Utility and Pitfalls of Dose Ranging Trials with Multiple Study Objectives Fixed or Adaptive*

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Clinical/Statistical review teams/divisions/offices adaptive design case sharing education, discussion, contribution

Outline

- What are study objective(s)
- Approaches: fixed vs adaptive
- Randomization strategies
- Utility and Pitfalls
- Concluding Remarks

Study Objective(s)

- Detect dose-response (POC)
- Identify clinical relevant response (CRR) $\cong$ MCID ???
- Select dose(s) for Phase III planning
- Estimate the dose-response

- Screen drug for anti-disease activity
- Extend knowledge of toxicology and pharmacology of drug to hopefully benefit patients

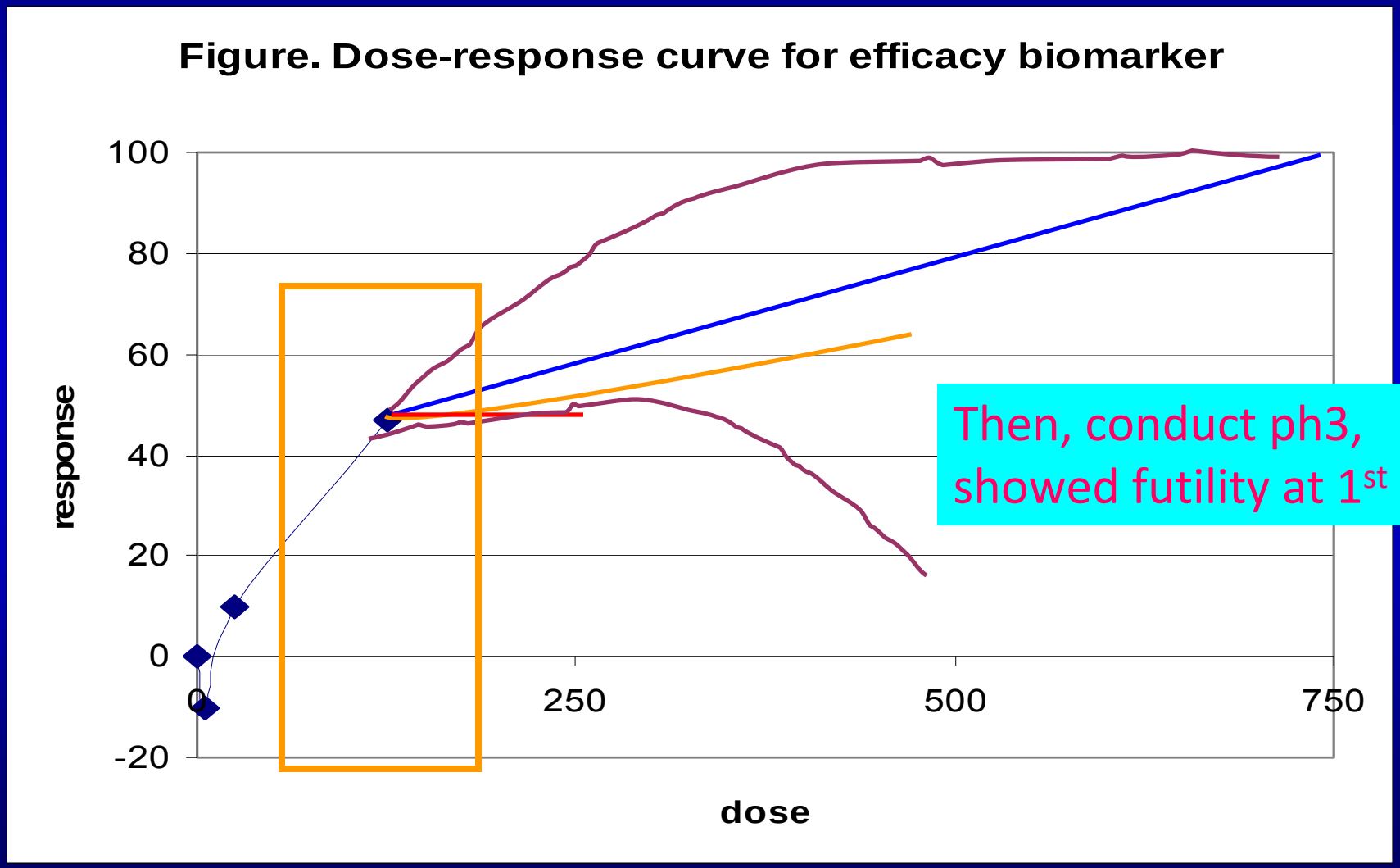
Conventional Fixed Designs

- Fixed randomization ratio
  - K-dose groups +/- placebo & dosing frequency
  - Sample size to detect dose-response, if significant, then, estimate target effect size
- Design fixed and analysis adaptive (selection)
  - MCPMod
    - Postulate a few plausible dose-response models
    - Dose-response characterization
  - Dunnett
    - Formally incorporates selection into decision process

