Innovative Approaches for Designing and Analyzing Adaptive Dose-Ranging Trials

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on behalf of the PhRMA Adaptive Dose Finding Studies Working Group

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Acknowledgments: Adaptive Dose Ranging Studies WG

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- Qing Liu, J & J
- Rick Sax, AstraZeneca [a]
- Tom Parke, Tessella

[a]Co-leaders

Outline

- Background, motivation, and goals: PhRMA Adaptive Dose Ranging Studies (ADRS) WG
- Simulation study: comparative evaluation of designs and methods for adaptive dose selection
  - Methods
  - Results
  - Conclusions
- Recommendations of the ADRS WG

- Pharmaceutical industry pipeline problem: fewer approvals and increasing costs, despite advances in basic science
- FDA's Critical Path Initiative: "Innovation vs. Stagnation" White Paper
- PhRMA's response:
  - BCG survey identified key drivers of poor performance and proposed solutions
  - Pharmaceutical Innnovation Steering Committee (PISC) formed 10 working groups to implement proposals, including
    - Adaptive Designs (AD) WG
    - Adaptive Dose Ranging Studies (ADRS) WG

Motivation

- Poor understanding of dose response (DR) for both efficacy and safety is pervasive in drug development
- Sub-optimal dose selection has been identified by both FDA and industry as one of root causes of late phase attrition and post-marketing problems
- Need to improve current dose selection methods, in which a registrational study dose is generally selected from one of a fixed (usually small) number of tested doses, based on pairwise hypothesis tests
- Optimize patient treatment within a study, by minimizing patients exposed to ineffective treatments

What is an Adaptive Clinical Study Design?[a]

- Adaptive Clinical Study Design: A design in which data from the ongoing study is used to modify the conduct of the study
  - Need to define objective of the adaption
  - Adaption could involve any design element, not just dose
- Adaptive BY design: Adaption is a design feature, not a remedy for indadequate planning
  - Through upfront planning is required
  - Decision rules for adaption are prespecified

[a] Adapted from: *Adaptive Design in Exploratory Development*, Brenda Gaydos, Joint Statistical Meeting, August 2006

ADRS WG: Goals

- Investigate and develop designs and methods for efficiently learning about safety and efficacy dose-response $\Longrightarrow$ benefit/risk profile
- More accurate and faster decision making on dose selection and improved labeling
- Evaluate statistical operating characteristics of alternative designs and methods, and make recommendations on their use
- Document and publish findings of the ADRS WG, and increase awareness of this class of designs

ADRS: Definition and Scope

- 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 reduced timelines

- Emphasis on modeling/estimation (learning) as opposed to hypothesis testing (confirming)

- Compare new and existing ADRS designs and methods for a variety of scenarios via simulation, and make recommendations on their application

Dose Finding Methods – Fixed Doses

- ANOVA: Conventional method based on pairwise comparisons and multiplicity adjustment (Dunnett); common approach used in dose finding studies – Amit Roy and Frank Shen
- MCP-Mod combination of a multiple comparison procedure (MCP) to identify presence of DR, and modeling to estimate target dose(s) and DR profile (Bretz, Pinheiro and Branson, 2005) – José Pinheiro and Frank Bretz
- MTT: novel method based on Multiple Trend Tests (Liu, 2006) – Qing Liu
- BMA: Bayesian Model Averaging (Hoeting, Madigan, Raftery and Volinsky, 1999)– Beat Neuenschwander and Amy Racine
- LOCFIT: Nonparametric local regression fitting – Björn Bornkamp and Frank Bretz

