

**Adaptive Dose Ranging Studies to
Establish Dose Response:
Case Studies and Computer Simulations**

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- Background, goals and scope
- Simulation study and sample results
- Conclusions
- Recommendations

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Background

- Pharma industry **pipeline** problem: fewer approvals and increasing costs
- FDA **Critical Path Initiative** – “Innovation vs. Stagnation” white paper
- PhRMA’s response: BCG survey and report identifying **key drivers** of poor performance and proposing solutions
- Pharmaceutical Innovation Steering Committee (**PISC**) formed 10 working groups to implement BCG proposals: Rolling Dose Studies (later Adaptive Dose Ranging Studies) and Novel Adaptive Designs among them

ADRS initiative – Goals

- 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

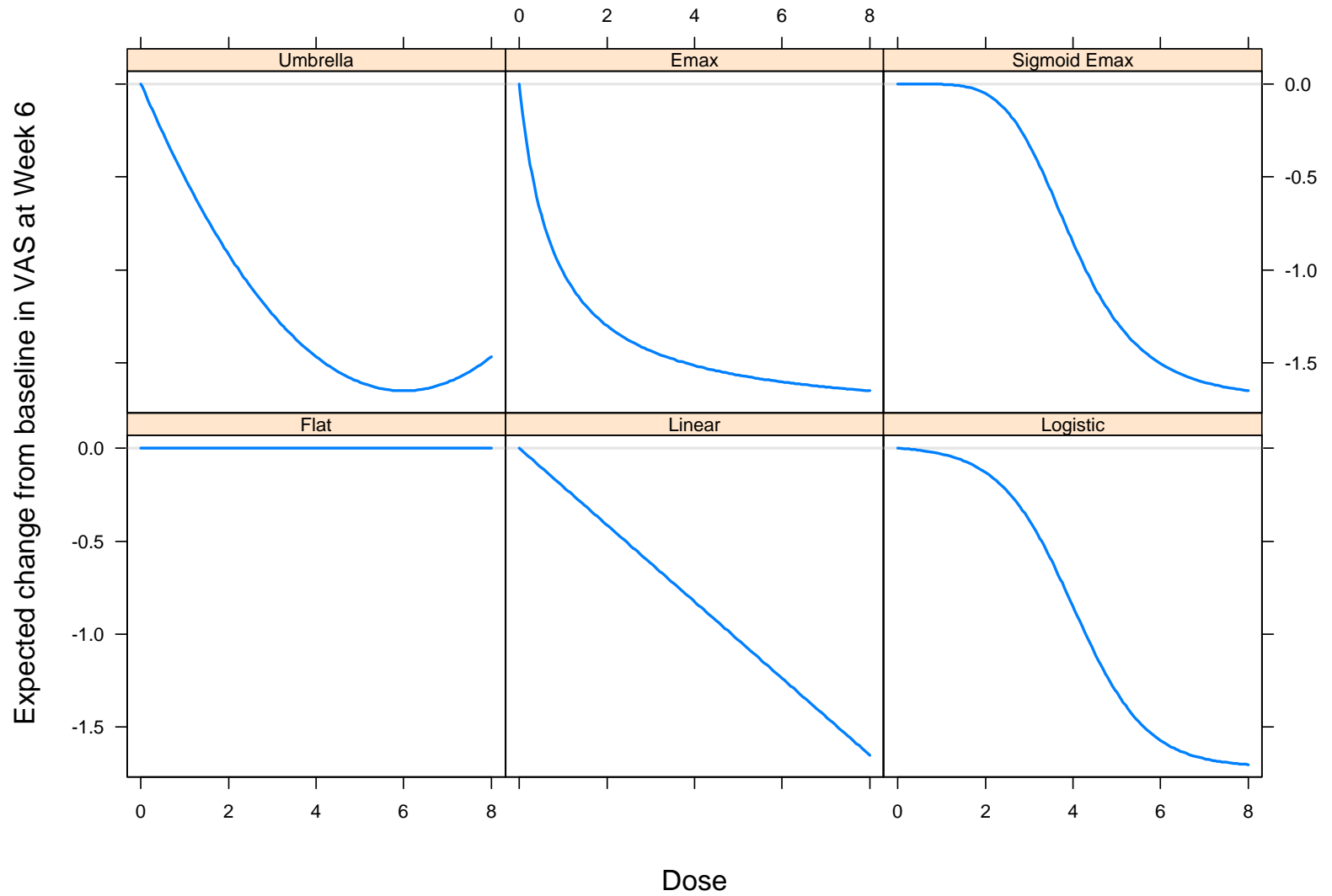
ADRS – Definition and Scope

- Adaptive 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 ADRS methods via simulation
- Evaluate potential benefits over traditional dose-ranging designs over variety of scenarios to make recommendations on practical usefulness of ADRS methods