Utility and Pitfall with Fixed Designs

- Learn from experience to design properly → can be A&WC
  - E2 = E3 with knowledge of successful similar developments
  - Sufficiently powered to detect T-effect → Dunnett's useful
  - Can also characterize DR relationship with good precision
- Learning mode without existing experience → Sufficient 'n' ?
  - What's endpoint? E2 = Early time point of E3; E2 <> E3
  - E2 correlated with E3? E2 predictive of E3 ?
  - Little prior to size the trial
- Model dose-response relationship – lack precision
- Dunnett can be inefficient
- Dose choice difficult, though may have apparent DR pattern

Danger of extrapolation without formal investigation



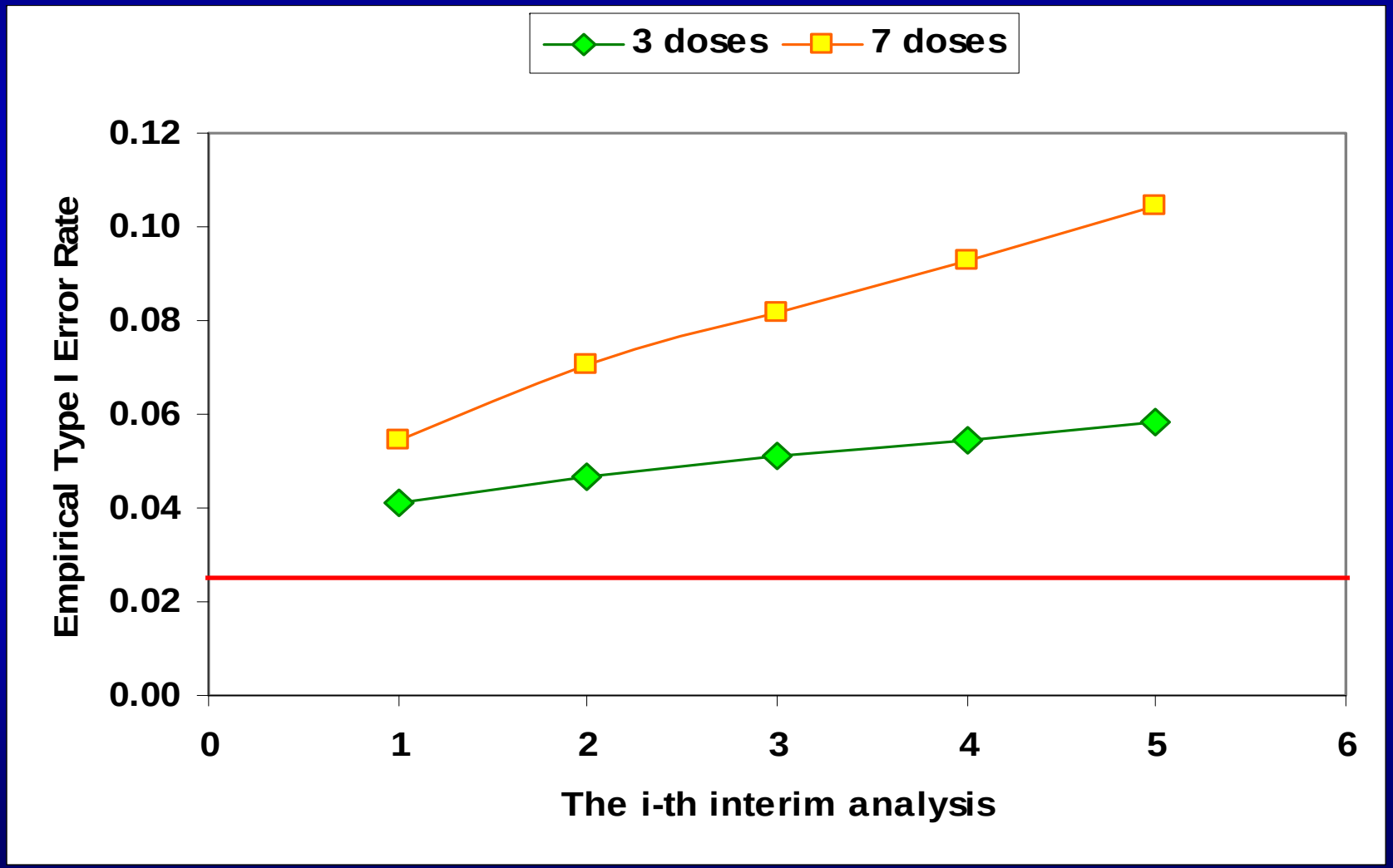
Utility and Pitfall with Hybrid Designs

- Selection, sequential, fixed randomization ratio both stages
- Single-stage randomization selection w/o pbo
