

**PhRMA Critical Path Initiatives**

**Rolling Dose Studies**

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**On behalf of the RDS Working Group**

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## Rolling Dose Studies WG members

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- Alex Dmitrienko, Eli Lilly
- Amit Roy, BMS
- Brenda Gaydos, Eli Lilly
- Frank Bretz, Novartis
- Franz König, Med. Univ. Vienna
- Frank Shen, BMS
- Greg Enas, Eli Lilly
- José Pinheiro, Novartis
- Michael Krams, Pfizer
- Qing Liu, J & J
- Rick Sax, AstraZeneca
- Tom Parke, Tessella

- Background: FDA's Critical Path Initiative and PhRMA PISC projects
- Leading a multi-company project: challenges and goals
- Rolling Dose Studies initiative
- Simulation study and sample of results
- Discussion

## Background

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- Pharmaceutical industry “pipeline problem”: decreasing number of approved drugs, despite advances in basic science
- FDA’s Critical Path Initiative — “Innovation vs. Stagnation” White Paper
- Pharmaceutical Research and Manufacturers of America (PhRMA) contracted Boston Consulting Group (BCG) to survey pharma executives, Health Authorities, and academics to identify key poor performance drivers
- 10 Pharmaceutical Innovation Steering Committee (PISC) working groups formed to address key issues
- Rolling Dose Studies (RDS), Novel Adaptive Designs, and Efficiency of Late-Stage Clinical Research among them

## Leading a PISC initiative: getting started

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- Chairs identified and nominated
- Need to clearly identify problem, goals, deliverables, and deadlines – project plan
- Form team: company nominations and volunteers
- Rediscuss project plan to reflect team's view
- Define how team will operate: conference calls, face-to-face meetings, etc

## Setting goals

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- Pre-competitive collaboration among pharma companies – potential anti-trust concerns (PhRMA supervision)
- Main goal is to identify and promote use of best practices across pharma industry
- Produce recommendations to be later discussed with FDA and other Health Authorities (HAs)
- Create greater awareness of recommended practices among pharma companies – internal and external presentations

## Challenges

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- Defining problem and goals in a clear and “productive” way
- Forming the team: right mix of talent, interest, availability, and long-term commitment
- Planning the work: feasible, yet relevant goals and deadlines
- Keeping motivation and productivity: everyone’s very busy with their regular jobs, natural decrease of interest over time – lots of e-mail, phone calls, building interpersonal relationships

- Interaction with colleagues from other pharma companies – learn about common methodological problems and their approaches to solve them
- Interaction with other PISC WGs, like Novel Adaptive Designs
- Access to industry-wide information, via PhRMA
- Channel to discuss methodological issues with FDA statisticians
- Possibility to influence the statistical thinking and practices across industry and with HAs

## RDS initiative – Motivation

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- Poor understanding of dose response (DR) for both efficacy and safety is pervasive in drug development
- Indicated by both FDA and industry as one of root causes of late phase attrition and post-marketing problems with approved drugs
- Current dose finding designs and methods focus on selection of MED out of fixed, generally small number of dose levels, via pairwise hypothesis testing  $\implies$  inefficient

## RDS initiative – Goals

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- Investigate and develop designs and methods for efficiently learning about safety and efficacy DR profile  $\implies$  benefit/risk profile
- More accurate and faster decision making on dose selection and improved labeling
- Evaluate statistical operational characteristics of alternative designs and methods to make recommendations on their use in practice
- Increase awareness about this class of designs, promoting their use, when advantageous

