




Compass

Get the Dose Right with Compass®
Adaptive Dose-Finding Trial Design Software

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Objectives

Learn how Compass® helps:

- Design dose-finding studies using either frequentist or Bayesian adaptive methods
- Adaptively allocate subjects to doses during the trial
- Integrate your R code: running existing or writing new scripts within Compass
- Generate trial simulations to assess operating characteristics of different designs
- Lead to a clearer understanding of trial dynamics with tables/charts & graphs to help select best design options

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Outline

- Introduction to dose-finding studies
- Simulation guided clinical trial design
- Dental pain example
- T-test based up and down method
- Bayesian four parameter logistic model
- Implementation challenges

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Paradigm shift: the adaptive imperative

- **FDA Critical Path Initiative (2004)**

"...modernize the scientific process through which a potential human drug, biological product, or medical device is transformed from a discovery or "proof of concept" into a medical product."

Essential idea : Introduce more promising drugs into development!

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Paradigm shift: the adaptive imperative

- **Adaptive clinical trial innovations**

- Improves the clinical process and increases likelihood of approval
 - Right number of patients
 - Right dose
 - Right endpoint
 - Right duration
- Adaptive designs also **enable early stopping** for futility, and also have considerable **ethical advantages**

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Benefits of the adaptive approach

- Allocate subjects to optimal therapy
- Limit the number of subjects allocated to ineffective or overly toxic doses
- Estimate the dose-response relationship with fewer subjects
- Find dose(s) that yield a desired level of response more efficiently
- Stop a trial early for futility or efficacy

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Dose selection logic (fixed)

- **Standard Fixed-Allocation Design**
 - Pre-defined doses and number of subjects per dose
 - Up to 4 arms is standard
- **Questions:**
 - Are we able to select an optimal dose?
 - Are we able to estimate the dose-response relationship?

Dose Response Curves

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What is adaptive dose-finding?

- **Enroll subjects in successive cohorts**
Allocate them based on responses of previous cohorts

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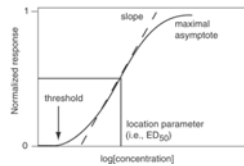
What is adaptive allocation ?

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What is adaptive dose-finding?

- Address multiple objectives in a single trial

Demonstrate Proof-of-Concept
 Characterize Dose-Response curve
 Identify correct dose to take into phase 3
 Succeed early and “efficiently”
 Fail early and “efficiently”

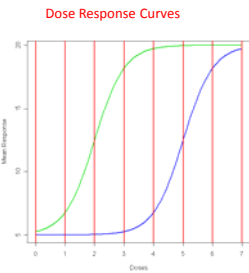


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Dose selection logic (adaptive)

- Response-Adaptive Design

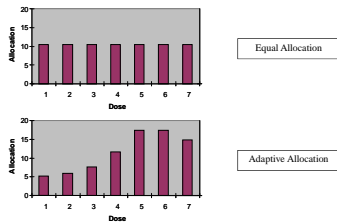
1. Split sample into successive cohorts
2. Fixed-dose design for first few cohorts
3. Use responses after each cohort to estimate dose-response relationship
4. Update randomization schedule to focus on “interesting” part of curve
5. Repeat 1-4 until study completion or early termination



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Response adaptive vs. fixed

- For blue curve, doses 4 to 7 are “interesting”:



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What is Compass?

Compass is a fully validated, user-friendly statistical software environment that provides design and simulation tools for dose-finding studies

- Compass is a:
 - Simple and Intuitive tool
 - Tested and Validated tool
 - Productivity tool
 - Communication tool

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What are the key design methods?

- Frequentist methods
 - Up and Down
 - Two target Up and Down
 - t-Test based Up and Down
 - Maximizing
- Bayesian methods
 - Normal Dynamic Linear Model (NDLM)
 - Four Parameter Logistic (4PL)
 - Emax

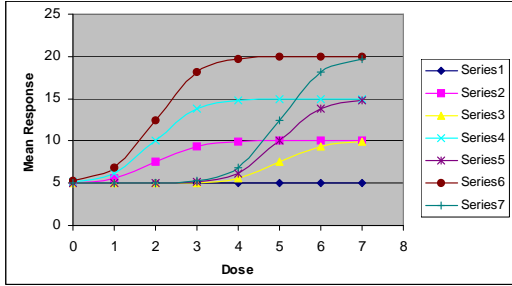
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Example : Dental Pain

- Single-dose dental pain study (total 120 patients)
- 7 Doses and Placebo
- Primary endpoint is Total Pain Relief (AUC) during 0-8 hours post dose (TOPAR8)
- Sequential groups of 12 patients (4 placebo, 8 test drug)
- Response (both conditions satisfied):
 - Mean test drug – mean placebo ≥ 10 units TOPAR8

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Example : Dental Pain cont.



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Implementation challenges

- Availability and flow of information/data required to support adaptive decision making
- Rapid and smooth implementation of changes to the randomization scheme
- Drug supply planning and optimization
- Composition and responsibilities of data monitoring committees
- Documentation and process validation

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Conclusions

- Adaptive dose-finding designs are viable for PoC and dose-ranging in a single study
 - Yield similar, maybe better, dose-response information as larger parallel group designs
 - Likely to use substantially fewer patients than parallel group design
 - Likely to save development time in Phase II
- Logistic details need to be workable
 - Response observable reasonably quickly relative to patient entry
 - Dynamic allocation issues
 - Drug Supply & Labeling more complicated

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Conclusions

- Simulation tools such as Compass are critical to designing adaptive designs in time and under constraints
- Compass is based on four key principles
 - Provision of both frequentist and Bayesian adaptive methods
 - Integration within Cytel's family of software products
 - Openness to modification and extension by users
 - Intuitive interface with strong support for management of simulation runs

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Roadmap (sample future extensions)

- Add more adaptive methods for Phase 2
- Add adaptive designs for Phase 1, especially for oncology trials
- Support a wider set of priors for Bayesian models
- Add dose response models with different standard deviations at different doses
- Incorporate longitudinal models for responses and missing data
- Incorporate more sophisticated models for accruals
- Add models for safety responses

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