  - Ranking and selection with prob (correct selection)
  - No hypothesis test, rely on existence of best dose
  - False+ (impressive arm) rate ↑ as K ↑ unless large difference
  - Left to mandatory follow-on in ph3 where α-controlled
- Two-stage randomization selection → (prelude of adaptive)
  - control conditional type I error when w/o pbo
  - strong control of overall type I error when include pbo
- SPRT to identify 1-arm > C by elimination of inferior arms
  - pr (correct selection |Ho) vs pr (correct selection |Ha)
  - also, strong control of overall type I error; allow stop futile trial?
- Properly recognized as Phase 2 trials

When ignoring multiplicity

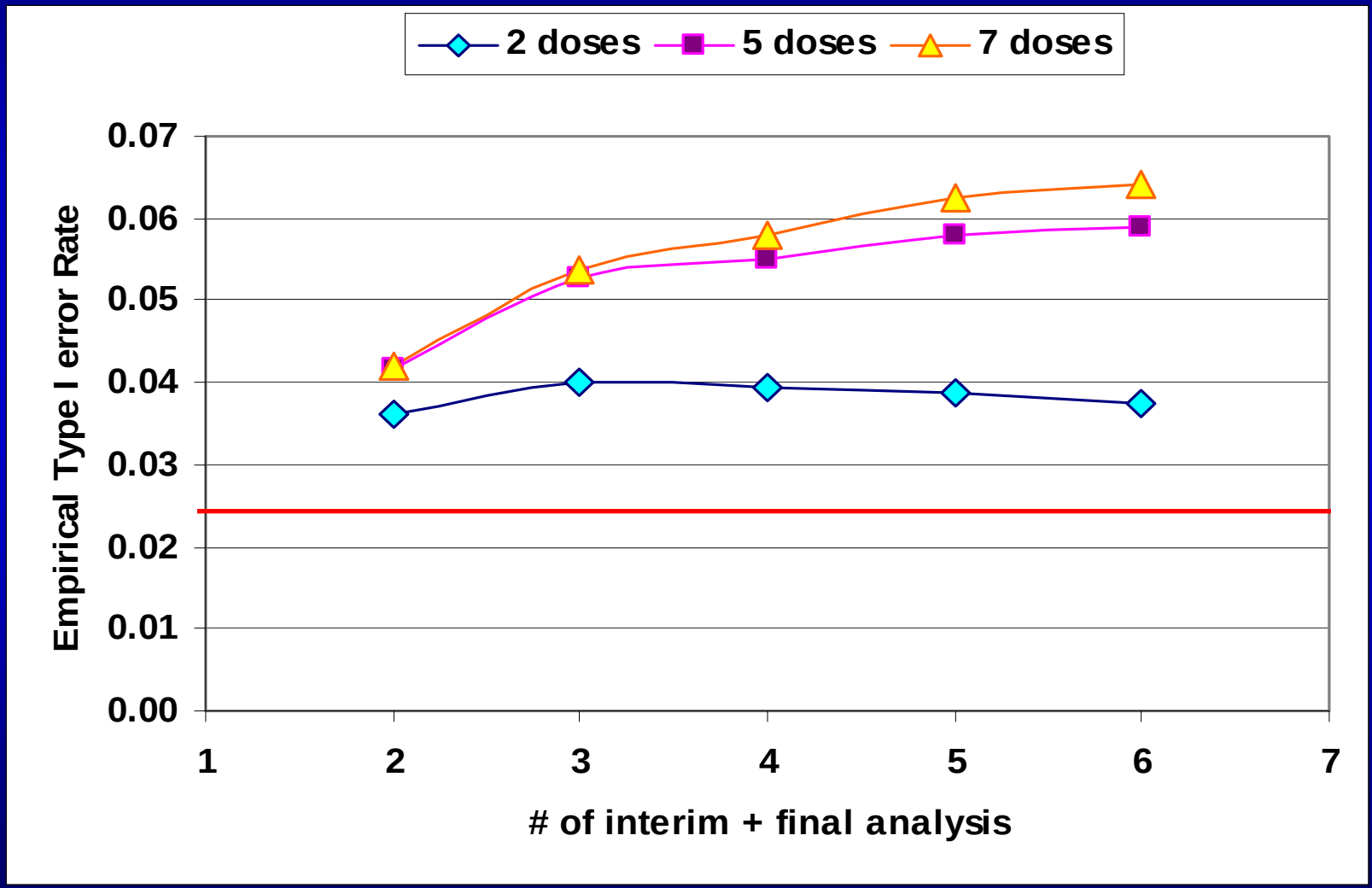
- The type I error rate based on the adaptation process as a two-stage randomized selection in group sequential setting
- Selection based on clinical endpoint
- Selection based on biomarker for testing clinical endpoint

