

Adaptive Designs Classification and Taxonomy

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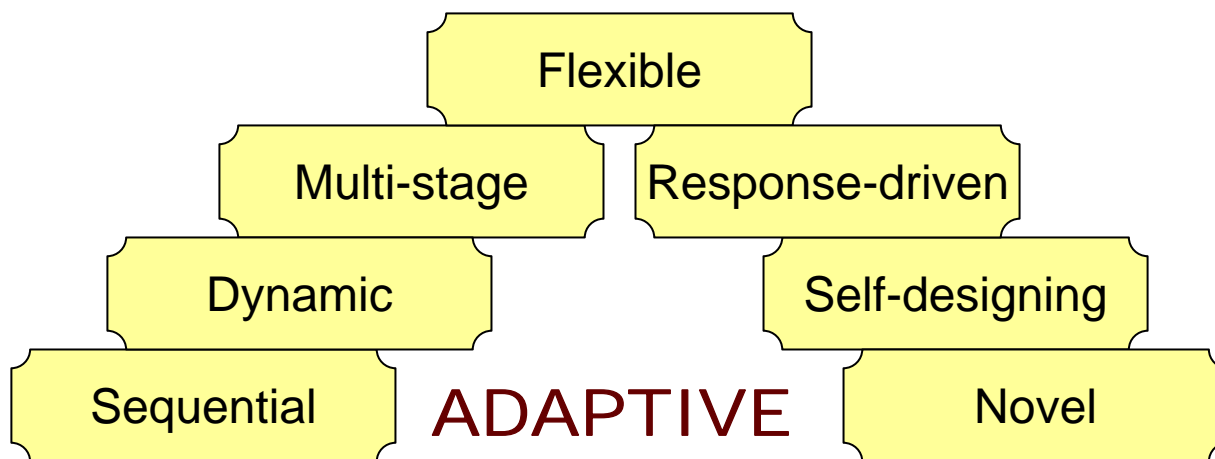
Global Biostatistics & Programming

Wyeth
Research

Outline

- Definition of adaptive designs
- General structure
- Classification of adaptive designs in drug development
- Achieving the goals

What are Adaptive Designs?



- An adaptive design should be adaptive by "design" not an *ad hoc* change of the trial conduct and analysis
- Adaptation is a design feature, not a remedy for poor planning

What are Adaptive Designs?

Adaptive Plan



... not Adaptive Plane

Definition

Adaptive Design

- uses accumulating data to decide on how to modify aspects of the study
- without undermining the *validity* and *integrity* of the trial

Validity means

- providing correct statistical inference (such as adjusted p-values, unbiased estimates and adjusted confidence intervals, etc)
- assuring consistency between different stages of the study
- minimizing operational bias

Integrity means

- providing convincing results to a broader scientific community
- preplanning, as much as possible, based on intended adaptations
- maintaining confidentiality of data

General Structure

- An adaptive design requires the trial to be conducted in several stages with access to the accumulated data
- An adaptive design may have one or more rules:
 - **Allocation Rule:** how subjects will be allocated to available arms
 - **Sampling Rule:** how many subjects will be sampled at next stage
 - **Stopping Rule:** when to stop the trial (for efficacy, harm, futility)
 - **Decision Rule:** the final decision and interim decisions pertaining to design change not covered by the previous three rules
- At any stage, the data may be analyzed and next stages redesigned taking into account all available data

Examples

- Group Sequential Designs: only **Stopping Rule**
- Response Adaptive Allocation: only **Allocation Rule**
- Sample Size Re-assessment: only **Sampling Rule**
- Flexible Designs:
 - Adaptive AR: changing the randomization ratio
 - Adaptive SaR: the timing of the next IA
 - Stopping Rule
 - Adaptive DR: changing the target treatment difference; changing the primary endpoint; varying the form of the primary analysis; etc