Simulation study: design and assumptions

- Proof-of-concept + dose finding trial, motivated by neuropathic pain indication (conclusions and recommendations can be generalized)
- 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 (continuous, normally distributed)
- Dose design scenarios (parallel arms):
 - 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

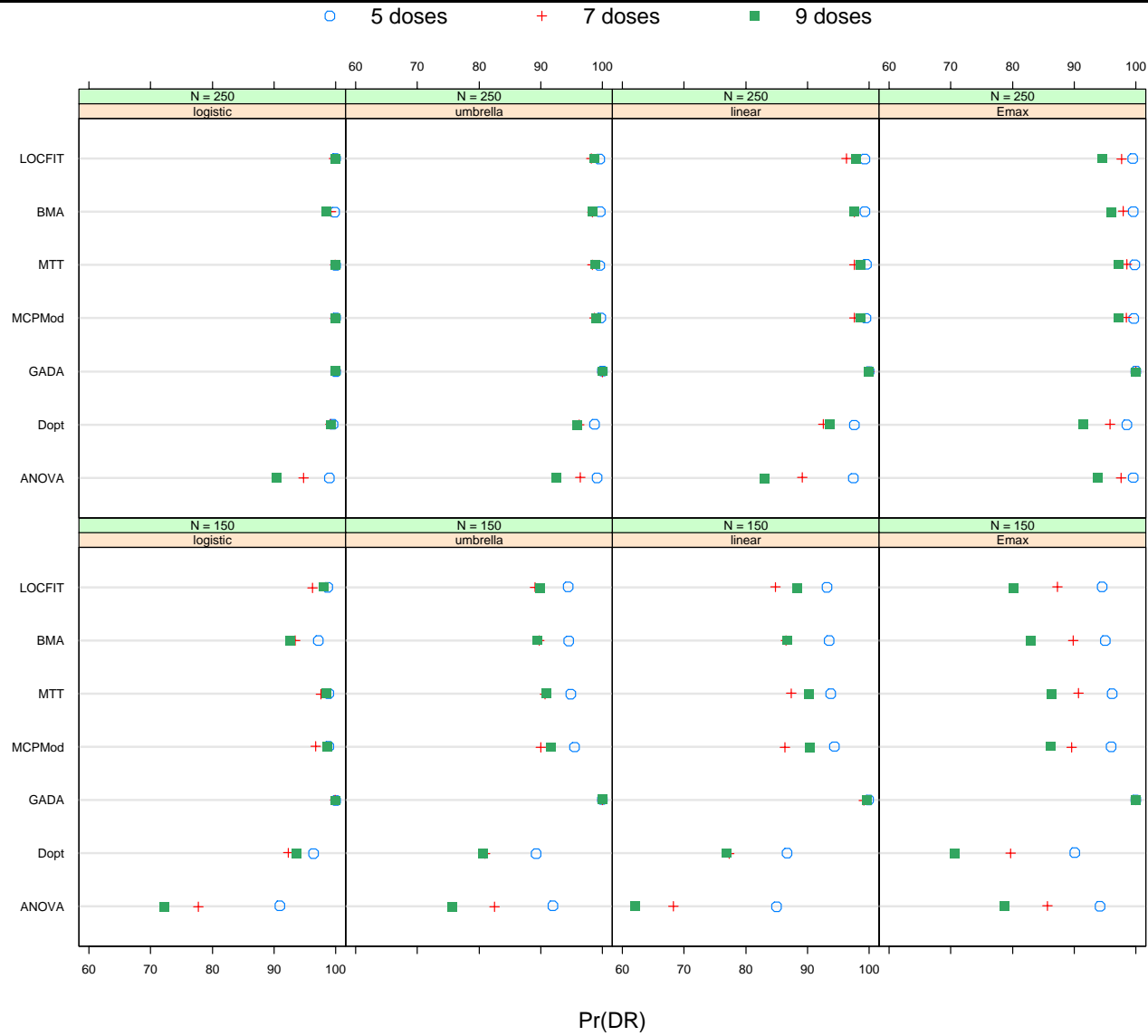


Dose finding methods in simulation

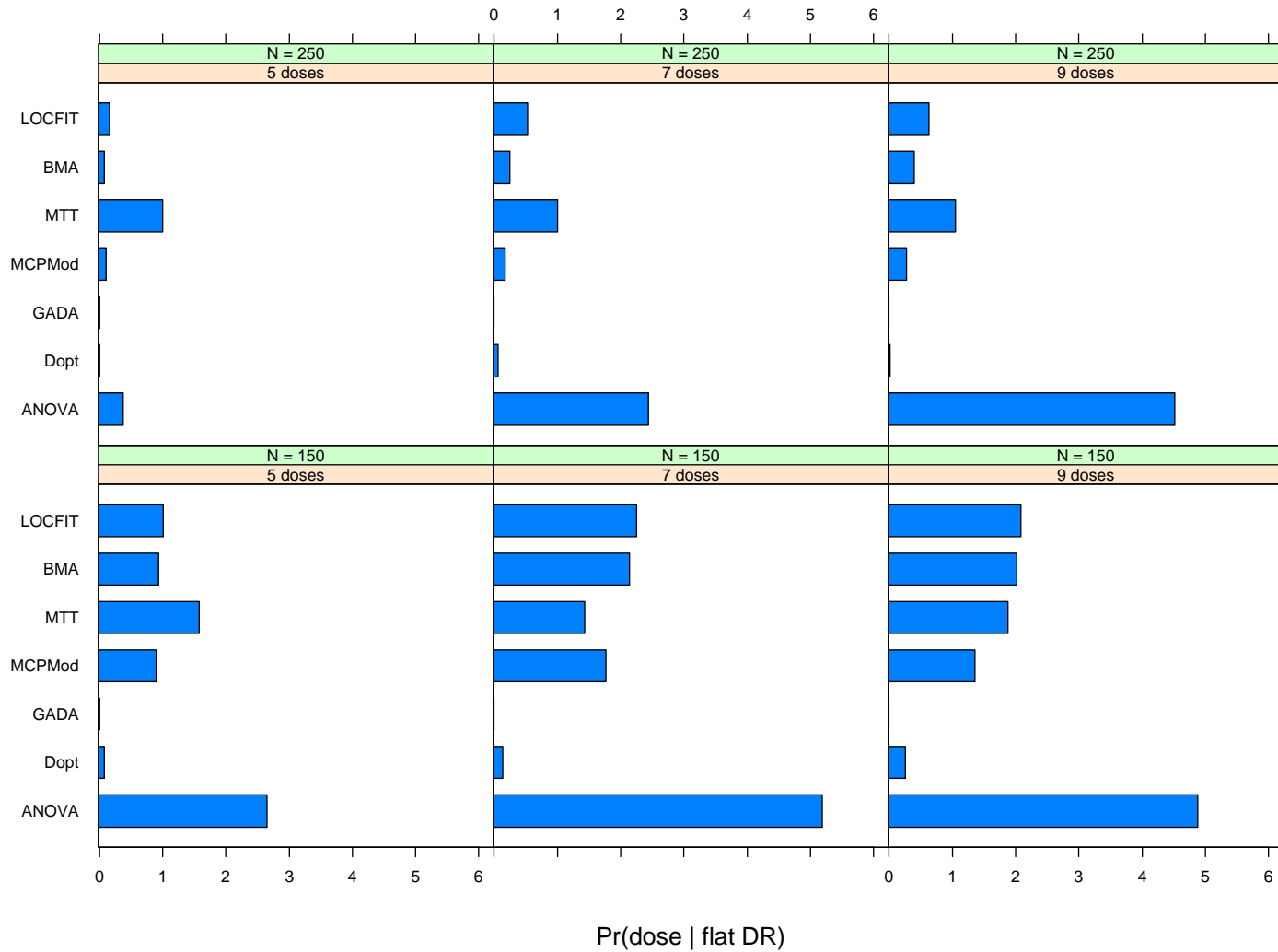
- Traditional **ANOVA** based on pairwise comparisons and multiplicity adjustment (Dunnett)
- **MCP-Mod** combination of multiple comparison procedure (MCP) and modeling (Bretz, Pinheiro and Branson, 2005)
- **MTT**: novel method based on Multiple Trend Tests
- Bayesian Model Averaging: **BMA**
- Nonparametric local regression fitting: **LOCFIT**
- **GADA**: Dynamic dose allocation based on Bayesian normal dynamic linear model (Krams, Lees and Berry, 2005)
- **D-opt**: adaptive dose allocation based on D-optimality criterion