Select among doses most promising at k-th interim, e.g. Max(Z1, …, Zk)



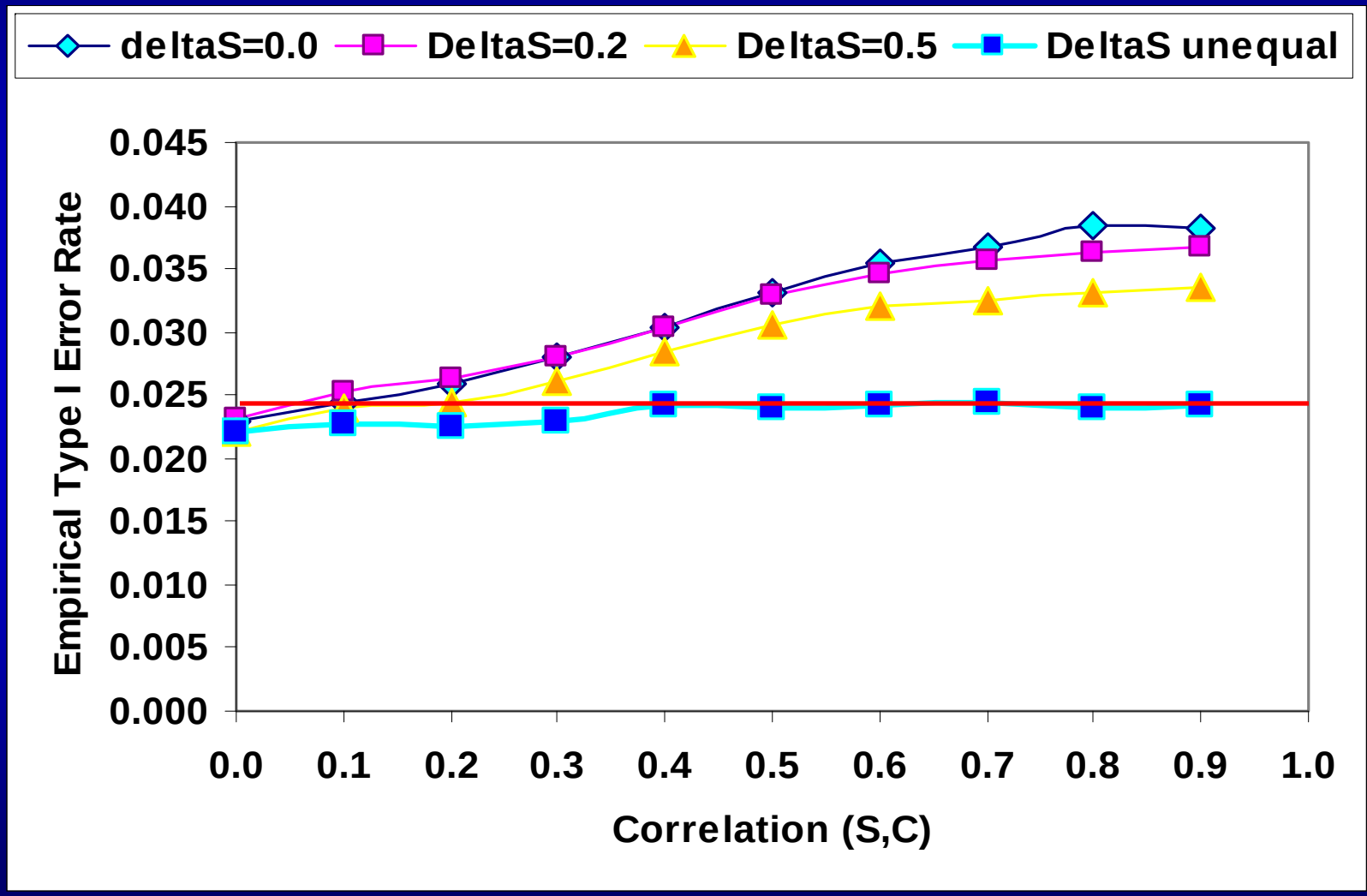
Wang et al. (Biometrical J, 2010)

