
# Adaptive Design in CNS Trials

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# Summary

- Motivation and challenges for Adaptive Design
- Adaptive Dose-Ranging Designs
  - Case study in Multiple Sclerosis
- Confirmatory Adaptive Clinical Trials
  - Case Study in Neuropathic Pain

# Adaptive Designs: What are they?

**PhRMA Adaptive Designs WG (2006):**

"By adaptive design we refer to a clinical study design that uses accumulating data to modify aspects of the study as it continues, without undermining the validity and integrity of the trial."

"…changes are made by design, and not on an ad hoc basis"

"… not a remedy for inadequate planning."

http://biopharmnet.com/doc/doc12004.html, accessed 0917/2011

# Motivation for Adaptive Design

- Opportunity to calibrate initial assumptions used at trial design based on partial observed information
- Improved knowledge efficiency vs. conventional (i.e., non-adaptive) designs
  - Same or more information
  - Faster/less expensive
  - More information for same investment
- Increase likelihood of success, or reliable early termination (e.g., futility rule)
- Improved understanding of treatment effect
  - Dose-response
  - Subgroups effects

# Challenges for Adaptive Design

- Adaptive designs (AD) offer considerable opportunities for improving drug development, but come with risks and costs
- Industry mindset favoring traditional development approaches ⇨ change management
- Need adequate operational infrastructure: drug supply, recruitment, data management, etc
- Regulatory concerns with new approaches, especially in confirmatory studies: FDA draft guidance on AD quite helpful in that regard

  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm201790.pdf

- Resource needs: increased planning, more people with proper expertise; adequate commercial software for design and implementation; hardware for intensive computing

# Planning and Evaluating AD

- Quantify cost/benefit of an AD vs. conventional approach
- Evaluate operating characteristics (OC) of proposed designs
- Calculate statistical OC to include power to detect signal
  - treatment effect
  - precision of estimate
  - expected duration
  - probability of early stopping ⇨ used to determine sample size, number of arms, allocation ratios
- Additional, non-statistical operational characteristics
  - Drug supply
  - Costs
  - IV(W)RS

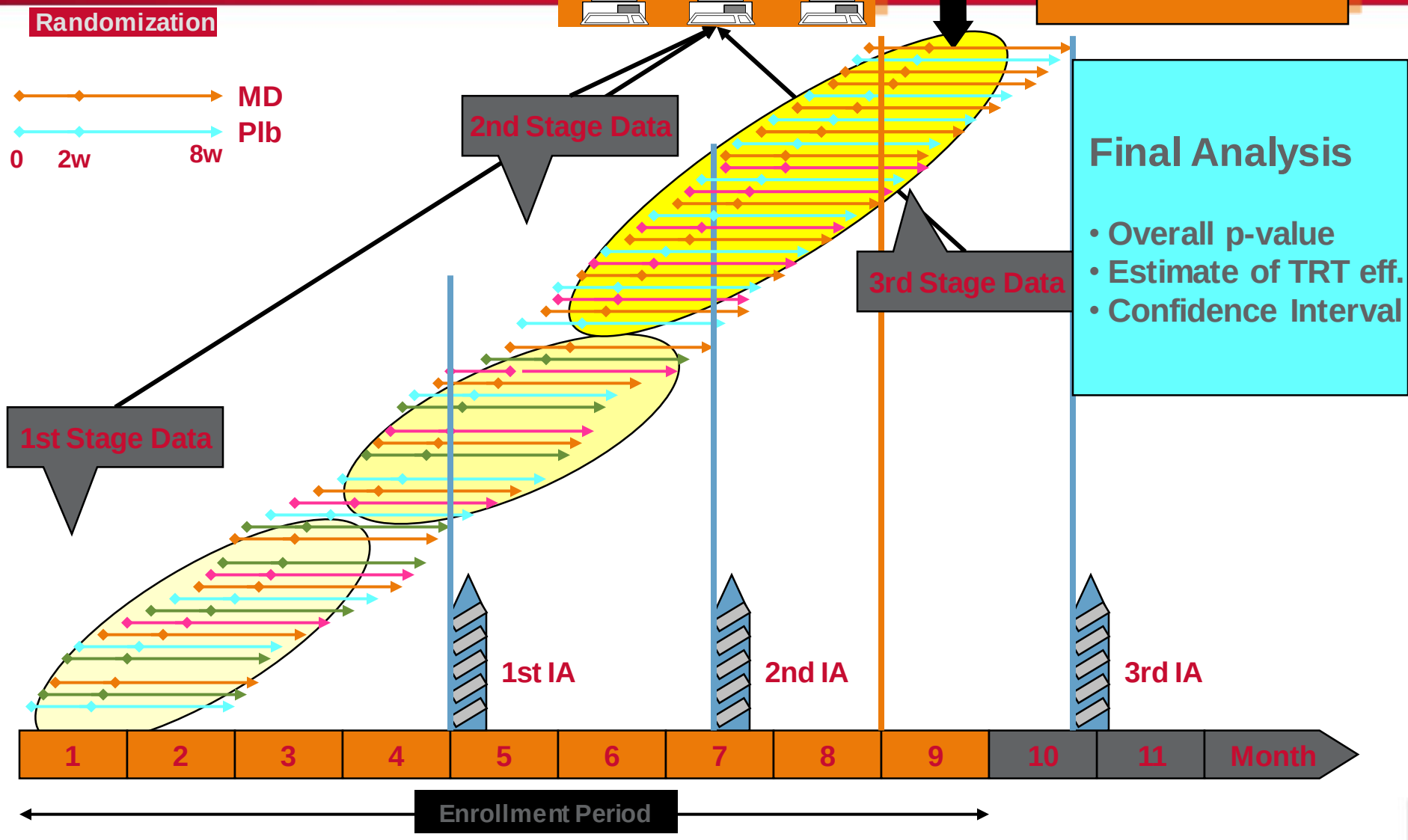
# Two-period Adaptive Dose-Ranging Design

- Motivation
  - Learn about DR from data in Period 1 and select most informative doses for Period 2 at interim analysis (IA)
- Period 1 doses: 0 (placebo), 0.5, 2, and 10 mg
- Two additional doses selected for Period based on DR profile observed in Period 1
- Placebo arm used in Period 2 to preserve blinding (avoid bias)
- Possible Period 2 doses: 0.25, 1, 1.25, 4, 5, and 8 mg
- Dose selection rule for Period 2 based on classification of observed DR profile into one of 6 pre-defined profiles
- Sample sizes: 44 on active arm, 55 on placebo (11 in Per. 2)

# Confirmatory Adaptive Clinical Trials

- New drug ND
  - lead indication in Psychiatry (anxiety & depression)
  - secondary indications in Neuropathic pain, RLS & FMS
- Objectives : To establish superiority of ND dose(s) versus placebo in Neuropathic pain patients
  - Confirm efficacy (and durability of response)
    - 8 week treatment, but expect treatment effect at 2 weeks
    - correlation between early and late treatment effects
  - Establish safety profile
  - Establish dose-response
- Strategic Aim:
  - pivotal quality to potentially support registration

# 3rd Stage



# Group Insights

- Uncertainty about dose range and response shape
- Tendency for over-excitement by some – temper with simulations
  - Formerly 4-6 months
  - More published case studies, guidance
  - Software availability
- When is AD more useful?
  - Type of adaptation varies based on knowledge of compound
  - Requires appropriate amount of resources
  - Efficiency may depend on economies of scale
- Confirmatory designs must have Type I error control
  - Appropriate methods exist to accomplish this
- Complexity of decision making in AD
  - External analytic groups, participation of sponsor in the DMC