided clinical drug development
### Types of Adaptive Design: Learn

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<th>Design Type</th>
<th>Description</th>
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| **First-in Human**   | • Single ascending dose escalation designs  
                        • Up-and-Down and CRM to find MTD  
                        • Establish Proof-of-Mechanism or Proof-of-Target Modulation |
| **Seamless Phase I/II Design** | • SAD or MAD combined with Biomarker-based Efficacy  
                                 • To identify the Optimal Safe Dose |
| **MAD and PoC**      | • Two-stage adaptive approach in patients  
                        • 1\textsuperscript{st} stage – to identify MTD  
                        • 2\textsuperscript{nd} stage – to select dose and exposure levels (necessary cond.) |
| **PoC and ADRS**     | • Start with the highest feasible tolerated dose and placebo  
                        • If a pre-specified futility condition is satisfied \(\Rightarrow\) stop  
                        • Otherwise, open enrollment to lower doses |
| **Adaptive Dose Ranging Design** | • Finding a target dose (MED, EDp)  
                                    • Response Adaptive Allocation  
                                    • Covariate Adjusted Response Adaptive Allocation |

**Abbreviations:**
- **CRM:** Continual Reassessment Method
- **MTD:** Maximum Tolerated Dose
- **MAD:** Multiple Ascending Dose
- **SAD:** Single Ascending Dose
- **MED:** Minimum Effective Dose
- **EDp:** Dose achieving 100p% of maximum effect
Types of Adaptive Design: Confirm

- **Sample Size Reassessment**
  - Sample size adjustment based on blinded or unblinded data:
    - Using nuisance parameter estimate
    - Using treatment effect estimate

- **Adaptive Group Sequential Design**
  - Early stopping for efficacy, futility, harm or safety
  - Adjusting the number and/or timing of interim analyses
  - Increasing the maximum sample size

- **Seamless Phase II/III Design**
  - Design combining the objectives of Phase II dose ranging study and confirmatory Phase III trial in a single protocol
  - Dose selection at the interim analysis

- **Population Enrichment Design**
  - Placebo run-in; Active control run-in; Dose titration
  - Adaptively enrich the population at the interim analysis
  - Enrich based on biomarker or clinical endpoint response

- **Drugs with Companion Diagnostics**
  - Marker by Treatment Design
  - Targeted Design
  - Marker x TRT Design with Response adaptive allocation within strata
Current Use and Future Growth

Source: Industry Standard Research, 2012
Seamless Adaptive Designs

• **Seamless AD** - adaptive design, applied on the program level of a compound that achieves efficiency by combining in a single trial, objectives that are usually addressed in two separate conventional studies

• Such a strategy provides the obvious benefit of
  - reducing the timeline by running the two studies seamlessly
  - under a single protocol, with the same clinical team, the same centers and
  - achieves trial efficiency by combining the information from subjects in both studies in the final analysis
Types of More Complex Adaptive Designs

- **Population Finder**
  - The fixed aspect of the trial is the indication (e.g., breast cancer) and the treatment (e.g., epidermal growth factor receptor inhibitor)
  - The design aims to establish which subset of the population benefits most

- **Indication Finder**
  - The fixed aspect of the trial is the compound
  - The competing options are different indications
  - The design aims to establish which of the indications show therapeutic benefit

- **Compound Finder**
  - The competing options are several different compounds for the same indication.
  - The design aims to identify the compound with the most impressive therapeutic index

- **Compound / Population Finder**
  - Multiple development candidates are assessed in parallel and matched with biomarker signatures of different subpopulations
  - The design aims to dynamically change the allocation of new patients with a given signature to different compounds
Summary

• Adaptive designs offer much more than just sample size re-estimation and early stopping, especially in exploratory phase

• Adaptive designs assist and enhance the decision on which product to develop

• Adaptive designs enable more effective decision-making throughout the whole development process

• The adoption of an adaptive design strategy across the drug development process brings a number of important benefits:
  - increased R&D efficiency,
  - increased R&D productivity,
  - increased probability of success at phase III