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

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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
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
What are the questions in phase 2?

- 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?

- 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”

Acknowledgement: Michael Krams
What are the chief benefits?

- 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
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
• 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
Example: Dental Pain cont.
• 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
- 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

Acknowledgement: Michael Krams
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
What is the future of Compass?

• 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
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

• West and Harrison (1997). Bayesian Forecasting and Dynamic Models.
• 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
• 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
• 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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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)