

Accelerating Clinical Development With Adaptive Study Designs

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- Background
- Adaptive Study Designs
 - Definitions
 - Types
 - Logistics
- Adaptive Dose Ranging Studies (ADRS)
 - Goals of ADRS Working Group
 - Simulation study to evaluate methods
 - Recommendations

- Pharmaceutical industry **pipeline problem**: decreasing number of drug approvals and increasing cost, despite advances in basic science
- US FDA white papers
 - *Challenge and Opportunity on Critical Path to New Medicinal Products* (2004)
 - *Critical Path Opportunities List* (2006)
- Pharmaceutical industry (PhRMA) response: Pharmaceutical Innovation Steering Committee (PISC) Working Groups

Critical Path Opportunities and PISC WGs

- Streamlining clinical trials
 - Adaptive Dose Ranging Studies WG
 - Adaptive Designs WG
 - Improving Efficiency of Late-Stage Clinical Research (ECR WG)
- Better evaluation tools: Biomarkers WG
- Harnessing bioinformatics: Data Mining Tool Validation WG
- Addressing public health needs: Predictive Models for Safety and Efficacy WG

What is an Adaptive Clinical Study?

- Definition^a: A multi-stage study in which data from the ongoing study is used to modify the conduct of the study without undermining the *validity* and *integrity* of the trial
- Adaptive BY design: Adaption is a **prospective** design feature, not a remedy for inadequate planning
 - Through upfront planning is required
 - Rules for adaption are prespecified

^aAdaptive Designs: Terminology and Classification (Dragalin, 2006)

Types of Adaption and Prespecified Rules^a

- Group sequential designs (Stopping Rule)
- Sample-size reassessment (Sampling Rule)
- Response adaptive designs (Allocation Rule)
- Flexible designs (e.g. Seamless Phase 2/3 designs)
 - Allocation Rule
 - Sampling Rule
 - Stopping Rule
 - Decision Rule

^aAdaptive Designs: Terminology and Classification (Dragalin, 2006)

Logistics of Implementing Adaptive Designs

- Planning and education
- Recruitment rate
- Data monitoring
- Randomization
- Drug supply

Motivation: ADRS WG

- Poor understanding of dose response (DR) for both **efficacy** and **safety** is pervasive in drug development
- Sub-optimal dose selection identified 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 registrational study dose out of fixed, generally small number of dose levels, via pairwise hypothesis testing \implies **inefficient**
- Optimize patient treatment within a study, by minimizing patients exposed to ineffective treatments

Goals: ADRS WG

- Investigate and develop designs and methods for efficiently **learning** about safety and efficacy dose-response \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
- Document and publish findings of the working group

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 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

