The Adaptive Design

Issues in current Research and Implementation

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Overview

- **Adaptive Designs**
- **Seamless Adaptive Designs**
- **Issues**
  - **Statistical**
  - **Regulatory**
  - **Ethical**
  - **Operational**
- **Example**
- **Summary**

Adaptive Designs

- **Adaptive designs allow for initial uncertainties in trial design to be confirmed/adapted during the trial.**

  Data collected before AND after the adaptation is used in the final analysis.

  - **Possible Adaptations :**
    - Sample size (sample size re-estimation)
    - Sample size allocation to treatments
    - Treatment arms (delete, add, change)
    - Population (e.g., inclusion/exclusion criteria, subgroups)
    - Statistical test strategy
  - **Possible Benefits**
    - Correct wrong assumptions
    - Make use of emerging information external to the trial
    - React earlier to "surprises" (+ and -)

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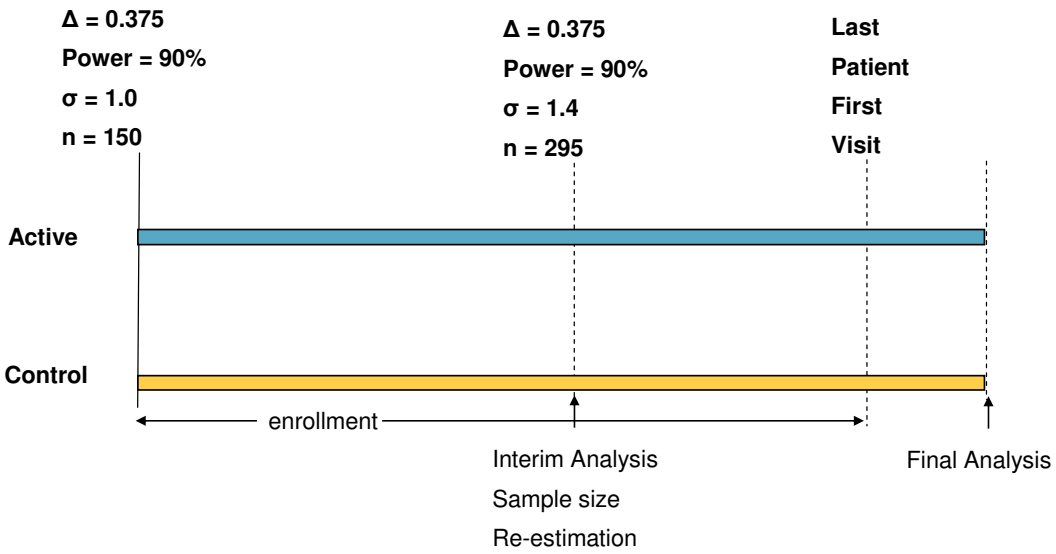
Adaptation – Sample Size Re-estimation



If the sample size is not increased, the power at the final analysis would be 64%

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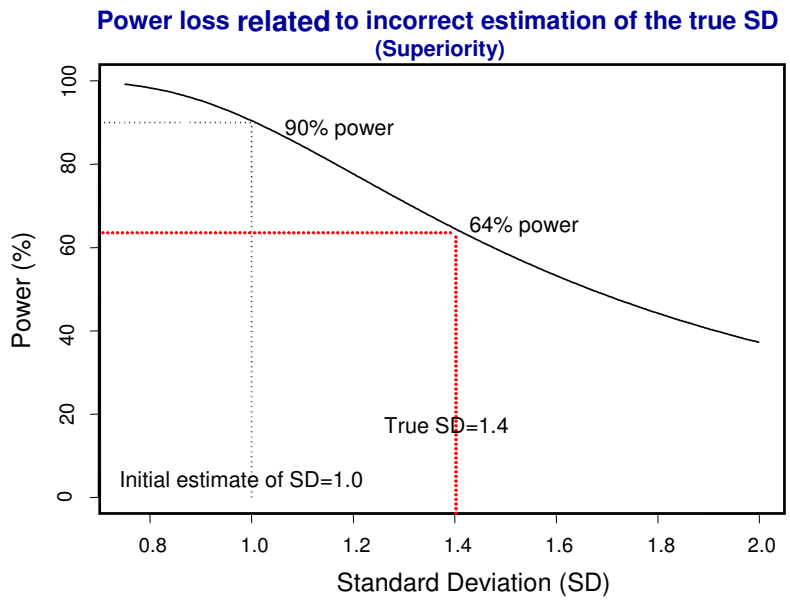
Power loss



The loss of power as the standard deviation increases from the pre-trial initial estimate.