Select among TRTs most promising at k-th interim, if Zmax - Z_j > 1 for all j



Wang et al. (Biometrical J, 2010)

Select b/t 2-Doses at τ=0.5 based on Efficacy Biomarker, if D*Z1<Z2, select T2, ow T1



Wang et al. (Biometrical J, 2010)

Adaptive Dose Ranging Designs #1
(White Paper, 2007)

- GADA: Bayesian dynamic dose allocation (non-para model)
- D-optimality adaptive allocation (parametric model)
- Design fixed, analysis adaptive
  - Dunnett's multi-arm test (select dose at study end)
  - MCPMod (identify dose-response model at study end)
  - Multiple Trend Tests (from a class of sigmoid Emax model, U, L, M DR)
  - Strong control of overall type I error for its primary study objective
- Bayesian model averaging; Non-para dose-response modeling

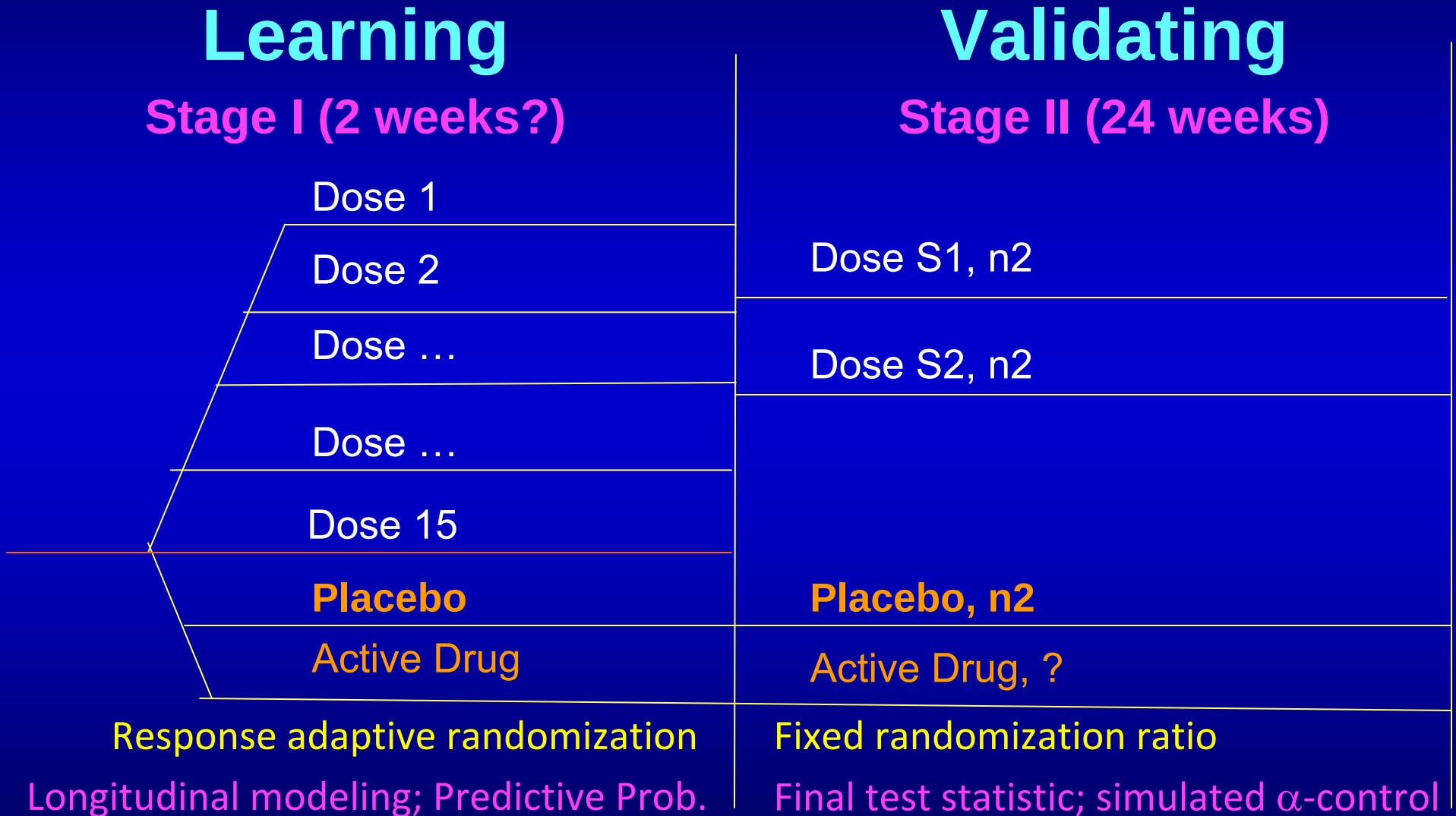
Adaptive Dose Ranging Designs #2 (2010)