Dose Finding Methods – Adaptive dose allocation

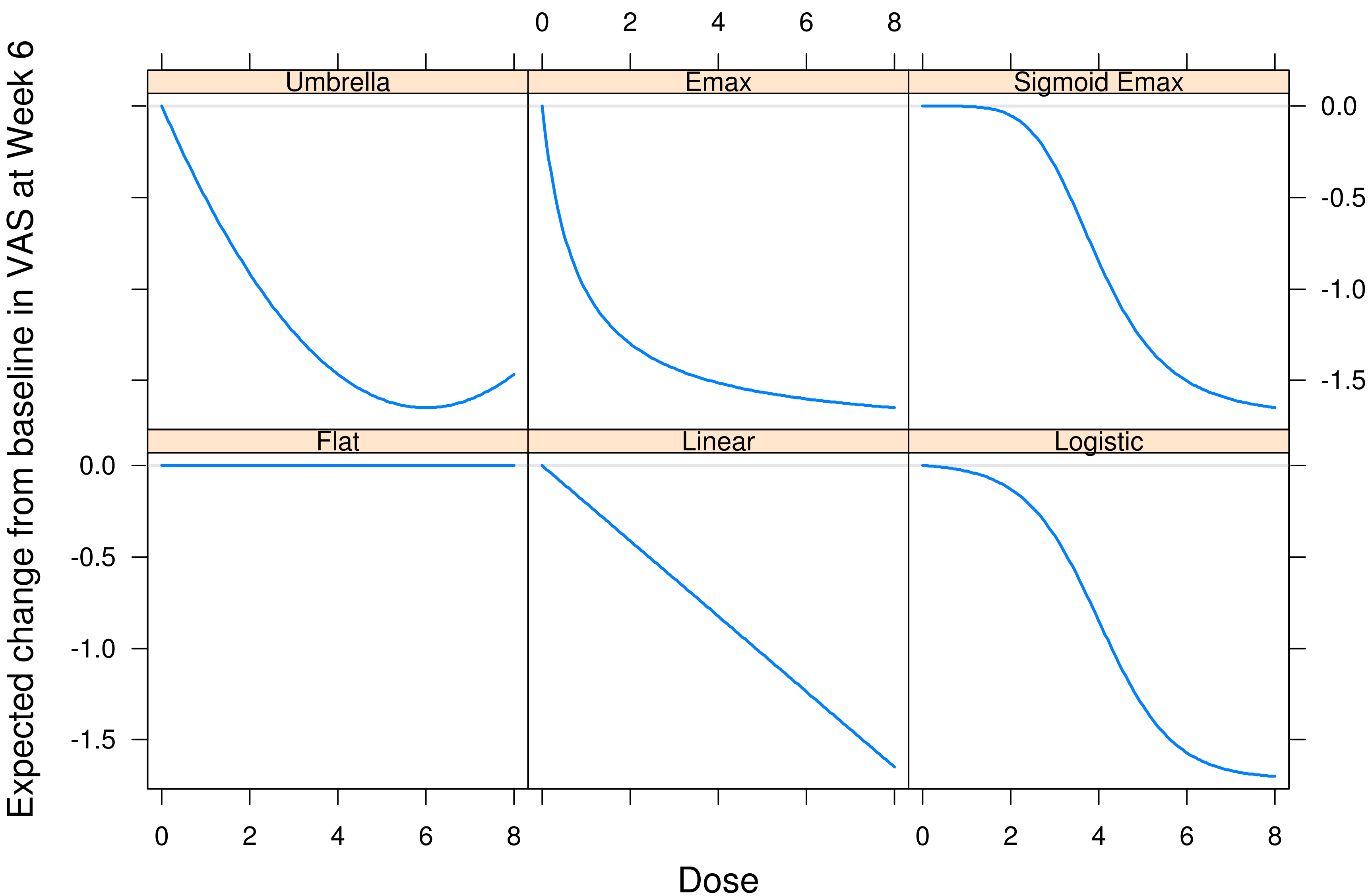
- GADA: General Adaptive Dose Allocation based on a Bayesian normal dynamic linear model (Krams, Lees and Berry, 2005); allocation of patients to dose changed adaptively according to model-based optimization criteria (e.g., variance of target dose estimate) – Tom Parke and Michael Krams
- D-opt: adaptive dose allocation based on D-Optimality criterion used with sigmoid-E_{max} model; model parameters re-estimated at interim analysis and corresponding D-optimal allocation determined for next interval – Alex Dmitrienko and Chyi-Hung Hsu

Simulation study: Design and assumptions

- Objective: proof-of-concept + dose finding for neuropathic pain
- Primary endpoint: change from baseline in pain score (VAS)
- Key questions:
  - is there evidence of a dose response
    - Significance level (one-sided FWER): 0.05
    - Clinically relevant change in VAS: 1.3
  - which dose(s) should be tested in large confirmatory trials
  - how well is the dose response (DR) curve estimated
- Study design scenarios:
  - Sample sizes: 150 and 250 patients
  - Number of doses: 5, 7, and 9 doses [a]

[a] 5 doses (0, 2, 4, 6, 8), 7 doses (0, 2, ..., 6 , 8), and 9 doses (0, 1, ..., 8)

Dose response profiles



- Probability of identifying dose response: $\Pr(DR)$
- Probability of identifying clinical relevance and selecting a dose for confirmatory phase: $\Pr(dose)$
- Dose selection: Distribution of selected doses (rounded to nearest integer, if continuous estimate possible)

Measuring performance (contd.)