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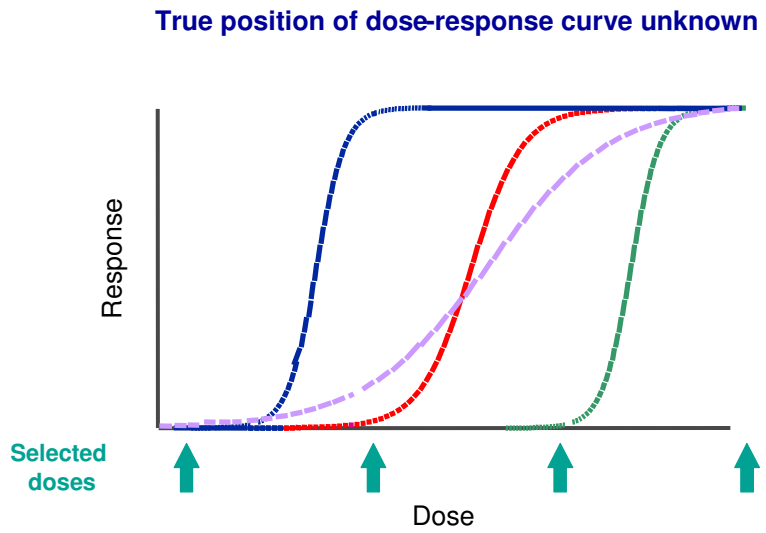
Dose Response



For most drugs the true dose-response relationship is unknown – as depicted by the diagram. Therefore, in this traditional dose-finding example, selecting a few doses may or may not adequately describe the dose- response relationship and many patients will be allocated to 'non-informative' doses.

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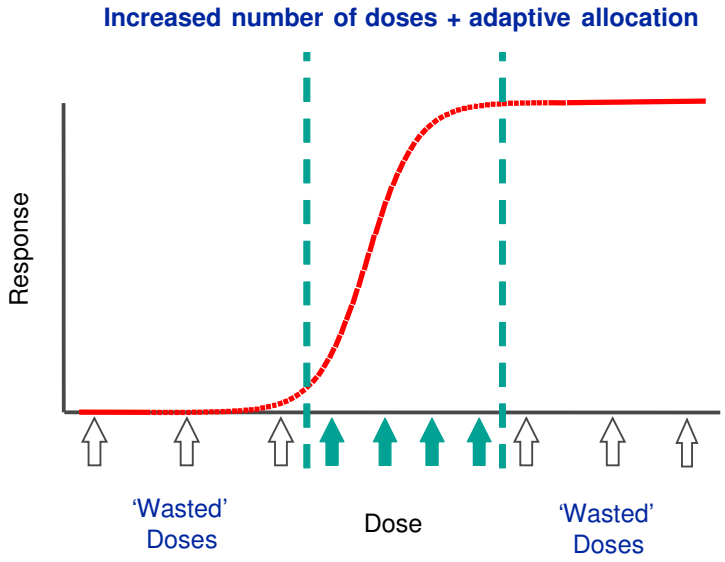
Adaptive Dose Response



In this example, the strategy is to initially include few patients on many doses to determine the dose-response, then to allocate more patients to the dose-range of interest – this reduces allocation of patients to 'non-informative' doses ('wasted doses').

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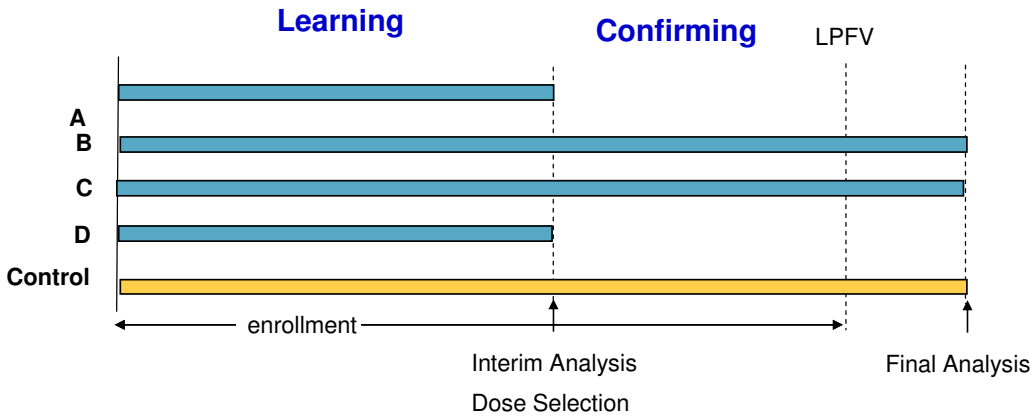
Dose Finding



Phase IIb Dose Selection Trial – ineffective or poorly tolerated are doses stopped early

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Seamless Designs

- **Seamless designs join two distinct sequential trials in a drug program into a single trial without combining the information.**

  The trials should not differ operationally (essentially the same CRF, centers, indication, …) and be defined in a single protocol.