- AMCPMod: Optimal design + Model (uncertainty) + Bayesian statistics (Bornkamp, Bretz, Pinheiro, Dette)
- DCoD: D-optimal followed by C-optimal design based on sigmoid Emax model (Dragalin, Padmanabhan)
- IntR – Bayesian design minimizing average variance of all LS-estimates for "interesting part" of dose-response curve (Miller)
- MultObj – Multi-objective optimal design incorporating 2nd order moments and based on inverse quadratic model (Smith)
- T-Stat – Dose-adaptive design: t-statistics (Patel, Perevozskaya)

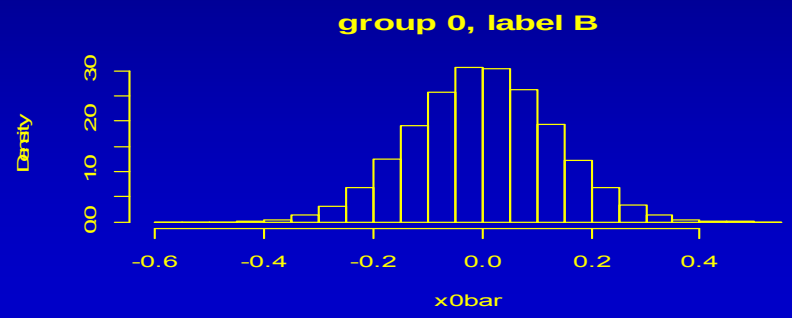
Utility/Pitfall - Adaptive Dose Selection

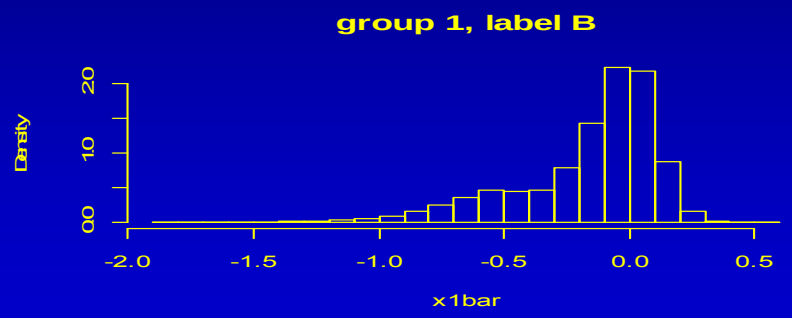
- Properly recognized as Ph2 learning trials
- Attractive because
  - Interested in a Ph2-like sample size
  - Can learn from several more doses if response adaptive used
  - Better precision to estimate doses of greater interests
  - Efficient learning of DR relationship for faster decision making on dose selection, though DR may not be fully characterized
- Adaptive learning trial – other design elements, e.g., multiple patient (sub)populations, from small to large and vice versa, efficacy endpoint not understood? Biomarker – how predictive? effect size if primary endpoint known