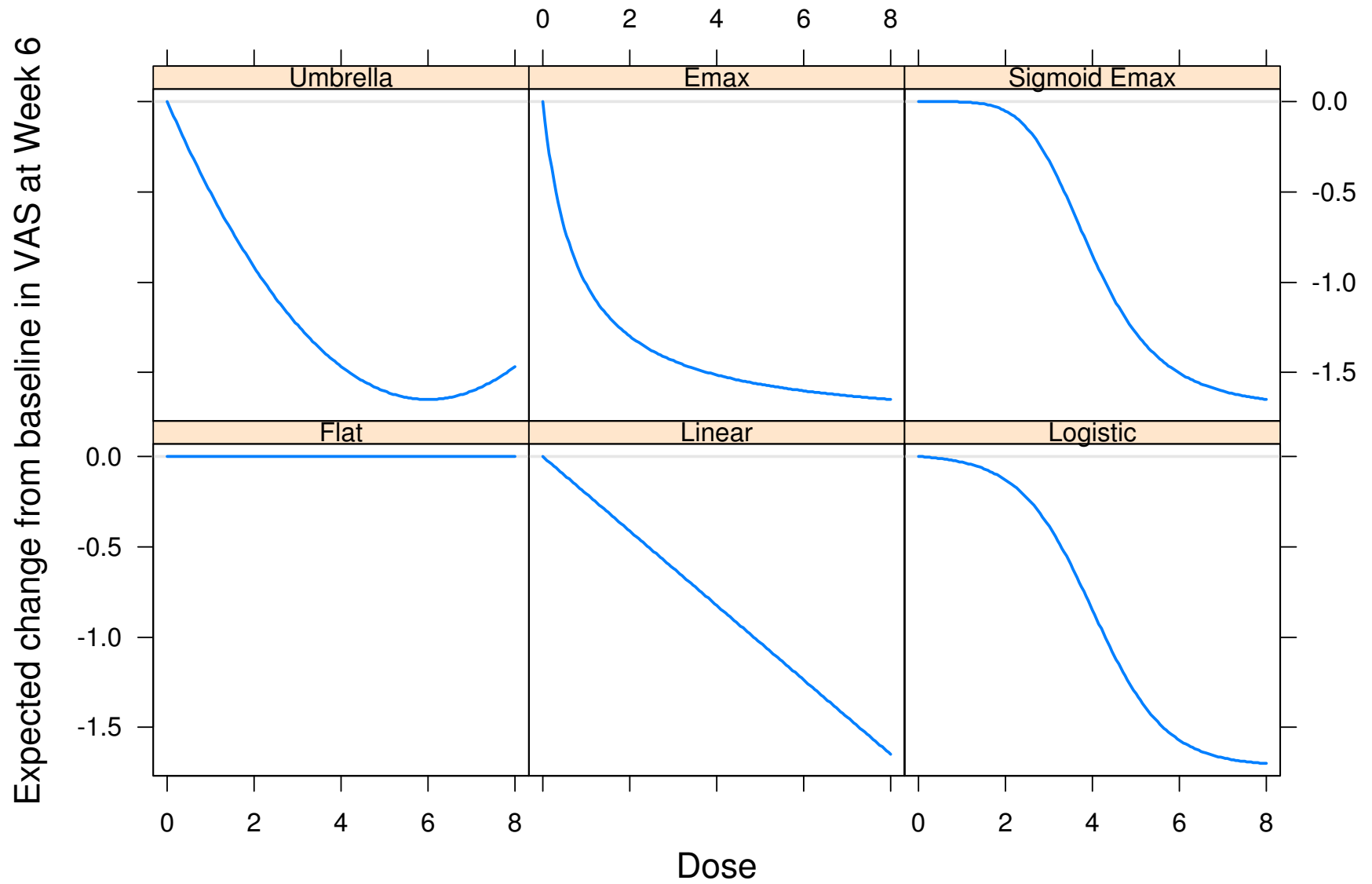
- **GADA**: Adaptive dose allocation based on Bayesian normal dynamic linear model (Krams, Lees and Berry, 2005); allocation of patients to dose adaptively changed according to model-based optimization criteria (e.g., variance of target dose estimate) – Tom Parke and Michael Krams
- **D-opt**: adaptive 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 on visual-analog scale (VAS)
- Key questions:
 - is there evidence of a dose response
 - * Significance level (one-sided): 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

^a5 doses (0, 2, 4, 6, 8), 7 doses (0, 2, ..., 6, 8), and 9 doses (0, 1, ..., 8)