Allocation Rules

- Fixed (static) AR:
 - Complete randomization uses equal allocation probabilities
- Adaptive (dynamic) AR:
 - Restricted randomization
 - ◆ allocation probabilities depend on previous assignments only
 - Covariate-adaptive randomization
 - ◆ allocation probabilities depend on previous assignments *and* the current and past covariate observations
 - ◆ to balance the distribution of the covariates across the treatment arms
 - Response-adaptive randomization
 - ◆ allocation probabilities depend on previous assignments and previous responses
 - Covariate-adjusted response-adaptive randomization
 - Bayesian AR
 - ◆ alters the allocation probabilities based on posterior probabilities of each treatment arm being the “best”

Sampling Rules

- Sample size re-estimation (SSR)
 - Restricted sampling rule
 - Blinded SSR or Unblinded SSR based on estimate of nuisance parameter
- Traditional Group Sequential Designs
 - Fixed sample sizes per stage
- Error Spending Approach
 - Variable sample sizes per stage (but do not depend on observations)
- Sequentially Planned Decision Procedures
 - Future stage sample size depends on the current value of test statistic
- Flexible SSR uses also the estimated treatment effect

Stopping Rules

- Early Stopping based on Boundary Crossing
 - Superiority
 - Harm
 - Futility
- Stochastic Curtailment
 - Conditional power
 - Predictive power
- Bayesian Stopping Rules
 - Based on posterior probabilities of hypotheses
 - Complemented by making predictions of the possible consequences of continuing

Decision Rules

- Changing the test statistics
 - Adaptive scores in trend test or under non proportional hazards
 - Adaptive weight in location-scale test
 - Including a covariate that shows variance reduction
- Redesigning multiple endpoints
 - Changing their pre-assigned hierarchical order in multiple testing
 - Updating their correlation in reverse multiplicity situation
- Switching from superiority to non-inferiority
- Changing the hierarchical order of hypotheses
- Changing the patient population
 - going forward either with the full population or with a pre-specified subpopulation

Classification

Compound Progression Stages



SINGLE ARM TRIALS	
Two-stage Designs	
Screening Designs	
TWO-ARM TRIALS	
Group Sequential Designs	
Information Based Designs	
Adaptive GSD (Flexible Designs)	
MULTI-ARM TRIALS	
Bayesian Designs	
Group Sequential Designs	
Flexible Designs	
DOSE-FINDING STUDIES	
Dose-escalation designs	
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Learning/Confirming in Phase II/III	

Two-Stage Designs

- **Objective:** single-arm studies using short-term endpoints; hypothesis testing about some minimal acceptable probability of response
- Gehan design: early stopping for futility; sample size of the 2nd stage gives a specified precision for response rate
- Group sequential designs: Fleming (1982), Simon (1989)
- Adaptive two-stage designs: Banerjee&Tsiatis (2006)
- Bayesian designs: Thall&Simon (1994)

Screening Designs

- **Objective:** adaptive design for the entire screening program
 - Minimize the shortest time to identify the “promising” compound
 - Subject to the given constraints on type I and type II risks for the entire screening program
 - ◆ type I risk = $\Pr(\text{screening procedures stops with a FP compound})$
 - ◆ type II risk = $\Pr(\text{any of the rejected compounds is a FN compound})$
- Two-stage design (Yao&Venkatraman, 1998)
- Adaptive screening designs (Stout and Hardwick, 2002)
- Bayesian screening designs (Berry, 2001)

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Fully Sequential Designs

- **Objective:** testing two hypotheses with given significance level and power at the prespecified alternative

- **AR:** fixed randomization
- **SaR:** after each observation
- **StR:** boundary crossing (e.g. SPRT, repeated significance test, triangular test)
- **DR:** final decision - to accept or reject the null hypothesis

- **References:** Siegmund (1985); Jennison&Turnbull (2000)

Group Sequential Designs

- **Objective:** testing two hypotheses with given significance level and power at the **specified alternative**, prefixed **maximum sample size**

- **AR:** fixed randomization
- **SaR:** after a fixed number (a **group**) of observations,
 - ◆ or using error-spending function,
 - ◆ or using “Christmas-tree” adjustment
- **StR:** boundary crossing
 - ◆ Haybittle, Pocock, O’Brien-Fleming type
 - ◆ linear boundaries
 - ◆ error-spending families
 - ◆ conditional power, stochastic curtailment
- **DR:** final decision - to accept or reject the null hypothesis