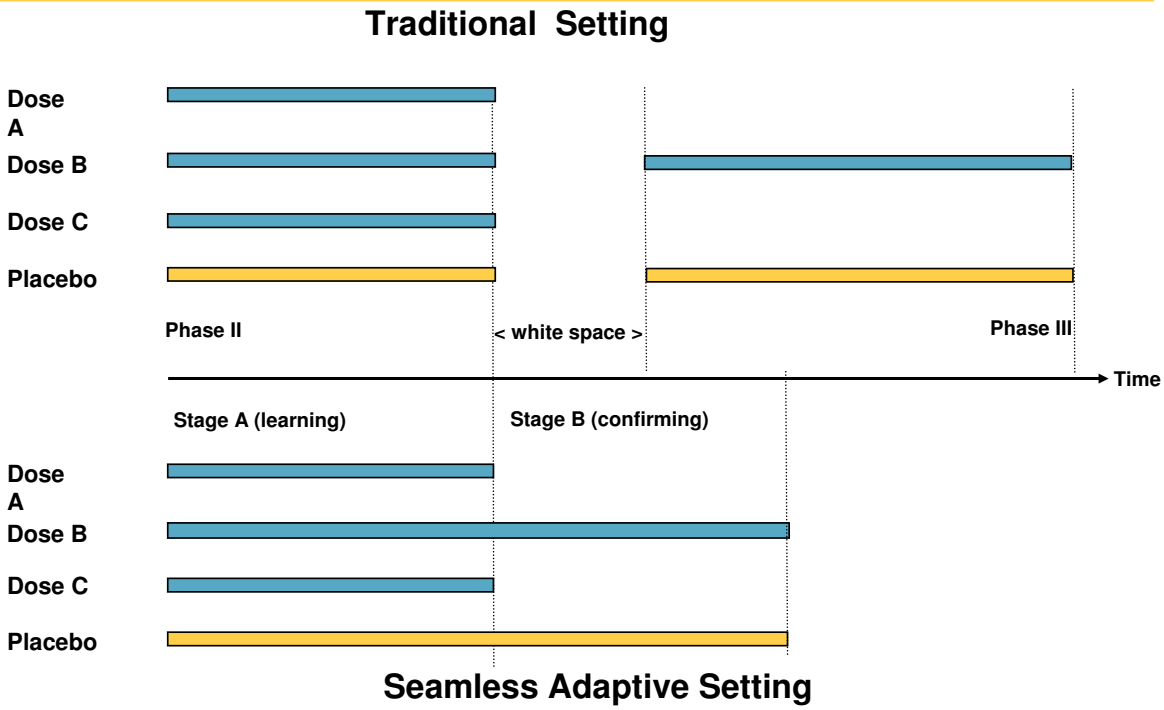
  - Allows two (or more) trials to be combined into a single trial:
    - Data from first stage could be used for go/no go for development program
    - First stage could be exploratory
  - Possible Benefits
    - Savings in time for clinical development program (no white space between studies)
    - Savings in study start-up efforts

Adaptive Seamless Design (ASD)

- **Adaptive seamless designs (ASD) takes advantage of both:**
  - **Information gathered from first stage**
  - **used to adapt the design for the next stage**
  - **Shorter overall development time**
    - **effective drugs are made available earlier for the patients**
    - **more economical overall use of resources**
  - **Fewer patients needed**

    or
  - **Increase of information value** given the same number of patients
  - **Integrated planning and evaluation of scenarios for both phases**
  - Long term safety data from patients become available earlier

Seamless Phase II/III design



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Health Authority Viewpoint

- Health Authority views on Adaptive and Seamless Adaptive Trials are evolving. Generally HA's are taking a cautious approach on a trial by trial basis.
- The CHMP recognise that Flexible Designs can speed up the process of drug development or can be used to allocate resources more efficiently without lowering regulatory standards.
- The CHMP especially welcome Flexible designs if the basis for regulatory decision-making is improved.
- FDA Critical Path initiative to 'Accelerate the Development of Medical Products' has identified Adaptive Designs as on opportunity to streamline clinical trials
- FDA support the use of adaptive designs when correctly conducted
- FDA preparing a guideline on Adaptive Trials, expected early 2007