Dose response profiles

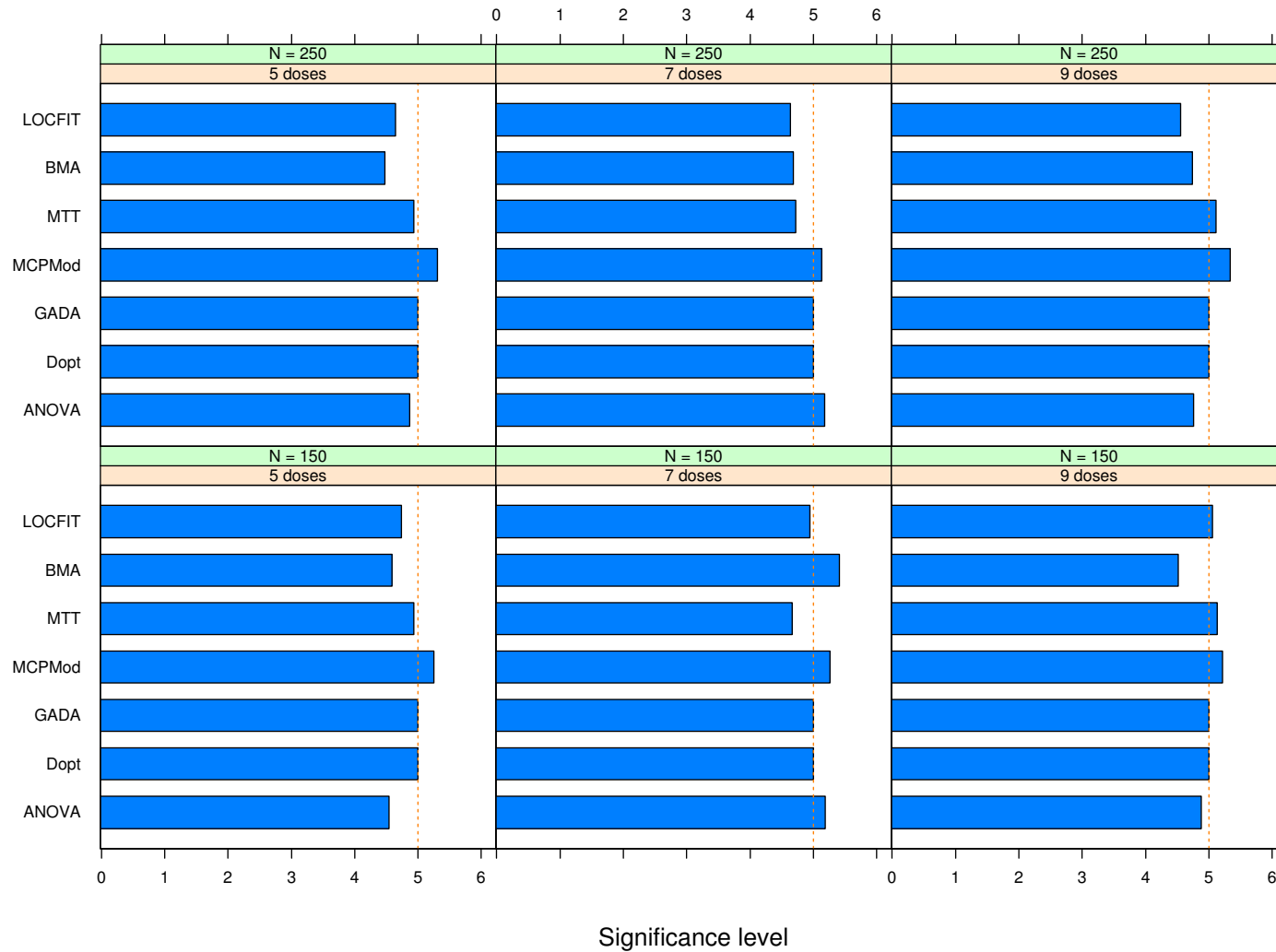


Measuring performance

- 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)