- **References:** Jennison&Turnbull (2000); Whitehead (1997)

Information Based Designs

- **Objective:** testing two hypotheses with given significance level and power at the **specified alternative**, prefixed **maximum information**

- **AR:** fixed randomization
- **SaR:** after fixed increments of information
- **StR:** boundary crossing as for Group Sequential Designs
- **DR:** adjust maximum sample size based on interim information about nuisance parameters

- **References:** Mehta&Tsiatis (2001); East (2005)

Adaptive GSD (Flexible Designs)

- **Objective:** testing two hypotheses with given significance level and power at the *specified alternative* or adaptively *changing the alternative* at which a specified power is to be attained

- **AR:** fixed or adaptive randomization
- **SaR:** sample size of the next stage depends on results at the time of interim analysis
- **StR:** p-value combination, conditional error, variance-spending
- **DR:** adapting alternative hypothesis, primary endpoint, test statistics, inserting or skipping IAs

- **References:** Bauer; Brannath et al; Müller&Schäfer; Fisher

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Bayesian Designs

- **Objective:** to use the posterior probabilities of hypotheses of interest as a basis for interim decisions (*Proper Bayesian*) or to explicitly assess the losses associated with consequences of stopping or continuing the study (*Decision-theoretic Bayesian*)
 - **AR:** equal randomization or *play-the-winner* (next patient is allocated to the currently superior treatment) or *bandit designs* (minimizing the number of patients allocated to the inferior treatment)
 - **SaR:** not specified
 - **StR:** not formally pre-specified stopping criterion, or using a *skeptical prior* for stopping for efficacy and an *enthusiastic prior* for stopping for futility, or using *backwards induction*
 - **DR:** update the posterior distribution; formal incorporation of external evidence; inference not affected by the number and timing of IAs
- **References:** Berry (2001, 2004); Berry et al. (2001); Spiegelhalter et al. (2004).

Pairwise comparisons with GSD

- **Objective:** compare multiple treatments with a control; focus on type I error rate rather than power

- A simple Bonferroni approximation is only slightly conservative
- Treatments may be dropped in the course of the trial if they are significantly inferior to others
- “Step-down” procedures allow critical values for remaining comparisons to be reduced after some treatments have been discarded

- **References:** Follmann et al (1994)

p-value combination tests

- **Objective:** compare multiple treatments with a control in a two-stage design allowing integration of data from both stages in a confirmatory trial
- **Focus:** control of multiple (familywise) Type I error level
- **Great flexibility:**
 - General distributional assumptions for the endpoints
 - General stopping rules and selection criteria
 - Early termination of the trial
 - Early elimination of treatments due to lack of efficacy or to safety issues or for ethical/economic reasons
- **References:** Bauer&Kieser (1994); Liu&Pledger (2005)

Classification

Compound Progression Stages



SINGLE ARM TRIALS	
Two-stage Designs	[Yellow bar in Phase II]
Screening Designs	[Yellow bar in Phase I]
TWO-ARM TRIALS	
Group Sequential Designs	[Yellow bars in Phase I, Phase II, and Phase III]
Information Based Designs	[Yellow bar in Phase III]
Adaptive GSD (Flexible Designs)	[Yellow bars in Phase II and Phase III]
MULTI-ARM TRIALS	
Bayesian Designs	[Yellow bar in Phase II]
Group Sequential Designs	[Yellow bar in Phase II]
Flexible Designs	[Yellow bar in Phase II]
DOSE-FINDING STUDIES	
Dose-escalation designs	[Yellow bar in Phase I]
Dose-finding designs (Flexible Designs)	[Yellow bar in Phase I]
Adaptive Model-based Dose-finding	[Yellow bar in Phase I]
SEAMLESS DESIGNS	
Dose-escalation based on efficacy/toxicity	[Yellow bar in Phase I]
Learning/Confirming in Phase II/III	[Yellow bar in Phase II and Phase III]