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Maintaining Integrity

- **Un-blinding can introduce bias, measures must be put in place to manage potential sources of bias**
  - **Adjustment of significance levels**
    - **Repeated testing and the adaptation must be allowed for in the statistical design and analysis**
  - **Limiting Access to the data**
    - **Clinical team must be isolated from un-blinded data**
  - **Limiting Access to the results**
    - **Clinical Team must be isolated from the results of the interim analysis**
  - **Controlling Communication**
    - **Communicate interim analysis decisions not results**

Operational Considerations - Design

- **Early Planning**
  - **Adaptive trial require more planning than conventional trials.**
- **Feasibility Assessment**
  - **Will the timing of the interim analysis allow sufficient time to make an adjustment?**
    - **Recruitment rates**
    - **Time to 'end point'**
- **Statistical Design**
  - **Statistical Methods**
  - **Interim Analysis Decision Rules**
- **Simulations**
  - **sample size**
  - **power**
  - **probability of success**

Ethical Considerations

The Protocol must specify the nature of the adaptation, have supporting statistical justification for the design, define the role of the Data Monitoring Committee and specify the decision rules.

Potential Benefits

- **fewer patients exposed to development drugs**
- **in dose finding trials; early stopping for ineffective dosage arms and dosages with unacceptable safely profiles.**
- **sample size re-estimation insures that trials are adequately powered reducing the chance of an inconclusive trial**
- **trials can be stopped for futility**

Where the risk/benefit is different in the two stages of the trial in may be necessary to have two Informed Consent Forms

If the decision following an interim analysis is line with DMC charter, generally there will not be any feedback from DMCs to ethics committees on the outcome.

Operational Considerations – Interim Analysis

- Interim Database Lock
  - Ensure timely entry and cleaning of Interim Analysis Data Set
- Isolated Clinical Teams from Interim Analysis data, results and in some cases decisions.
  - Interim analysis carried out by an independent statistician on partially blinded data (if sponsor statisticians perform the interim analysis, there must be demonstrable firewalls in place)
  - Independent Data Monitoring Committee review un-blinded data and recommend decisions based on the protocol decision rules and the results of the analysis. (There is an ongoing debate about sponsor involvement in DMCs)