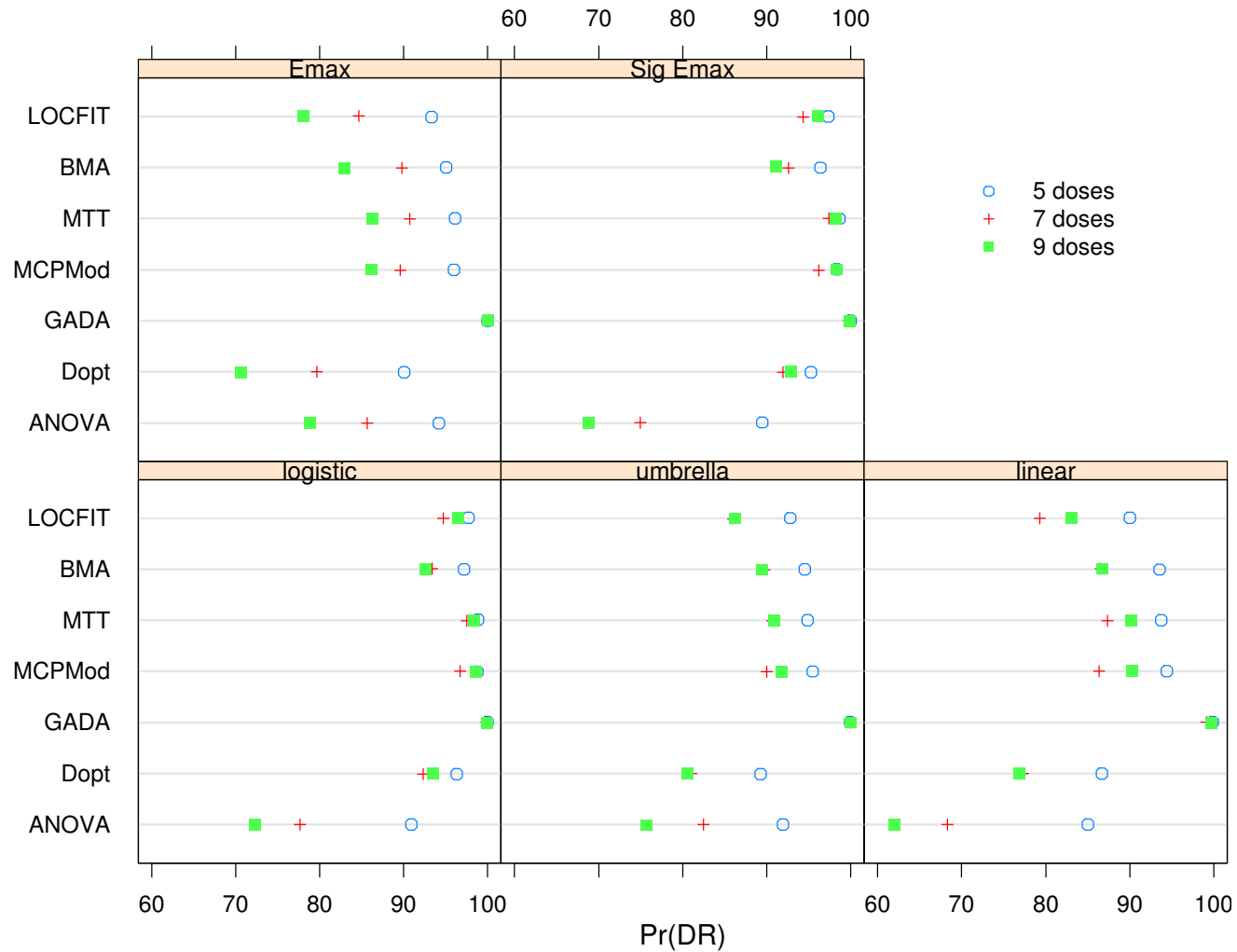
Selected Simulation Results

Probability Identifying DR – Flat DR



