



Get the Dose Right with Compass®
New Adaptive Trial Design Software Sneak Preview

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Outline: what will we learn?

Today you will learn how to use Compass to:

- Design an adaptive dose-finding study
- Compare operating characteristics of various designs
- Assess sensitivity of a design to underlying assumptions about the dose-response curve
- Adaptively allocate subjects to receive optimal therapy
- Maximize the information value of clinical data

$$G_U(z_1) = \Pr(Z_2 \geq b_2 | Z_1 = z_1, \delta = 0)$$

What is Compass?

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$$G_U(z) = \Pr(Z_2 \geq b_2 | Z_1 = z, \delta = 0)$$

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

$$c_{10}(z_1) = \Pr(Z_2 \geq b_2 | Z_1 = z_1, \delta = 0)$$

What are the questions in phase 2?

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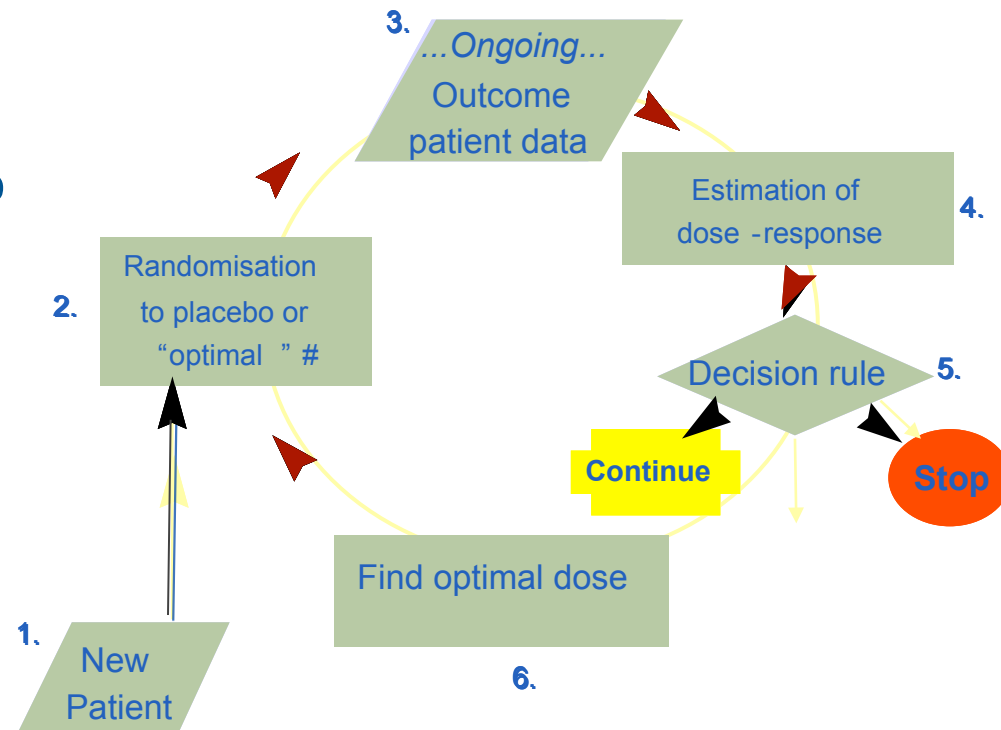
$$c_{10}(z) = \Pr(Z_2 \geq b_2 | Z_1 = z, \delta = 0)$$

- Is there proof of concept?
- Where is the interesting range of doses or therapeutic window?
- Which dose or doses should we carry forward to Phase 3?
- How do we estimate a minimum clinically effective dose?

What is adaptive dose-finding ?

Acknowledgement : Michael Krams

- **Enroll subjects in successive cohorts**
 Allocate them based on responses of previous cohorts
- **Identify the correct dose to take into phase 3**
 The first time round
 Better, faster, cheaper
- **“Learn”**: Adaptive dose-response finding
 “Succeeding efficiently”
 “Failing efficiently”



$$G_U(z_1) = \Pr(Z_2 \geq b_2 | Z_1 = z_1, \delta = 0)$$

What are the chief benefits?

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$$G_U(z) = \Pr(Z_2 \geq b_2 | Z_1 = z, \delta = 0)$$

- 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

$$C_U(z_1) = \Pr(Z_2 \geq b_2 | Z_1 = z_1, \delta = 0)$$

What are the key design methods?