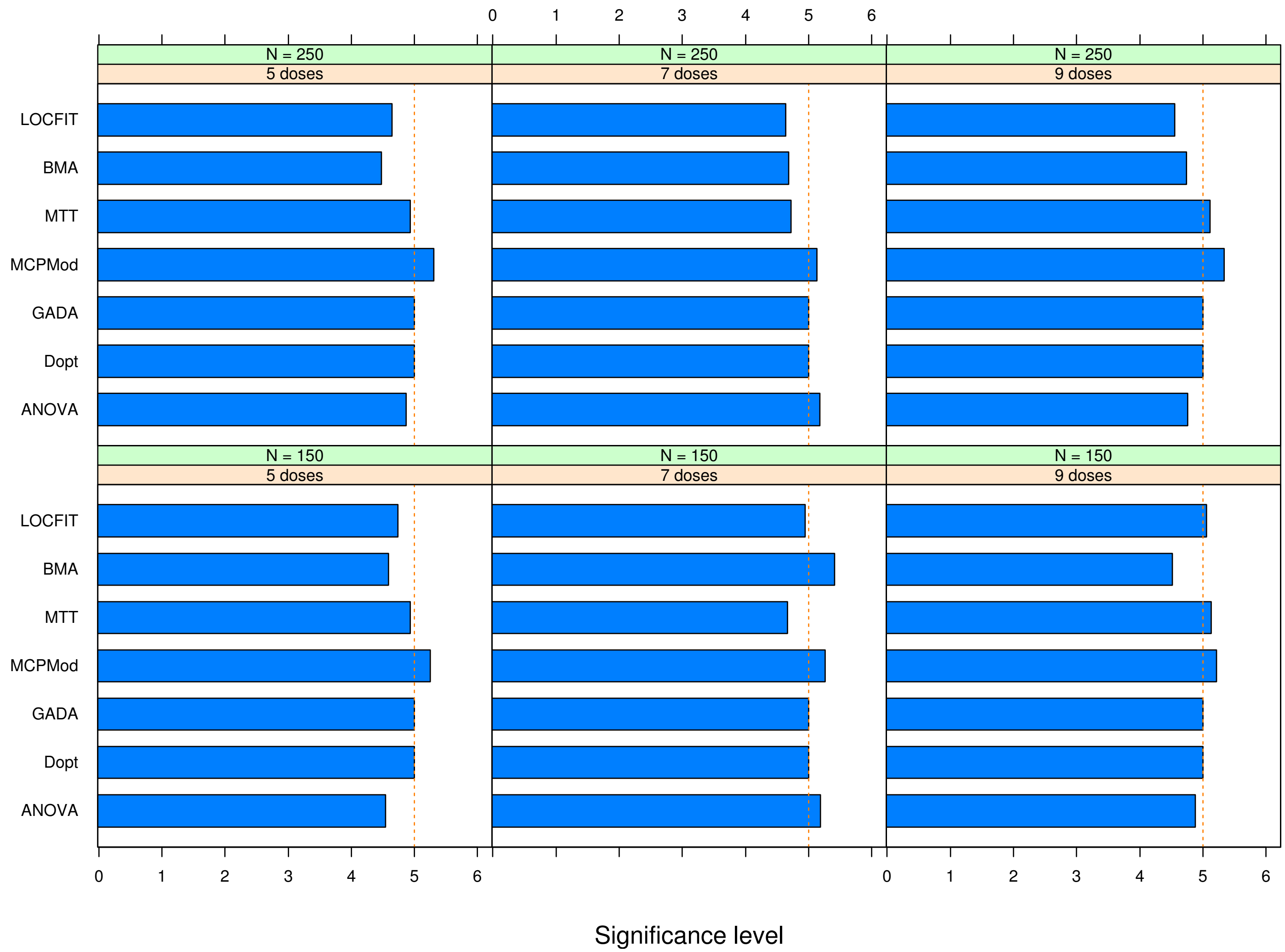
- Target dose interval – doses that produce effect within $\pm 10\%$ of target effect Δ

	Target dose		Target interval	
Model	actual	rounded	actual	rounded
Linear	6.30	6	(5.67, 6.93)	{6,7}
Logistic	4.96	5	(4.65, 5.35)	{5}
Umbrella	3.24	3	(2.76, 3.81)	{3,4}
Emax	2.00	2	(1.44, 2.95)	{2,3}
Sig-Emax	5.06	5	(4.68, 5.58)	{5}

- Probabilities of under-, over-, and correct interval estimation:
$\mathrm{Pr}^- = \mathrm{Pr}(\widehat{d}_{\mathrm{targ}} < d_{\mathrm{min}}),\ \mathrm{Pr}^+ = \mathrm{Pr}(\widehat{d}_{\mathrm{targ}} > d_{\mathrm{min}}),$
$\mathrm{Pr}^\circ = 1 - (\mathrm{Pr}^- + \mathrm{Pr}^+)$