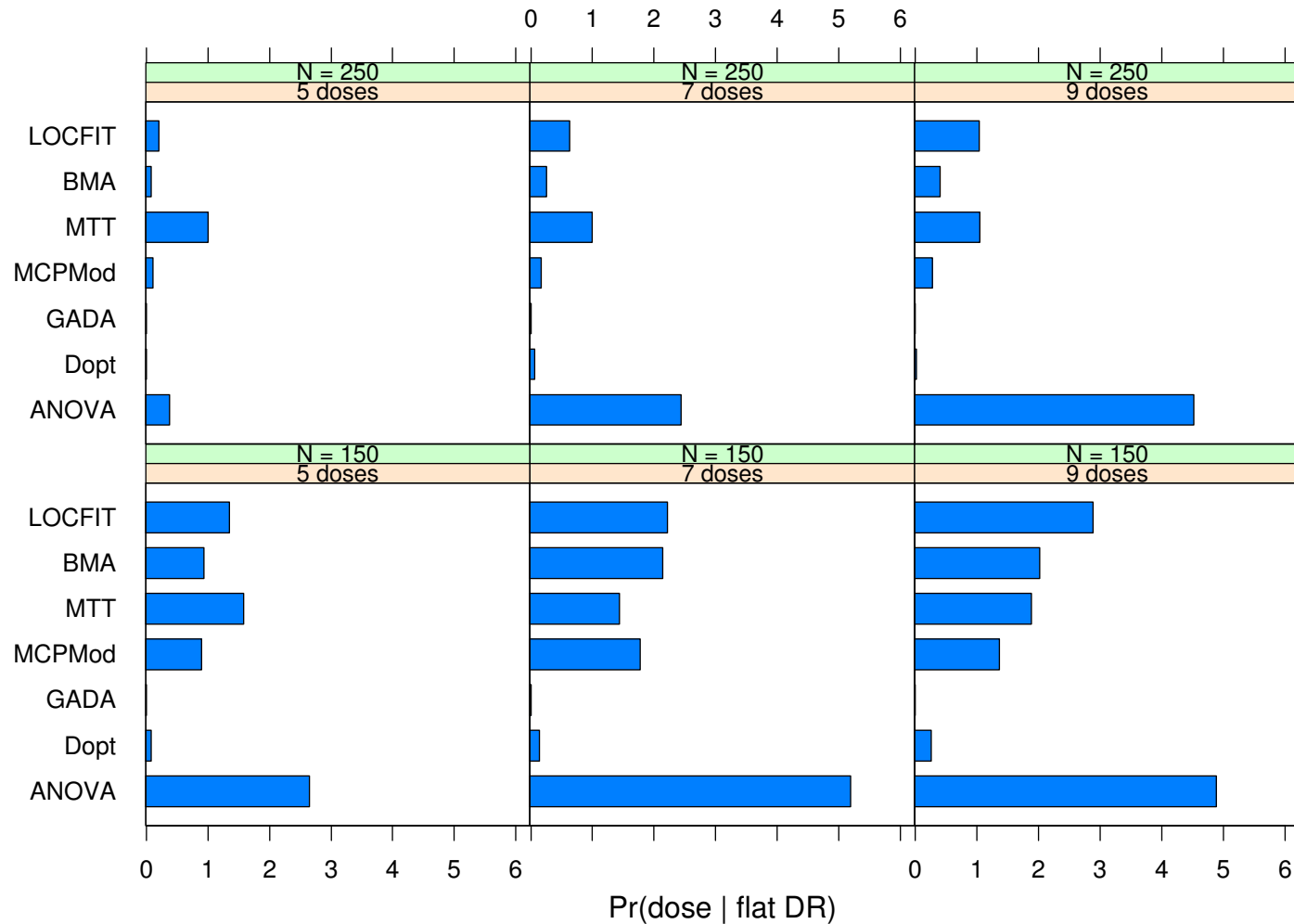
Type I Error is controlled at 5% by all methods

Probability of identifying DR (N = 150)