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$$C_D(z) = \Pr(Z_2 > b_2 | Z_1 = z, \delta = 0)$$

- **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

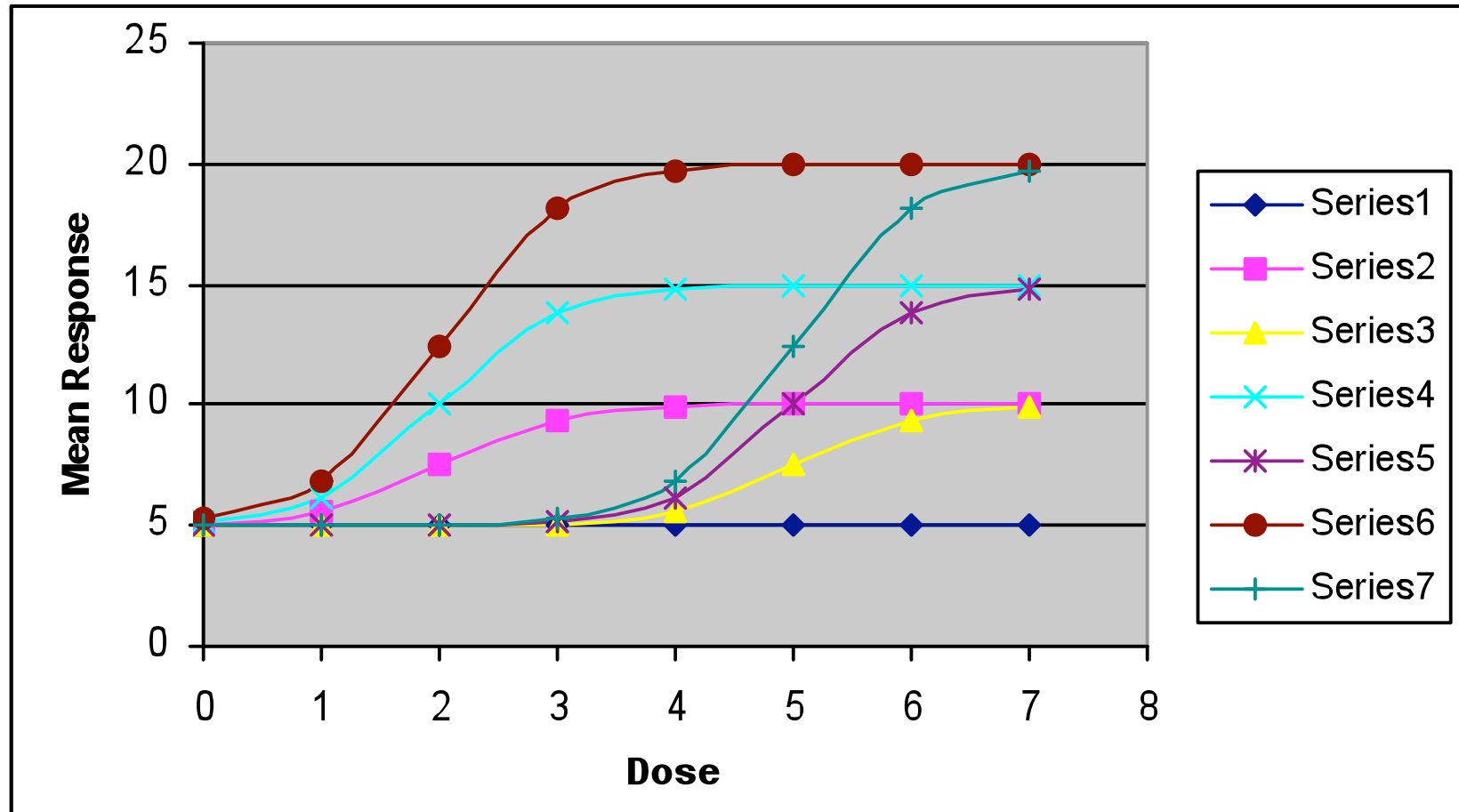
Example : Dental Pain

- 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

$$G_U(z_1) = \Pr(Z_2 \geq b_2 | Z_1 = z_1, \delta = 0)$$

Example : Dental Pain cont.