Sample of Simulation Results

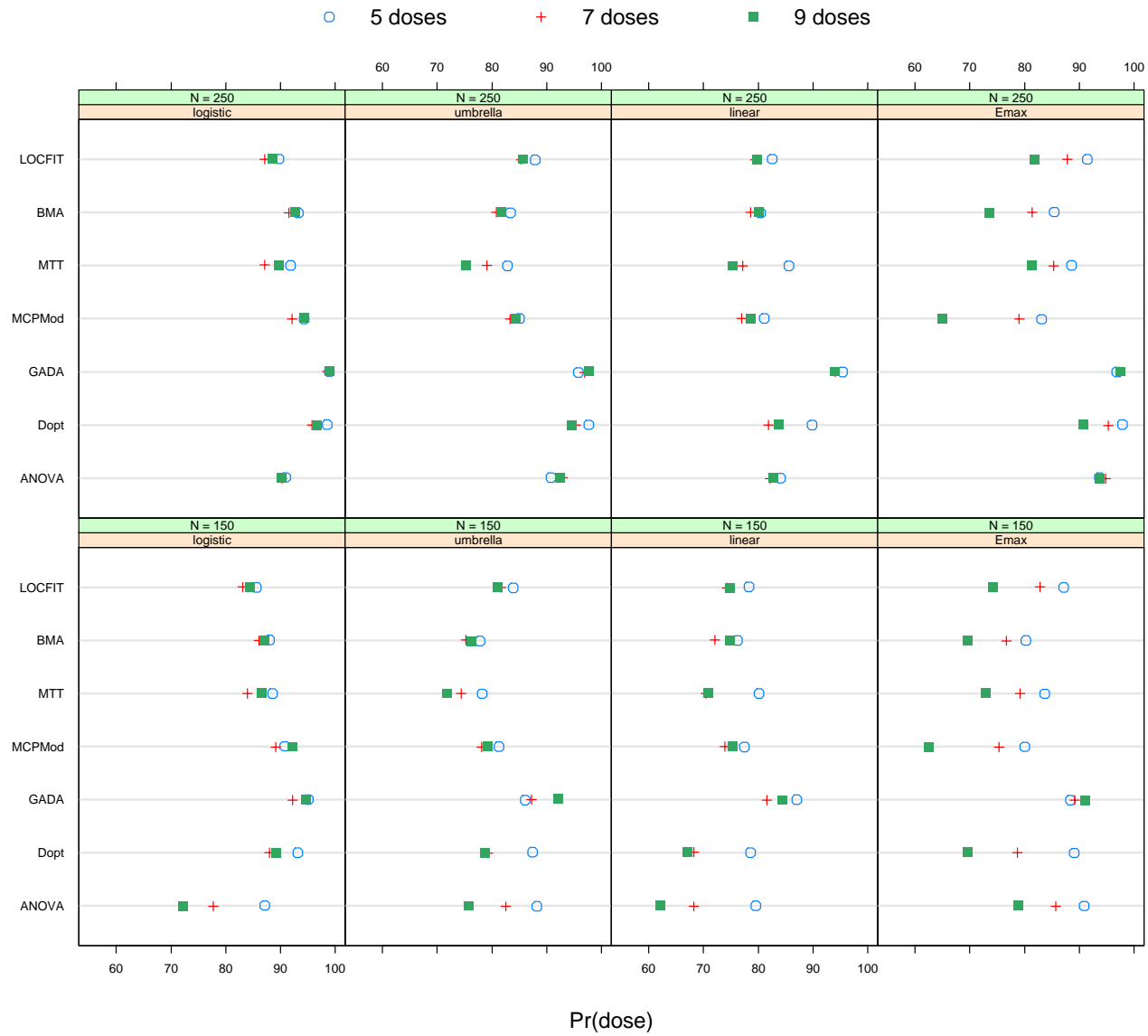
Probability of identifying DR