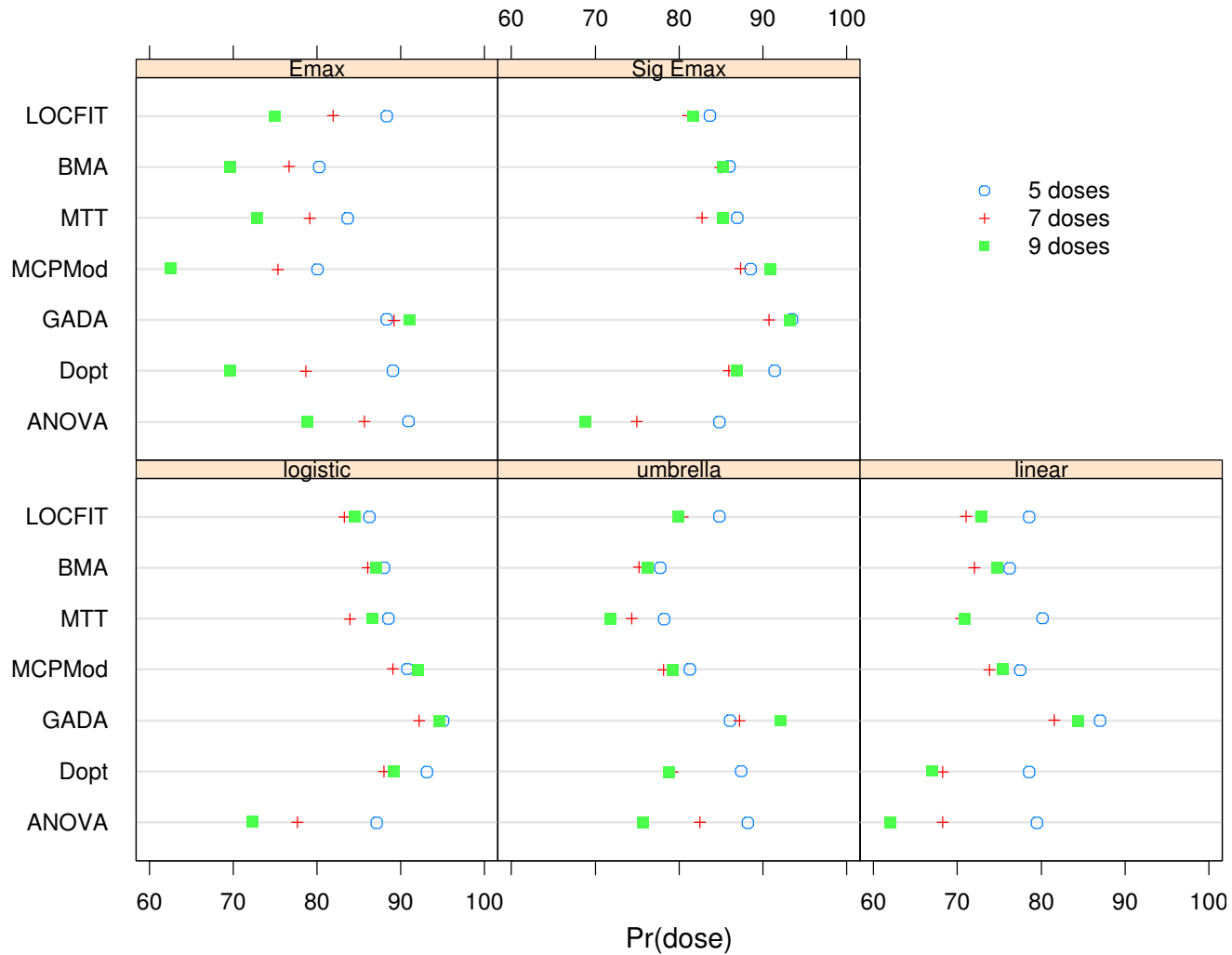
Pr(DR) generally \uparrow as # doses \downarrow (for fixed sample size)