$$G_U(z) = \Pr(Z_2 \geq b_2 | Z_1 = z, \delta = 0)$$



$$G_U(z_1) = \Pr(Z_2 \geq b_2 | Z_1 = z_1, \delta = 0)$$

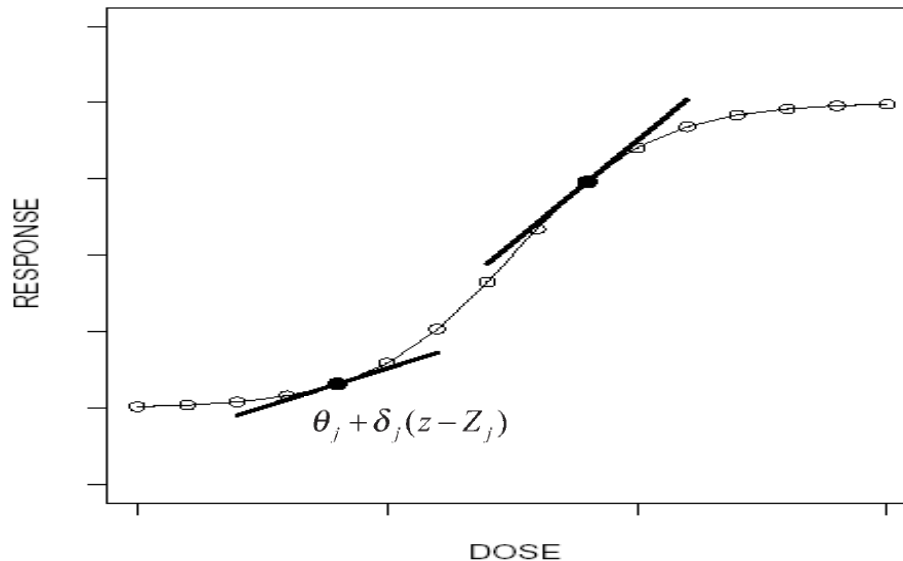
t-Test based up & down

$$G_D(z) = \Pr(Z_2 > b_2 | Z_1 = z, \delta = 0)$$

- One dose of drug allocated per cohort
- At each interim, compute a t-test based on all subjects enrolled since the start of the study to the latest assigned dose
- Compare the resulting t-statistic to pre-defined thresholds to decide whether to increase or decrease the dose

NDLM

- Normal Dynamic Linear Model: A flexible piece-wise linear model
- Smoothed transitions in the dose-response slope across the doses
- Assign next cohort of subjects to minimize standard deviation of the response at doses of interest



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

$$c_{10}(z_1) = \Pr(Z_2 \geq b_2 | Z_1 = z_1, \delta = 0)$$

What is the future of Compass?

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$$c_{11}(z) = \Pr(Z_2 > b_2 | Z_1 = z, \delta = 0)$$

- Many extensions already developed and exist as internal prototype software tools
 - Greater flexibility in exploring and analyzing data analytically and graphically
 - More flexible recruitment models
 - More complex decisions rules for early stopping
 - Phase 1 design methods such as CRM and its various modifications
 - Greater R integration

Conclusion: what did we learn?

Today we showed how Compass can help you:

- Design an adaptive dose-finding study
- Compare operating characteristics of various designs
- Assess sensitivity of a design to underlying assumptions about the dose-response curve
- Adaptively allocate subjects to receive optimal therapy
- Maximize the information value of clinical data

References

- Ivanova A, Bolognese J, Perevozskaya, I. Adaptive design based on t-statistic for dose response trials. *Stats. In Medicine* 2008; 27:1581-1592.
- West and Harrison (1997). *Bayesian Forecasting and Dynamic Models*.

Release of Compass and DIA

- **For more information today and evaluation requests**

connor@cytel.com

Connor Tubridy will answer your questions:
+1.617.528.7212

- **Visit our booth at DIA June 13 – 17 Washington, DC**

Further discussions with Cytel experts and demos

Booth **#1727** (close to Medidata)

- **Contact Cytel** +1.617.661.2011 info@cytel.com

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Questions and Answers

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- Yannis will address as many as the time allows
- Please submit your questions via your Webex viewer
- Helpful to make known your name and organization

Replay this Webinar 24/7

- Free, 24/7 replay of complete webinar starting this Monday

www.cytel.com/News/Webinars.aspx

or find the direct link on our home page:

www.cytel.com

- Replays help:
 - review salient points
 - introduce Compass to others interested
 - re-visit Architect platform and mode-of-operation (something every East® users should be aware of)



Thank you for joining today



Q&A

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System requirements

Hardware requirements:

- Hard Disk: 3 GB of free space. The product will use around 1.5 GB of disk space.
- Display: VGA or higher resolution: Minimum: 1,024x768 pixel; Recommended: 1280x1024 pixel.
- Memory: RAM: Minimum: 512 MB Recommended: 2 GB or more.
- Operating system: Windows XP SP3, Windows Vista 32 or 64 bit (x86 or x64) PC based, Windows 7 (both 32 bit and 64 bit), Windows Server 2003 (Network version only), Windows Server 2008 (Network version only)

Software requirements:

- - Acrobat Reader 9 (for user manual)
- - .NET Framework 2.0 SP 2 or higher
- - Windows Installer 4.5
- - Microsoft Internet Explorer version 6 or higher
- - SQL Server Express 2008 or higher
- - R 2.7 or higher (also the R2HTML package)