## RDS – Definition and Scope

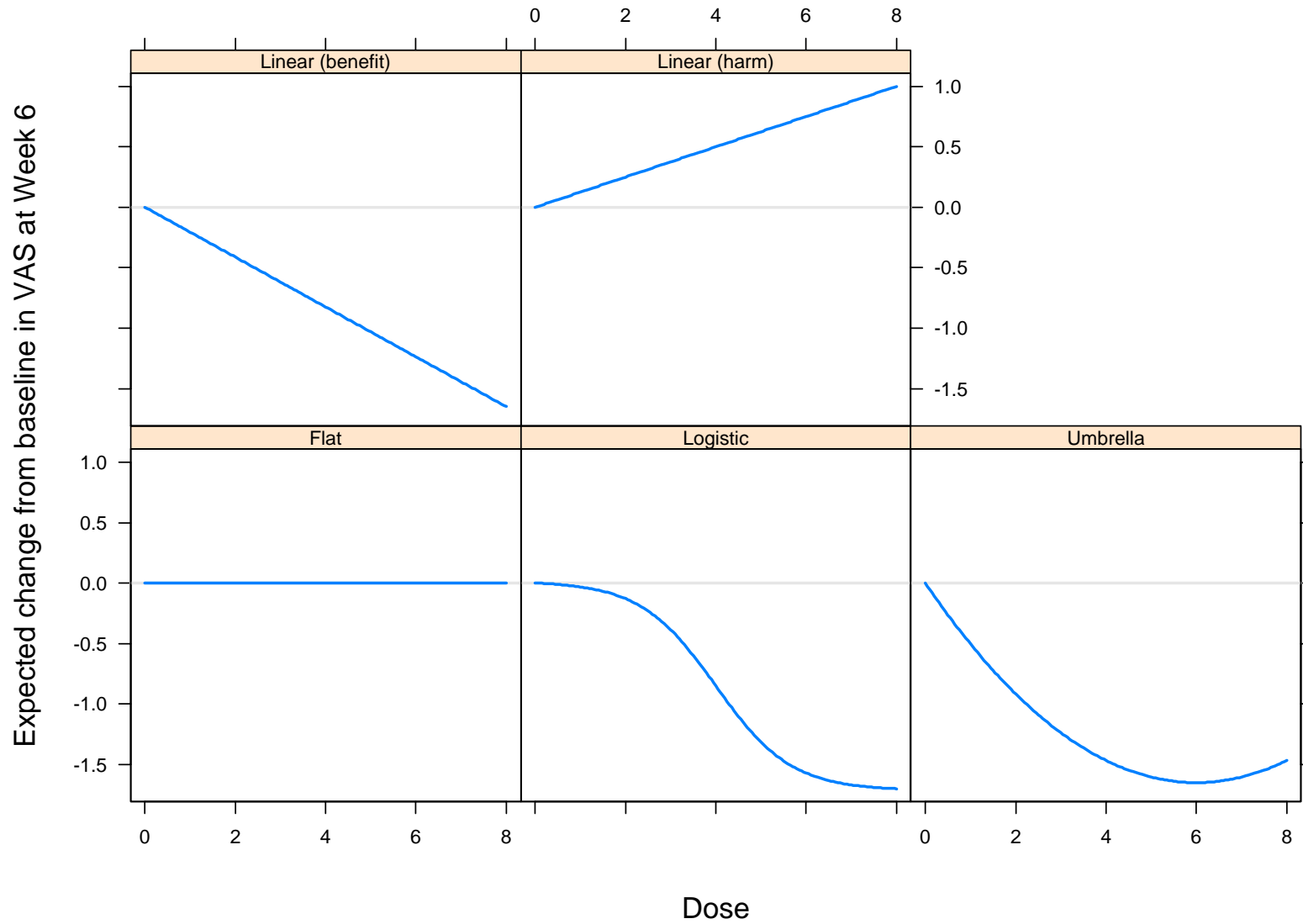
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- Flexible dose-ranging designs allowing dynamic allocation of patients and possibly variable number of dose levels based on accumulating information
- Intended to strike balance between need for additional DR information and increased costs and time-lines
- Emphasis on modeling/estimation (learning) as opposed to hypothesis testing (confirming)
- Investigate existing and new RDS methods via simulation
- Evaluate potential benefits over traditional dose-ranging designs over variety of scenarios to make recommendations on practical usefulness of RDS

## Simulation study: design and assumptions

- Proof-of-concept + dose finding trial, motivated by neuropathic pain indication
- Key questions: whether there is evidence of dose response and, if so, which dose level to bring to confirmatory phase and how well dose response (DR) curve is estimated
- Primary endpoint: change from baseline in VAS at Week 6
- Dose design scenarios:
  - 5 equally spaced doses levels 0, 2, 4, 6, 8
  - 7 unequally spaced dose levels: 0, 2, 3, 4, 5, 6, 8
  - 9 equally spaced dose levels: 0, 1, . . . , 8
- Significance level: one-sided FWER  $\alpha = 0.05$
- Sample sizes: 150 and 250 patients (total)