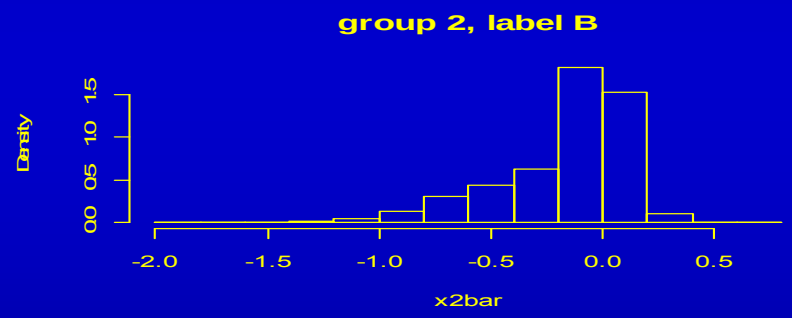
Two-Stage Adaptive Dose Selection #1

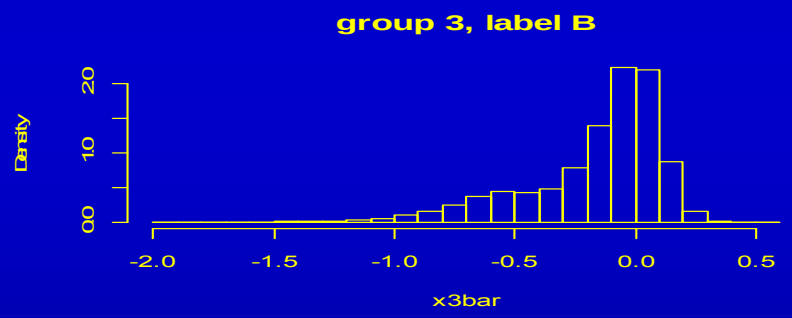


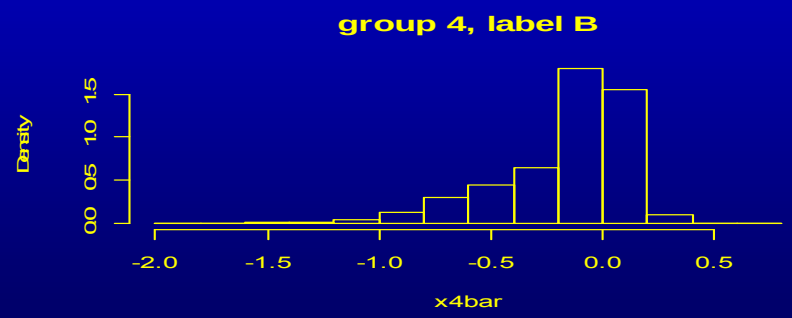
A Frequentist Version of response adaptive allocation