Probability dose selection – Flat DR



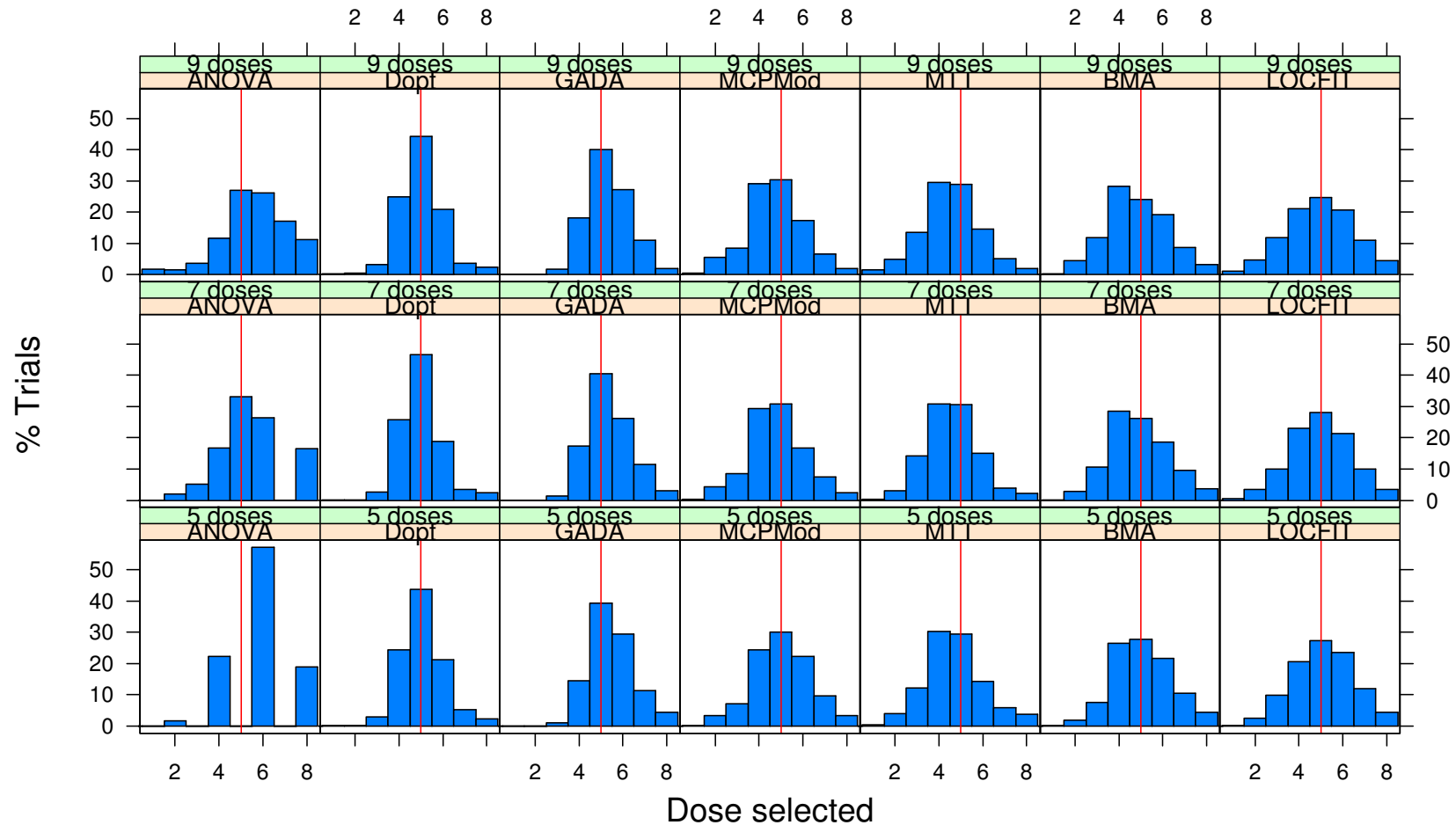
False positive for clinically relevant effect is generally greater for ANOVA

Probability dose selection (N = 150)