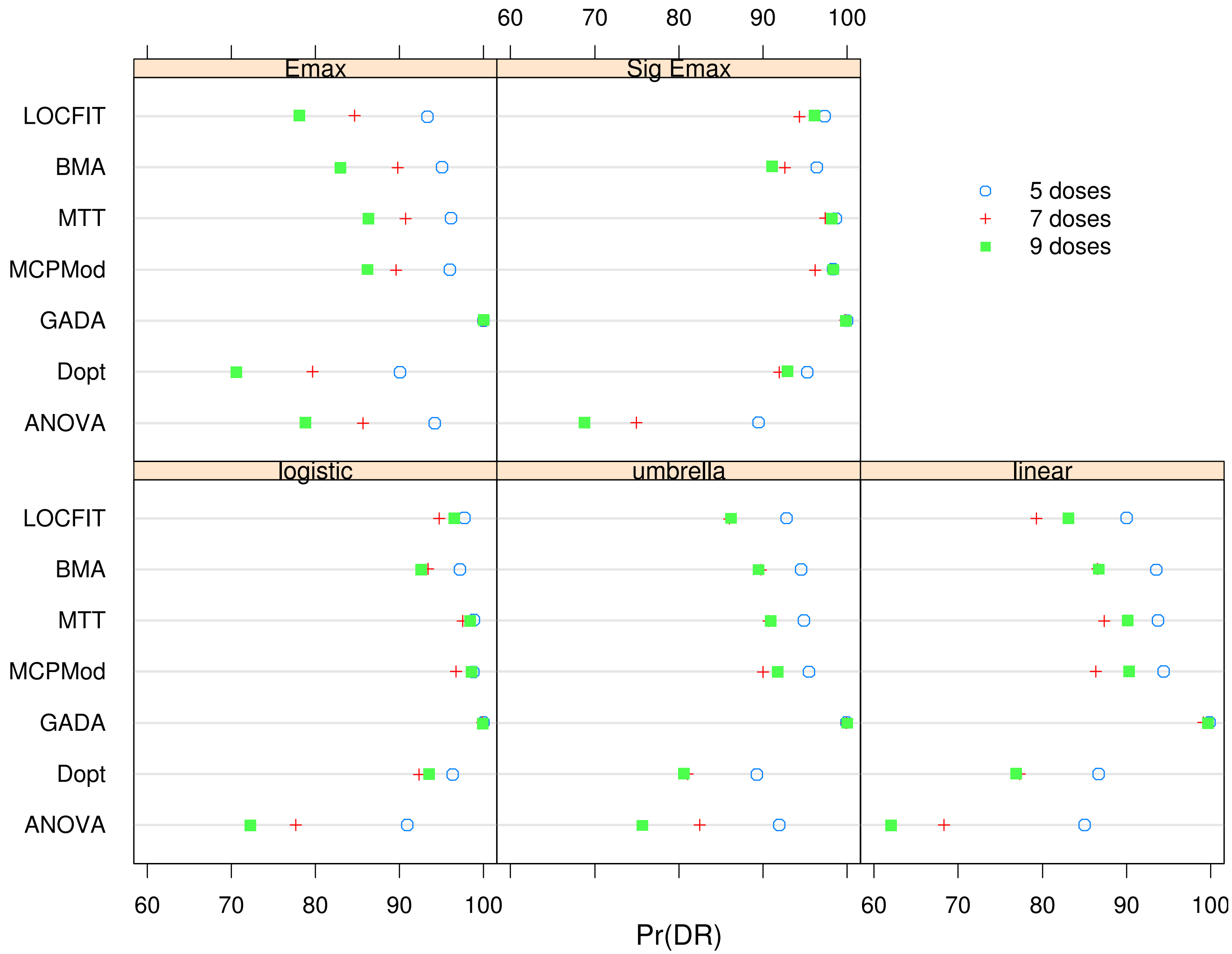
Selected Simulation Results

Probability Identifying DR – Flat DR



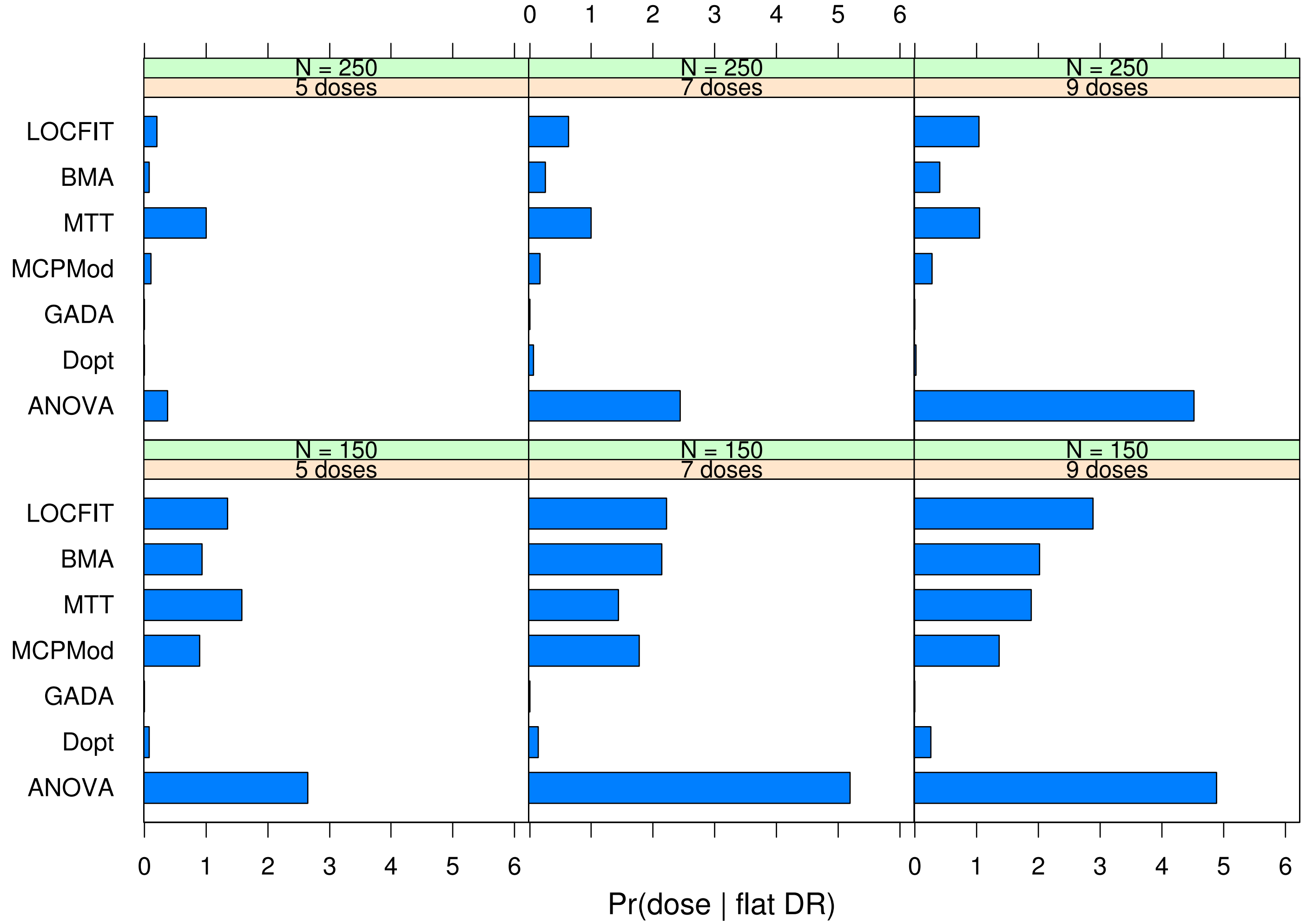
Type I Error is controlled at 5% by all methods