Dose-escalation designs

- **Objective:** target the MTD (Phase I) or the best safe dose (Phase I/II) or find the therapeutic window
 - **AR:** non-parametric (3+3 rule, up-and-down)
 - ◆ or model-based (Continual Reassessment Methods)
 - ◆ or Escalation With Overdose Control (EWOC)
 - ◆ or Bayesian Decision Design
 - ◆ or Bayesian Optimal Design
 - ◆ or Penalized Adaptive D-optimal Design
 - **SaR:** cohorts of fixed size or in two stages (Storer design)
 - **StR:** no early stopping or stopping by design (e.g. 3+3 rule)
 - **DR:** update model parameters (for model-based AR)
- **References:** O'Quigley et al.; Babb et al.; Edler; O'Quigley

Adaptive Model-based Dose-finding

- **Objective:** find the optimal dose; working model for the dose-response; dose sequence identified in advance

- **AR:** *Bayesian* (based on predictive probabilities: smallest average posterior variance) or *frequentist* (based on optimal experimental design: maximum information per cost)
- **SaR:** cohorts of fixed size or after each observation
- **StR:** stopping for futility or when the optimal dose for confirmatory stage is sufficiently well known (estimation!)
- **DR:** update model parameters, Bayesian predictions of long-term endpoint using a longitudinal model

- **References:** Berry et al. (2001); Dragalin&Fedorov; Fedorov&Leonov

Adaptive Dose-finding (Flexible Designs)

- **Objective:** establishing a dose-response relationship using p-value combination tests

- **AR:** drop or add doses
- **SaR:** sample size reassessment for the next stage
- **StR:** early stopping for futility or early termination of some inferior doses
- **DR:** adapting hypotheses, primary endpoint, test statistics, inserting or skipping IAs

- **References:** Bauer&Kohne; Lehmacher et al

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Seamless Designs

- Two-stage adaptive designs
 - 1st Stage: treatment (dose) selection – “learning”
 - 2nd Stage: comparison with control – “confirming”
- Treatment selection
 - may be based on a short-term endpoint (surrogate),
 - while confirmation stage uses a long-term (clinical) endpoint
- 2nd Stage data and the relevant groups from 1st Stage data are combined in a way that
 - Guarantees the Type I error rate for the comparison with control
 - Produces efficient unbiased estimates and confidence intervals with correct coverage probability

Selection and testing

- **Objective:** to select the “best” treatment in the 1st stage and proceed to the 2nd stage to compare with control
- **Focus:**
 - overall type I error rate is maintained (TSE)
 - trial power is also achieved (ST)
 - selection is based on surrogate (or short-term) endpoint (TS)
- **Method includes:**
 - early termination of the whole trial
 - early elimination of inferior treatments
- **References:** Thall, Simon&Ellenberg; Stallard&Todd; Todd&Stallard

Bayesian model-based designs

- **Objective:** adaptive dose ranging within a confirmatory trial
- **Focus:** efficient learning, effective treatment of patients in the trial
- **Method includes:**
 - **AR:** to maximize information about dose response
 - **SaR:** Frequent analysis of the data as it accumulates
 - Seamless switch to confirmatory stage without stopping enrollment in a double-blind fashion
 - Use of longitudinal model for prediction of the clinical endpoint
- **References:** Berry et al; Inoue et al

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Achieving the goals

- The objective of a clinical trial may be either
 - to target the MTD or MED or to find the therapeutic range
 - or to determine the OSD (Optimal Safe Dose) to be recommended for confirmation
 - or to confirm efficacy over control in Phase III clinical trial

- This clinical goal is usually determined by
 - the clinicians from the pharmaceutical industry
 - practicing physicians
 - key opinion leaders in the field, and
 - the regulatory agency

Achieving the goals

- Once agreement has been reached on the objective, it is the statistician's responsibility to provide the *appropriate design* and *statistical inferential structure* required to achieve that goal



Achieving the goals

- There are plenty of available designs on statistician's shelf
- The greatest challenge is their implementation



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