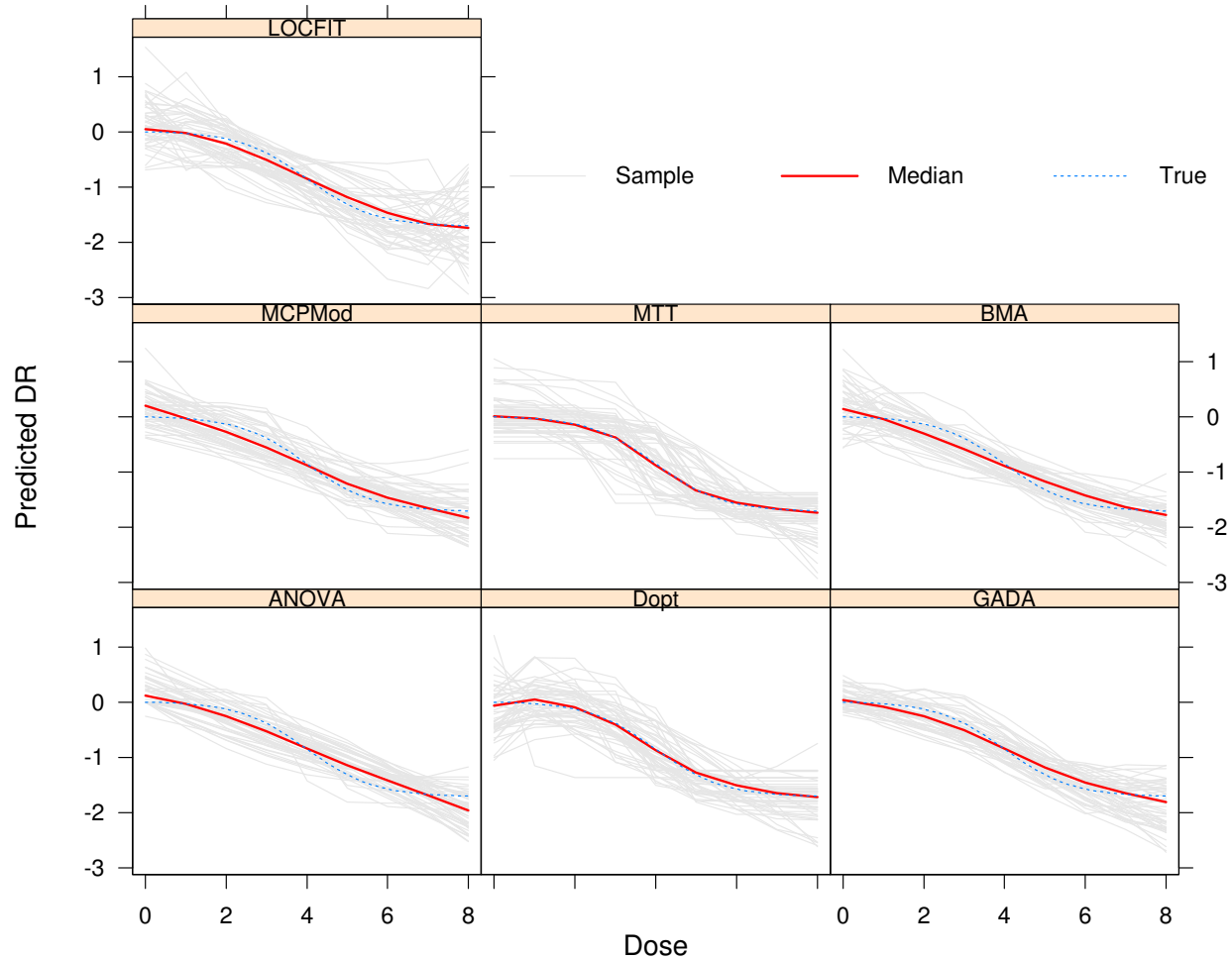
Most methods performed poorly, GADA generally best

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

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 <http://biopharmnet.editme.com/PhrmaAdrsHome>, and has been published 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)

Future Work

- Assess probability of success in Phase 3
- Determine sample sizes needed for adequate assessment of dose-response
- Investigate novel adaptive designs and analysis methods
- Evaluate utility of exposure-response modeling to target dose identification

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- Rick Sax, AstraZeneca^b
- Tom Parke, Tessella

^a Affiliations noted are as of initiation of ADRS WG

^b Leaders of ADRS WG

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