Probability of identifying DR (N = 150)



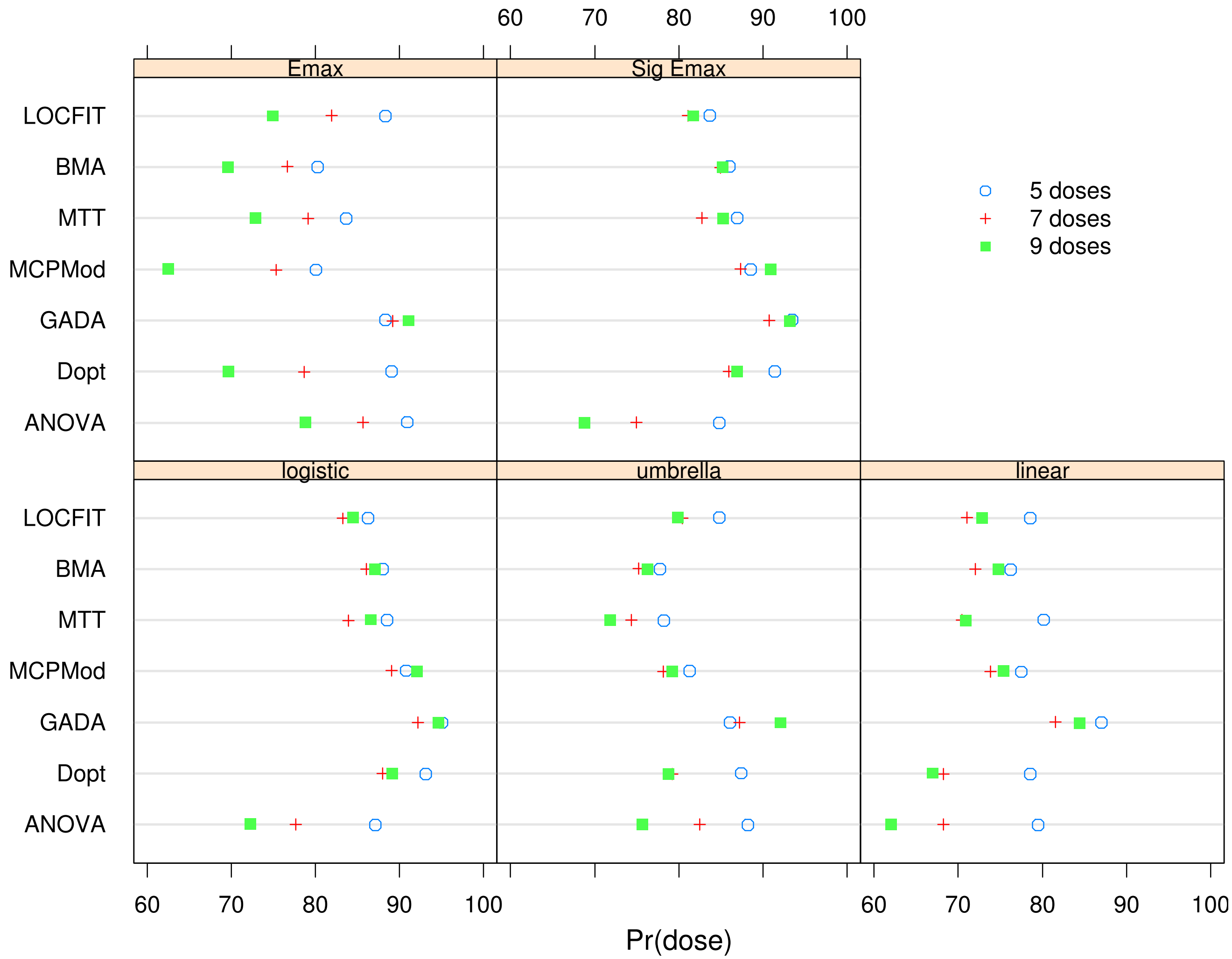
Pr(DR) generally ↑ as # doses ↓ (for fixed sample size)