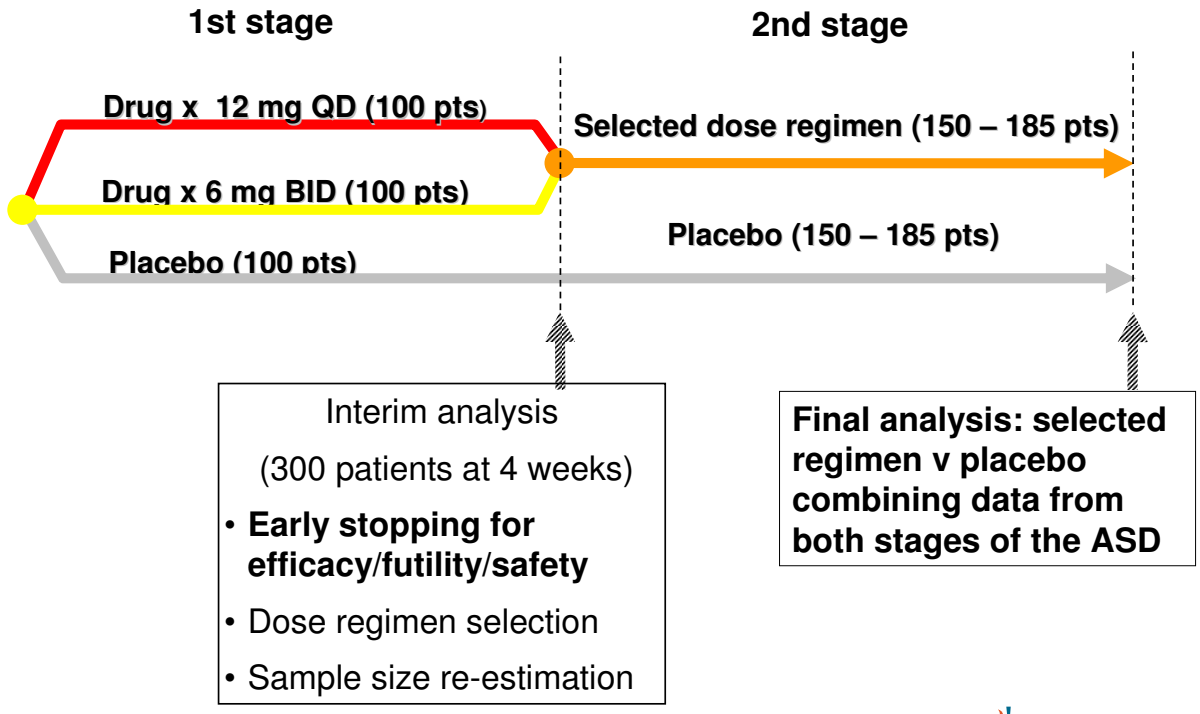
Operational Considerations - Logistics

- **Heath Authority Meetings**
  - **Early discussions with HA particularly for phase II/III ASDs.**
- **Drug Supplies**
  - **Early discussions with drug supplies on the adaptive element and the effect on patient numbers and treatment arms**
  - **IVRS (Interactive Voice Response System) for the optimum management clinical trial supplies**
- **Ethics**
  - **Ethics Committees / IRBs may not be familiar with AD and ASDs and should be made aware of the adaptive nature and the benefits of the design**
- **Centre Management**
  - **Adaptive Trials with a potential increase/decrease in patient numbers will require contingency planning for the possible interim decision outcomes**

ASD in phase II/III with treatment regimen adaptation

- **Population**: Patients with GI dysfunction induced by opioids
  - male and female patients with chronic non-malignant pain (lower back pain, osteoarthritis, rheumatoid arthritis) (600-670 pts)
- **Design**: 2-stage, adaptive design, double-blind, double-dummy randomized, parallel group (1:1:1, then 1:1), placebo-controlled. Patients enrolled in both stages have same visit schedule and CRF.
- **Dose regimens**: Drug x 12mg QD or 6mg BID, up to 12 weeks
- **Objectives:**
  - **Stage 1:** evaluation of efficacy and safety of 2 dose regimen, versus placebo, and selection of 1 dose regimen
  - **Stage 2:** evaluation of efficacy and safety of the dose regimen selected in Stage 1, versus placebo (analysis carried out on patients enrolled in both stages)
- **Study is part of registration program**

Phase II/III ASD trial



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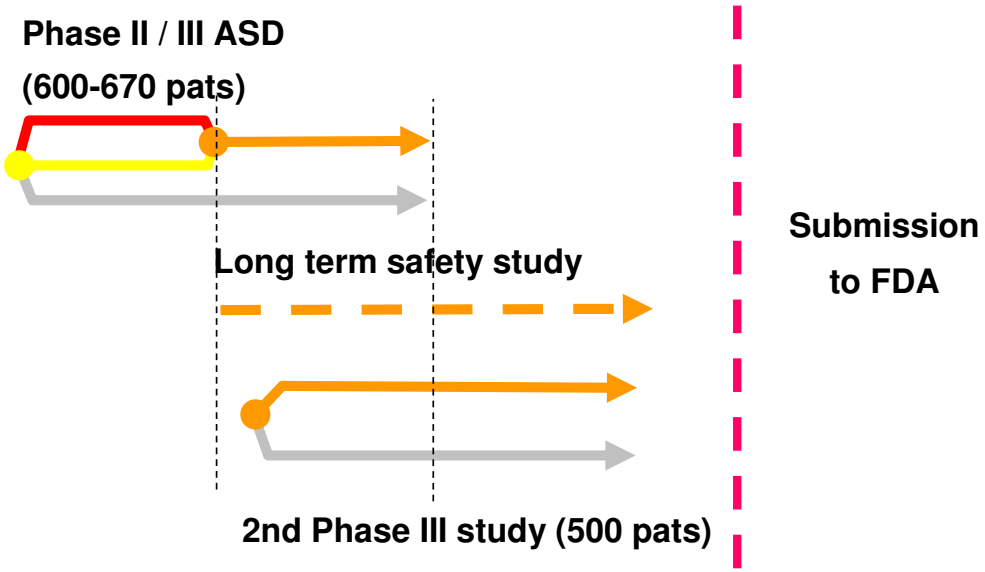
Second Confirmatory Trial



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Summary

- **Adaptive designs hold the promise of faster clinical development, programs involving fewer patients and having better informed decision points**
  - **Key value of adapting is in using data from an ongoing trial to make decisions to improve the likelihood of that trial being 'successful'.**
  - **When correctly conducted adaptive designs are acceptable to Health Authorities.**
  - **Adaptive trial designs require more planning, it is therefore important to make early decisions about using these designs**
  - **Benefits of combining learning and confirmation in one single trial outweigh in many cases the additional operational challanges and potential risks.**