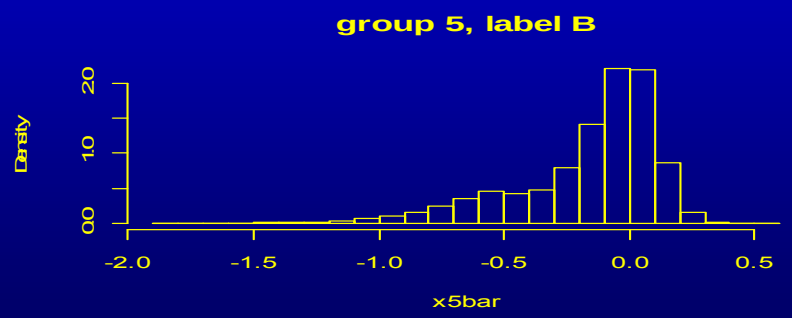










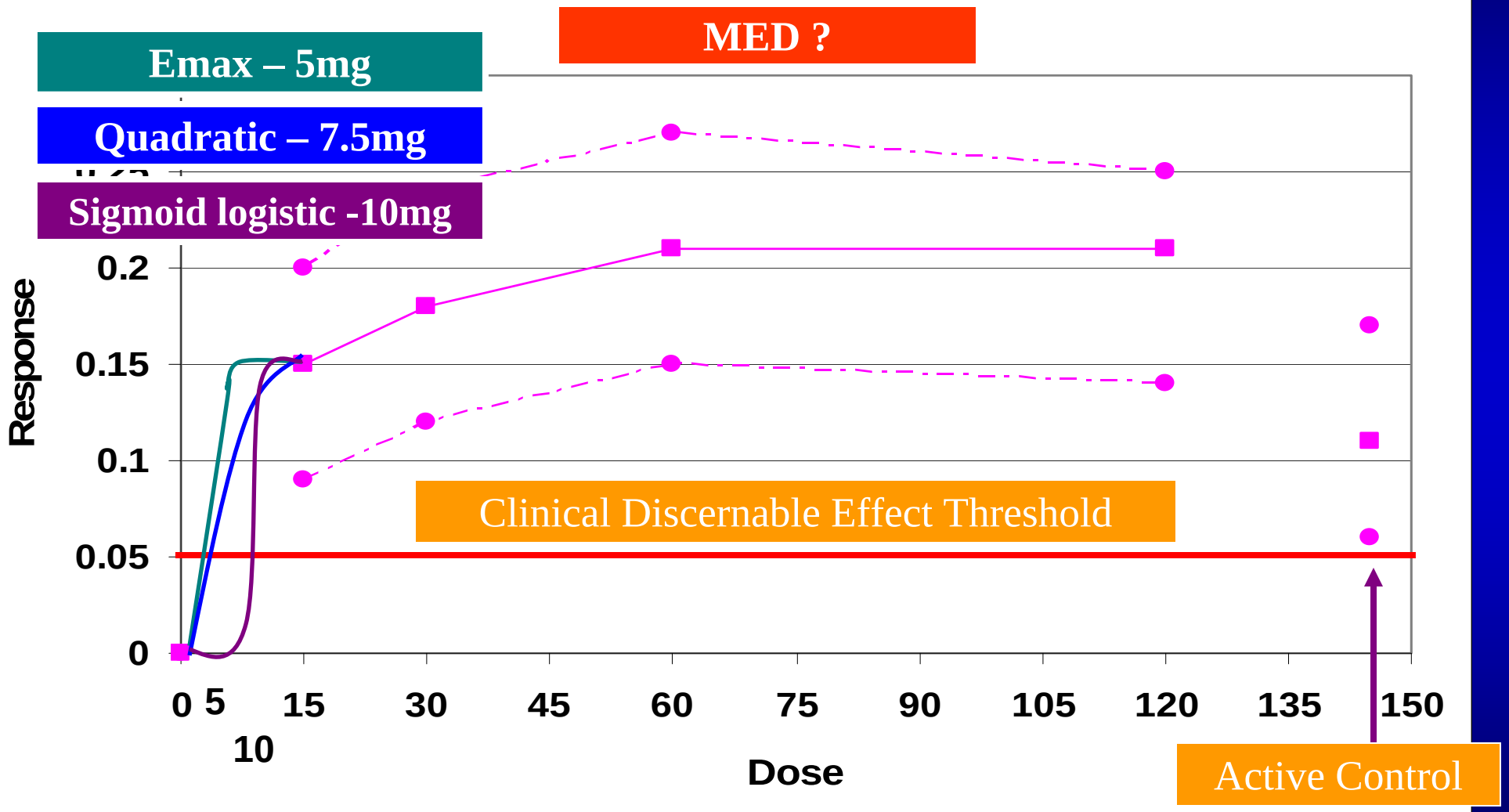


Wang SJ, SBR (2010) – based effect estimates

Discernable Effect

- Serve as a ‘guide’ in the exploratory stage
- Better than ‘eye-balling visual’ dose selection
- Can be very informative if safety issue is not a concern
- When benefit/risk profile can be a function of dosing frequency, dose-level
- Often efficacy biomarker, different from MCIE in confirmatory trial
- Even if clinical endpoint, MCIE is in the eyes of the beholder in exploratory studies
- When active control(s) are included

Figure. Estimated 95% DR Curve



Clinical Trial Designs

- Currently, clinical trial program in drug development mostly consists of
  - Learning phase
    Phase 1 trial, POC trial, Phase 2 trial
  - Confirming phase (or evidence setting)
    Phase 3 trial

Limitations of FD in Learning Trial

- Learning is often based on markers or endpoints other than 1° clinical endpoints
- Sample size is limited, not powered for studying 1° clinical endpoints
- Chance of very informative learning about key clinical endpoints is small
- Dose selection based on statistical significance is limited

Departing Remarks

- More opportunity for novel research/software developments
  - When dose-response exploration is based on biomarker
  - Inference based on response adaptive allocation procedure
  - Utility of response adaptive allocation: allow exploration of several more dose regimens than fixed design approach
- Willingness to include near ineffective or suboptimal doses
- Need to learn intelligently in exploratory adaptive trials, as fully commitment of resources may not be an option
- Strategic consideration of dose range, dose levels, frequency for adapting when safety is of potential concern
- US FDA draft guidance encourages use of AD in learning trials