Probability dose selection – Flat DR



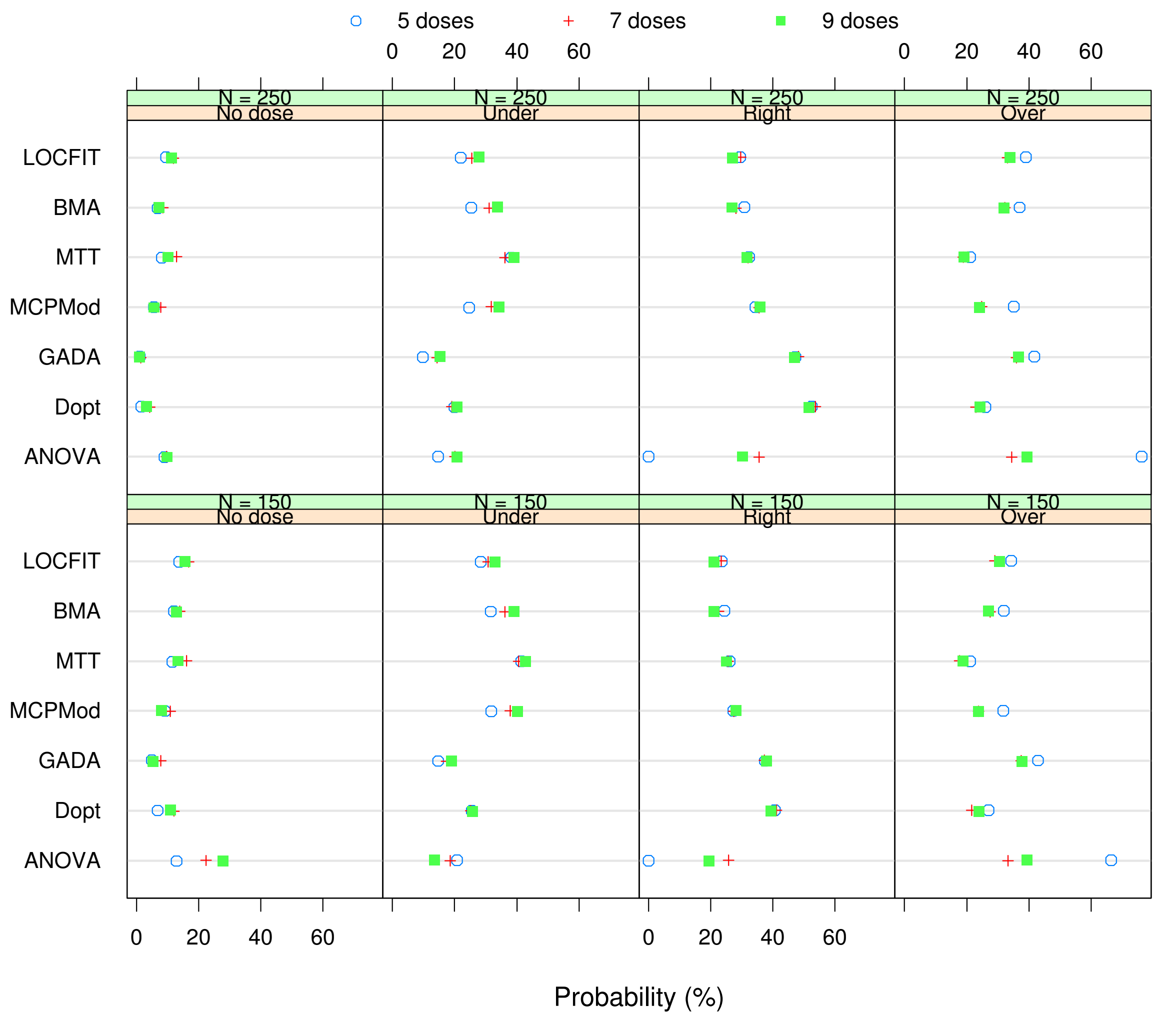
False positive for clinically relevant effect is generally greater for ANOVA

Probability dose selection (N = 150)