# Dose response profiles

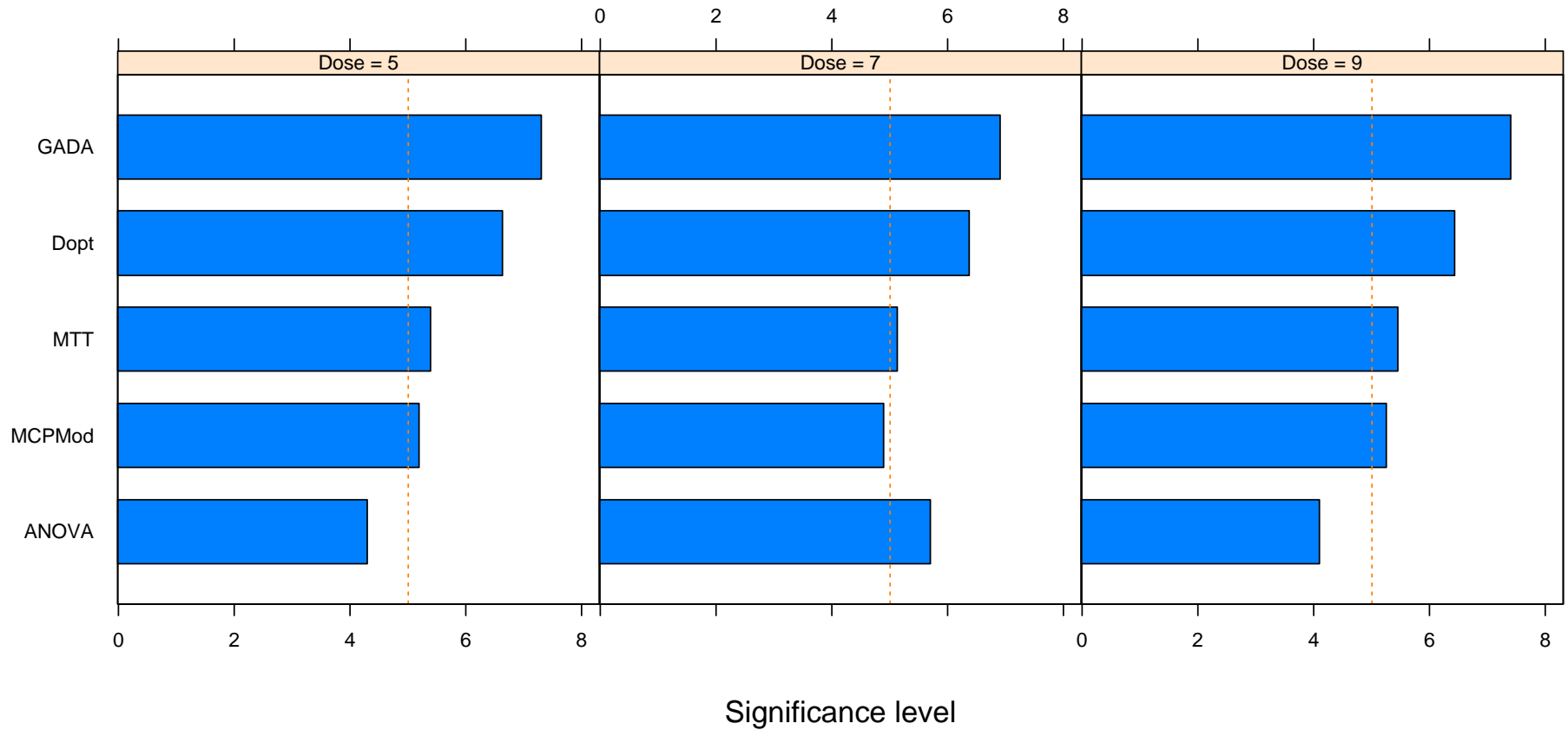


## Methods utilized in simulations

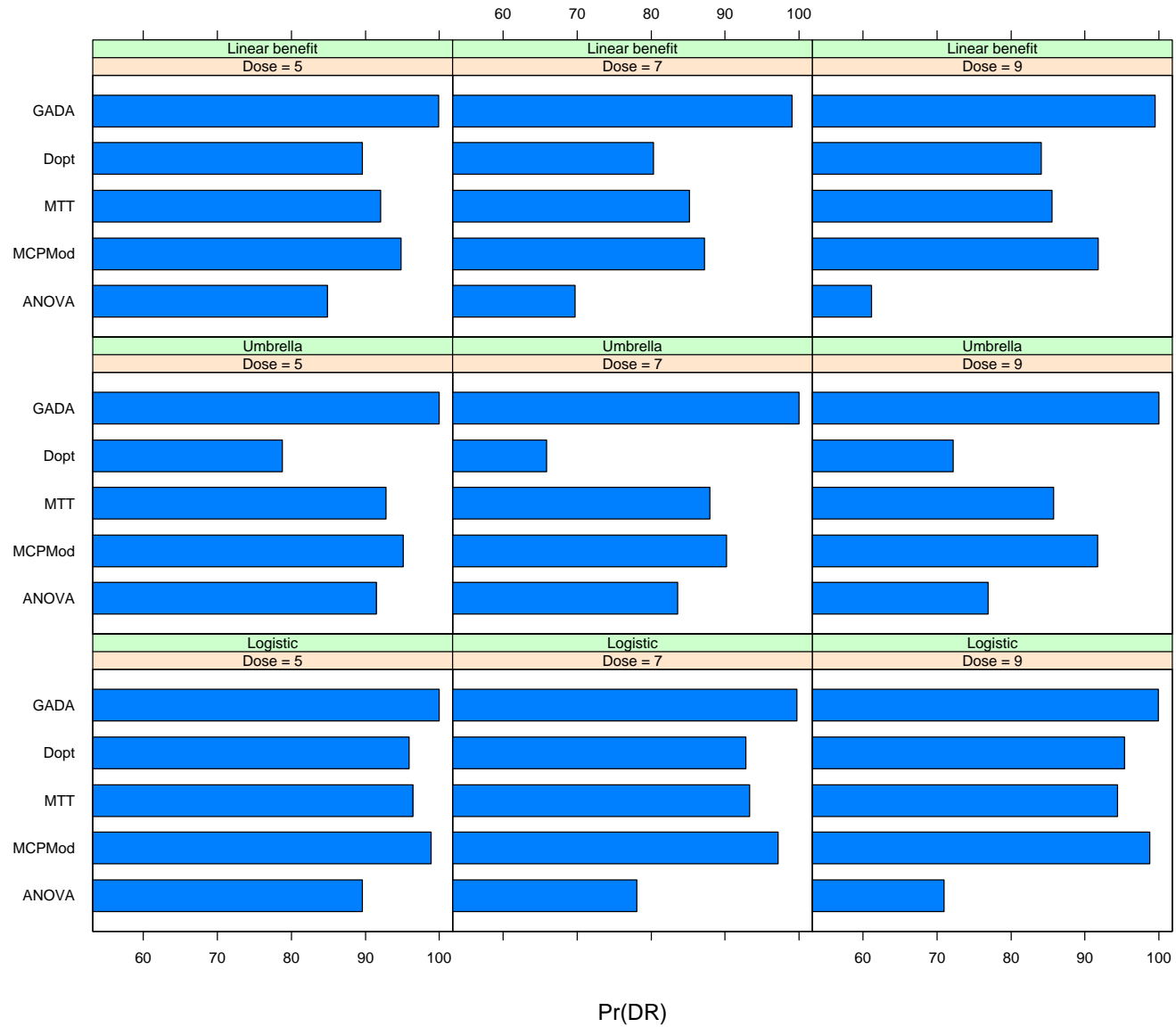
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- Fixed-dose methods for benchmarking
  - ANOVA with pairwise comparisons and multiplicity adjustment (Dunnett)
  - Multiple comparisons – modeling (MCP-Mod)
- RDS methods
  - GADA: Bayesian dynamic dose allocation based on non-parametric model
  - D-optimality adaptive allocation based on parametric model
- Non-adaptive, novel method (can potentially be made adaptive) based on Multiple Trend Tests (MTT)