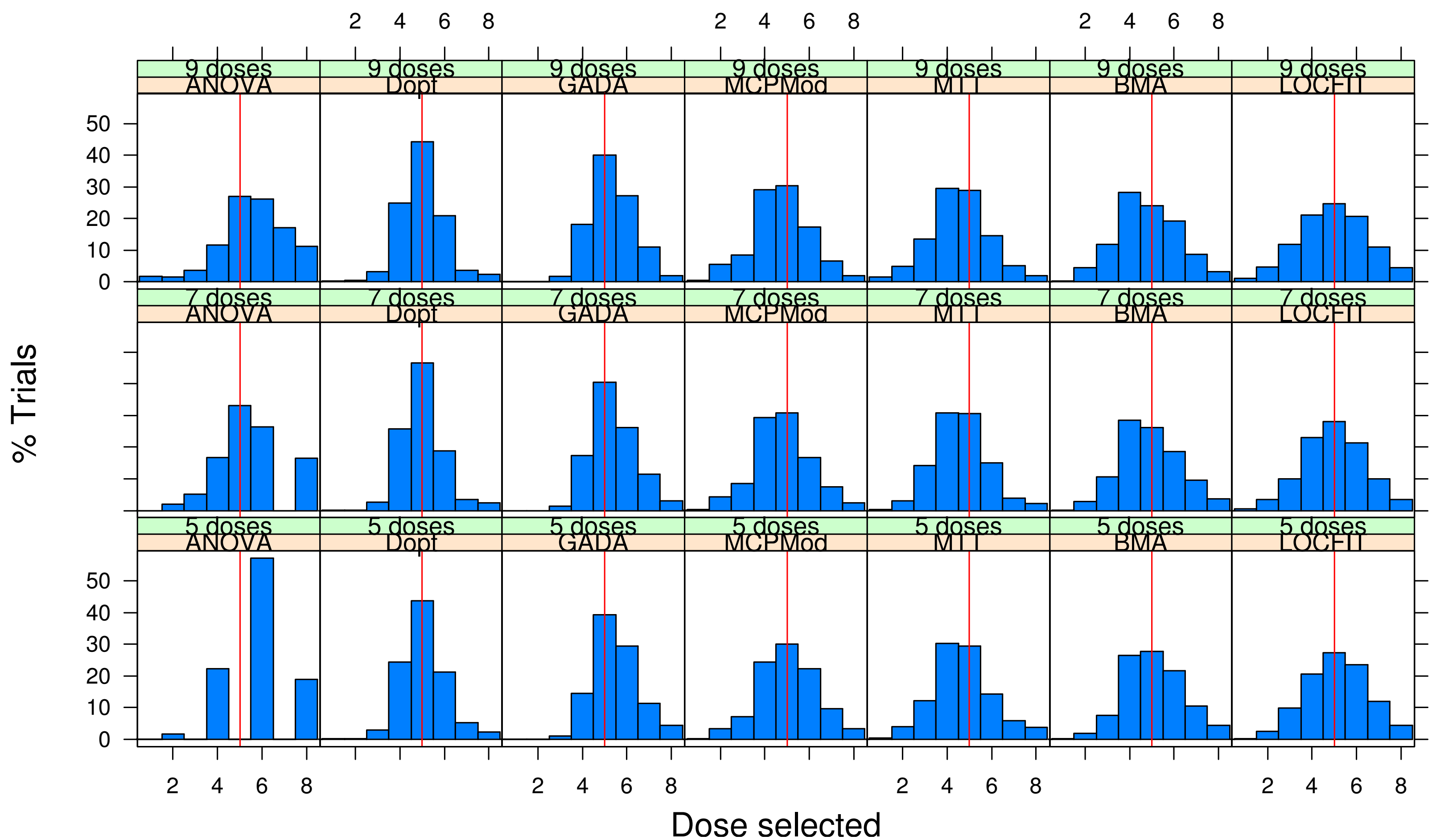
Most methods perfomed poorly, GADA generally best

Probability dose in target interval – Logistic DR



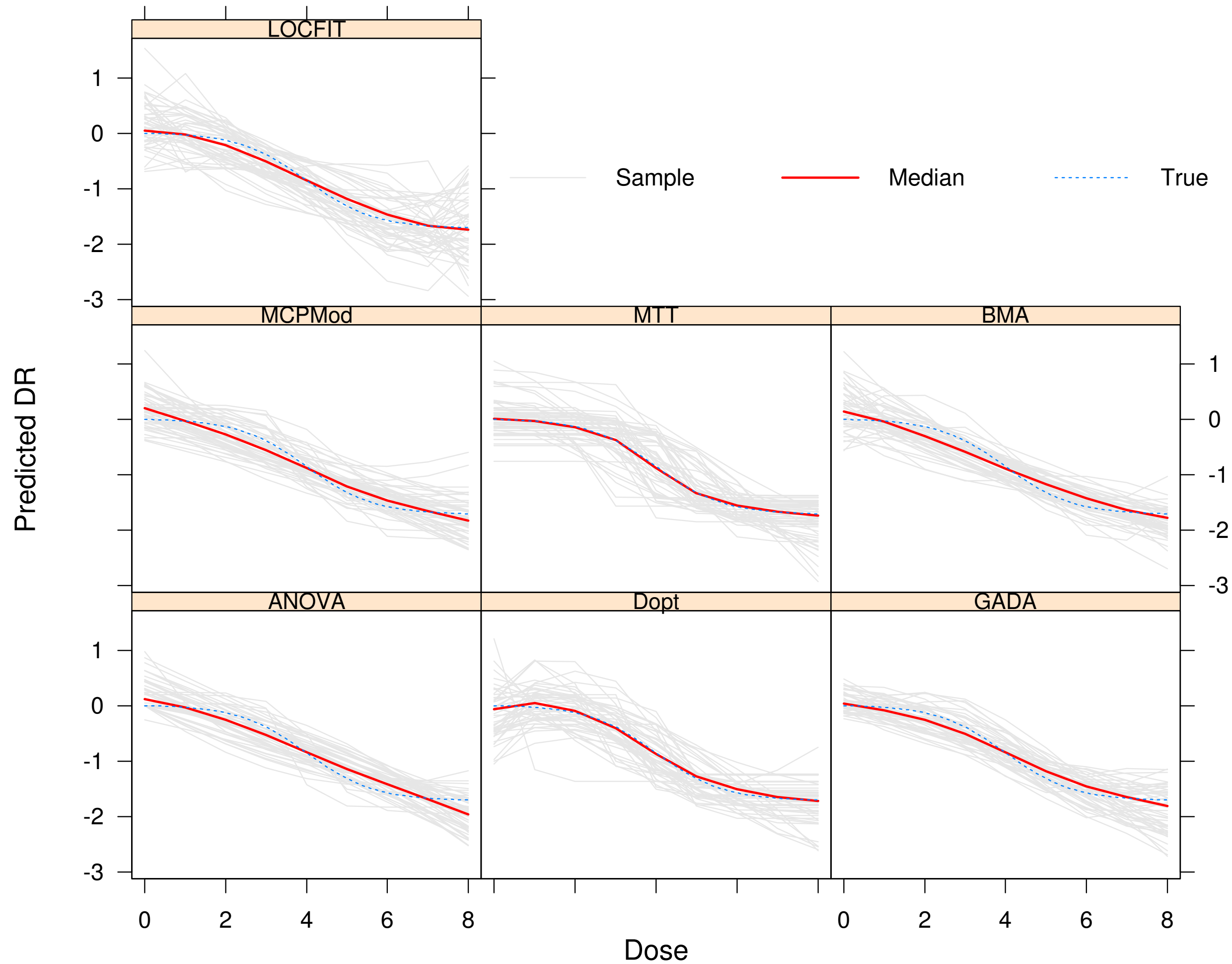
None of the methods were entirely adequate

Distribution of selected dose – Logistic DR (N = 150)



Distribution of selected doses is wide for all methods

Sample predicted curves – Logistic DR, 9 doses (N = 150)



Overall shape of DR was described fairly well by all methods

Overview of Relative Performance of Methods [a]

Method	$\Pr(DR)$	$\Pr(dose)$	Bias	Error	Dose Interval	DR
ANOVA	++	+	++	++	–	NA
GADA	+++	+++	++	++	++	+++
D-opt	+++	++	+++	++	++	++
MTT	+++	++	+++	++	+	++
MCP-Mod	+++	++	+++	++	+	++
BMA	+++	++	+++	++	+	++
LOCFIT	+++	++	+++	++	+	++

[a] Relative Performance: – (poor), + (fair), ++ (good), and +++ (very good)

Conclusions

- Detecting DR is considerably easier than estimating it, or identifying a target dose to advance into a confirmatory trial
- Sample sizes for DR studies that are based on power to detect a DR are generally inadequate for DR estimation and dose selection
- Adaptive dose finding methods lead to gains in power to detect DR, precision of DR estimation, and selecting correct target dose – greatest potential in the latter two
- In practice, need to balance gains associated with adaptive dose ranging designs approach against burden of greater methodological and operational complexity

Recommendations

- Adaptive, model-based designs should be routinely considered for dose ranging studies
- Proof-of-concept (PoC) and dose selection should be combined into a single seamless trial, when feasible
- Trial simulations should be used to determine the operating characteristics of designs/methods under consideration, and for sample sizes estimation
- Sample size calculations for Phase II studies should take into account desired precision of estimated target dose
- Consider using more than one dose in Phase III, when sample size of Phase II was inadequate

Recommendations (contd.)

- Early stopping rules, for both efficacy and futility, should be used when feasible
- Software for designing, implementing, and analyzing data from adaptive dose-ranging studies needs to be developed
- In practice, need to balance gains associated with adaptive dose ranging designs approach against greater methodological and operational complexity

NOTE: A white paper describing this work is available from BioPharmNet website (http://biopharmnet.com/doc/doc12005.html), and has been accepted for publication in the November 2007 issue of the *Journal of Biopharmaceutical Statistics*, along with commentary by Carl-Frederik Burman (Astra-Zeneca), Andy Grieve (King's College, Univ. of London), Robert Hemmings (MHRA, UK), Sergei Leonov (GSK), and Sue-Jane Wang (US FDA)

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