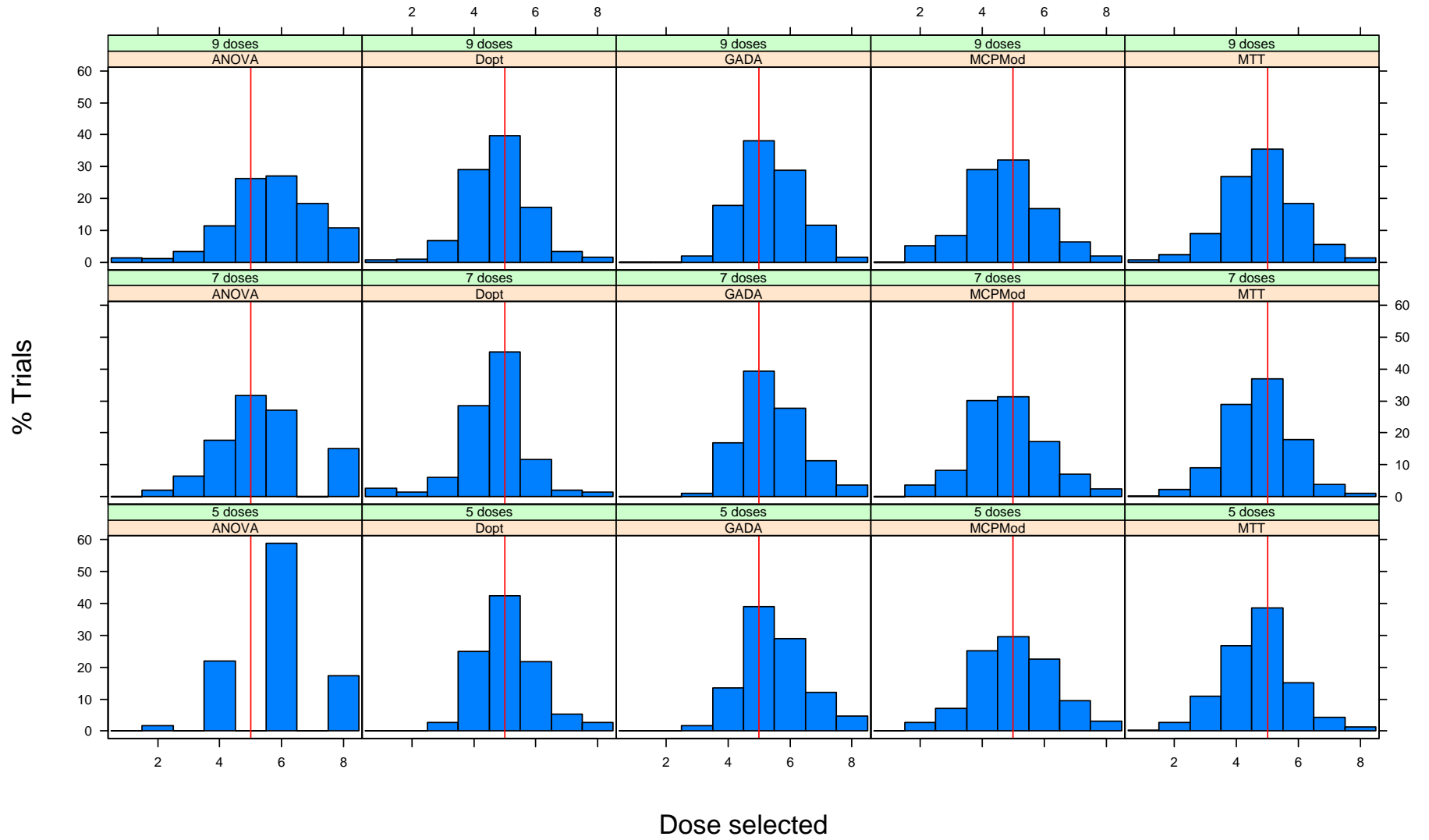
# Significance level, N=150



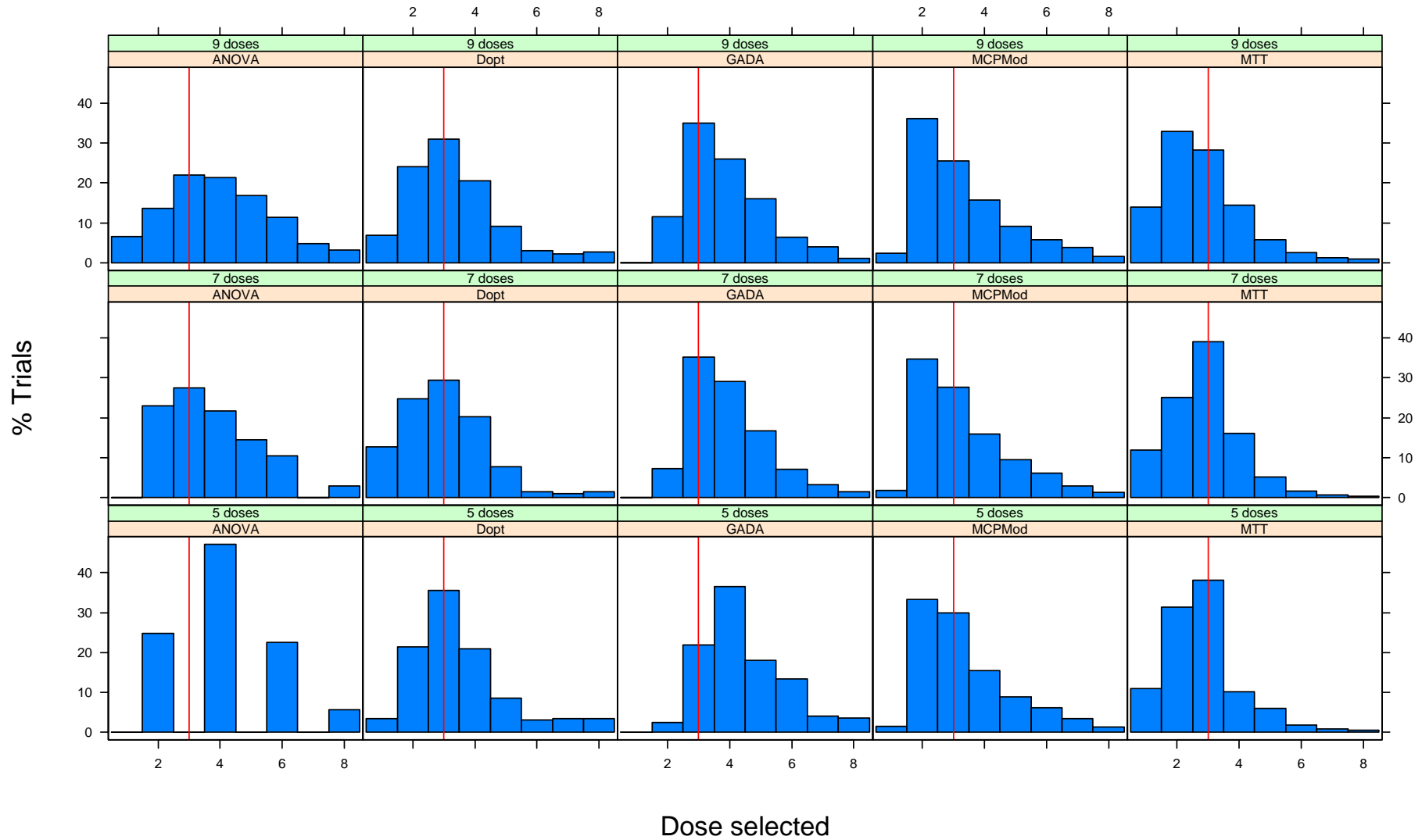
# Pr(identifying dose response), N=150



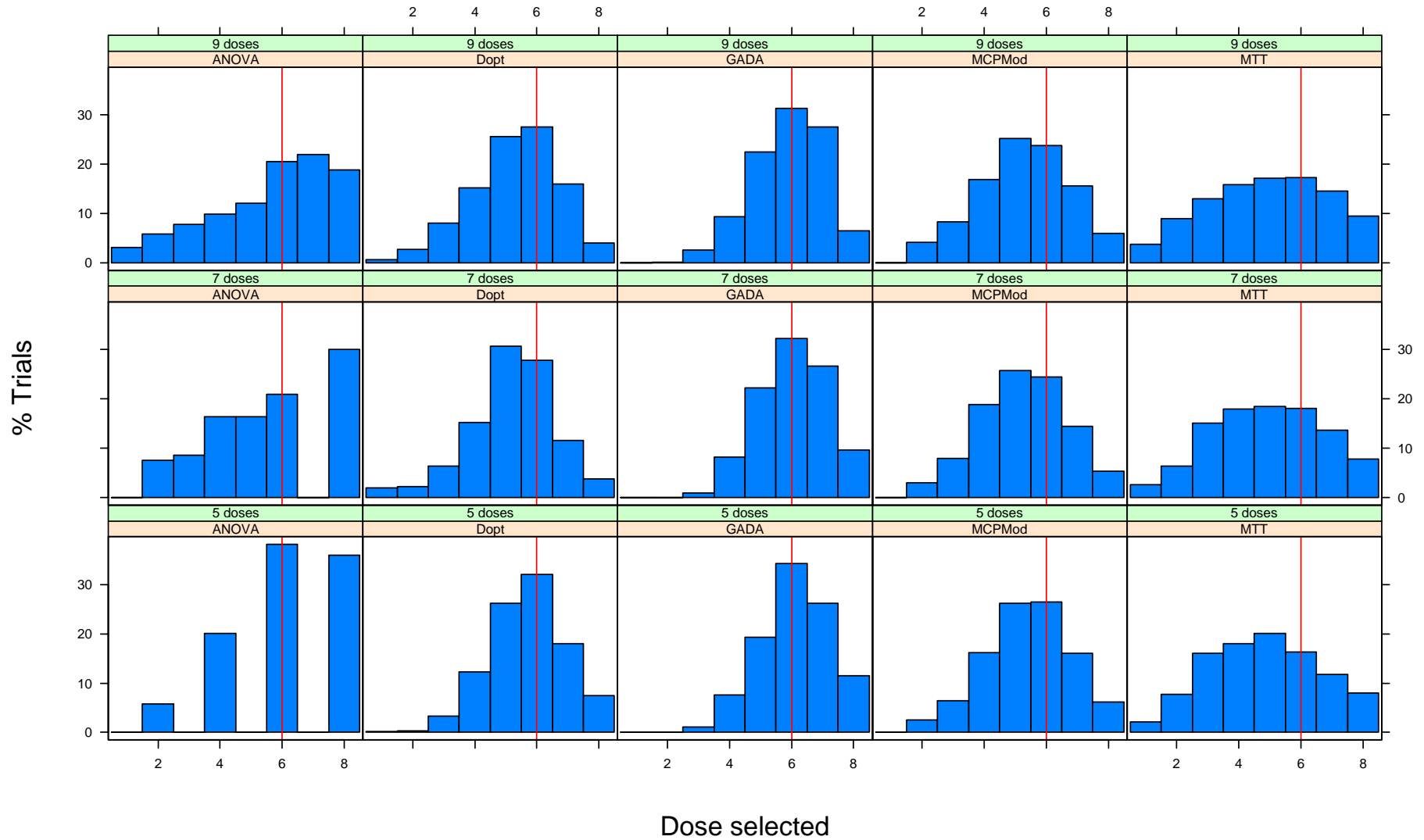
# Dose selected – Logistic DR, N=150



# Dose selected – Umbrella, N=150



# Dose selected – Linear benefit DR, N=150



- Detecting DR is considerably easier than estimating it
- Current sample sizes for DF studies are inappropriate for dose selection and DR estimation
- Model-based methods have superior performance
- RDS methods lead to gains in power and precision, but greater potential is in latter
- In practice, need to balance gains associated with RDS approach against greater methodological and operational complexity