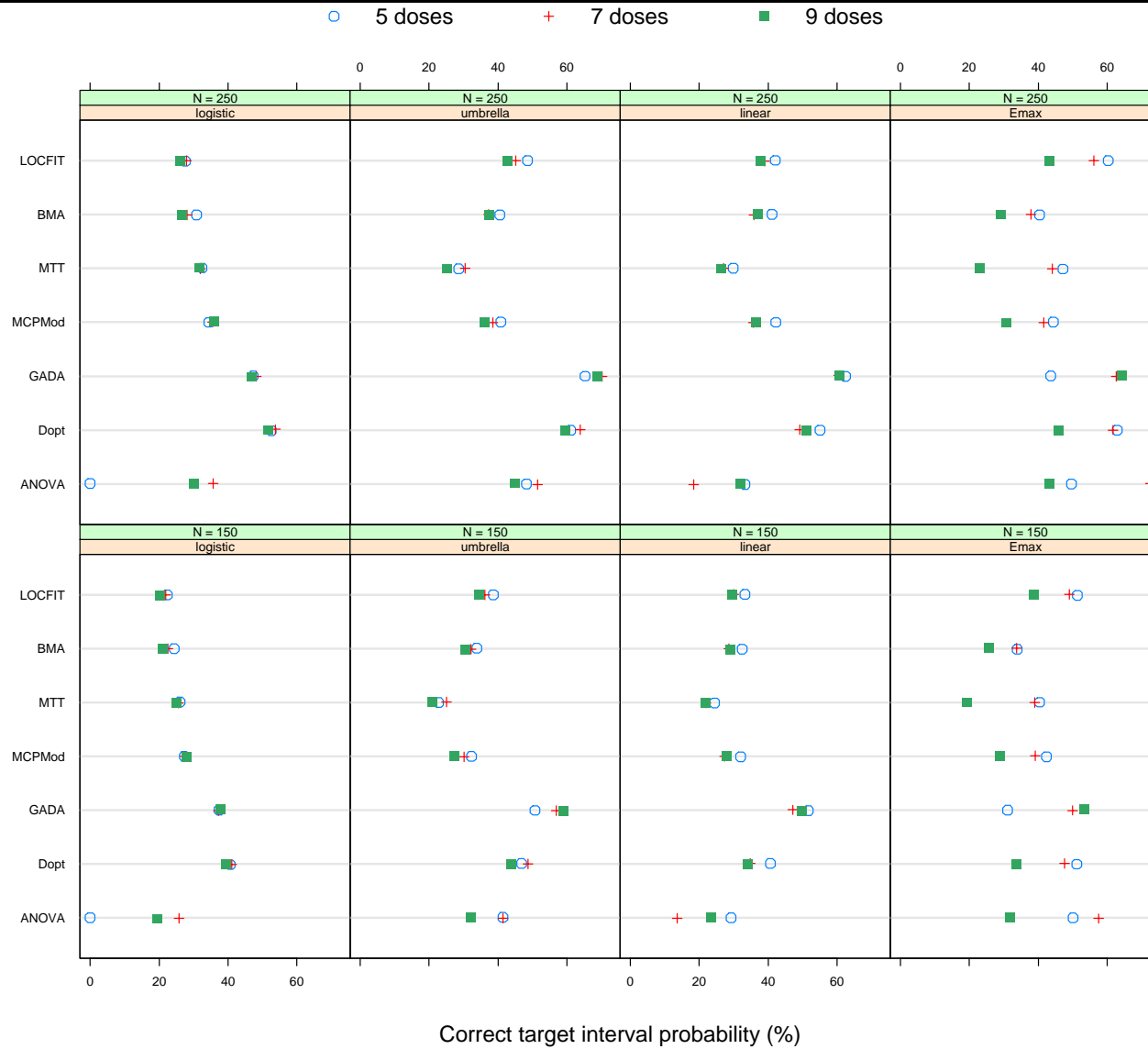
Probability dose selection under flat DR



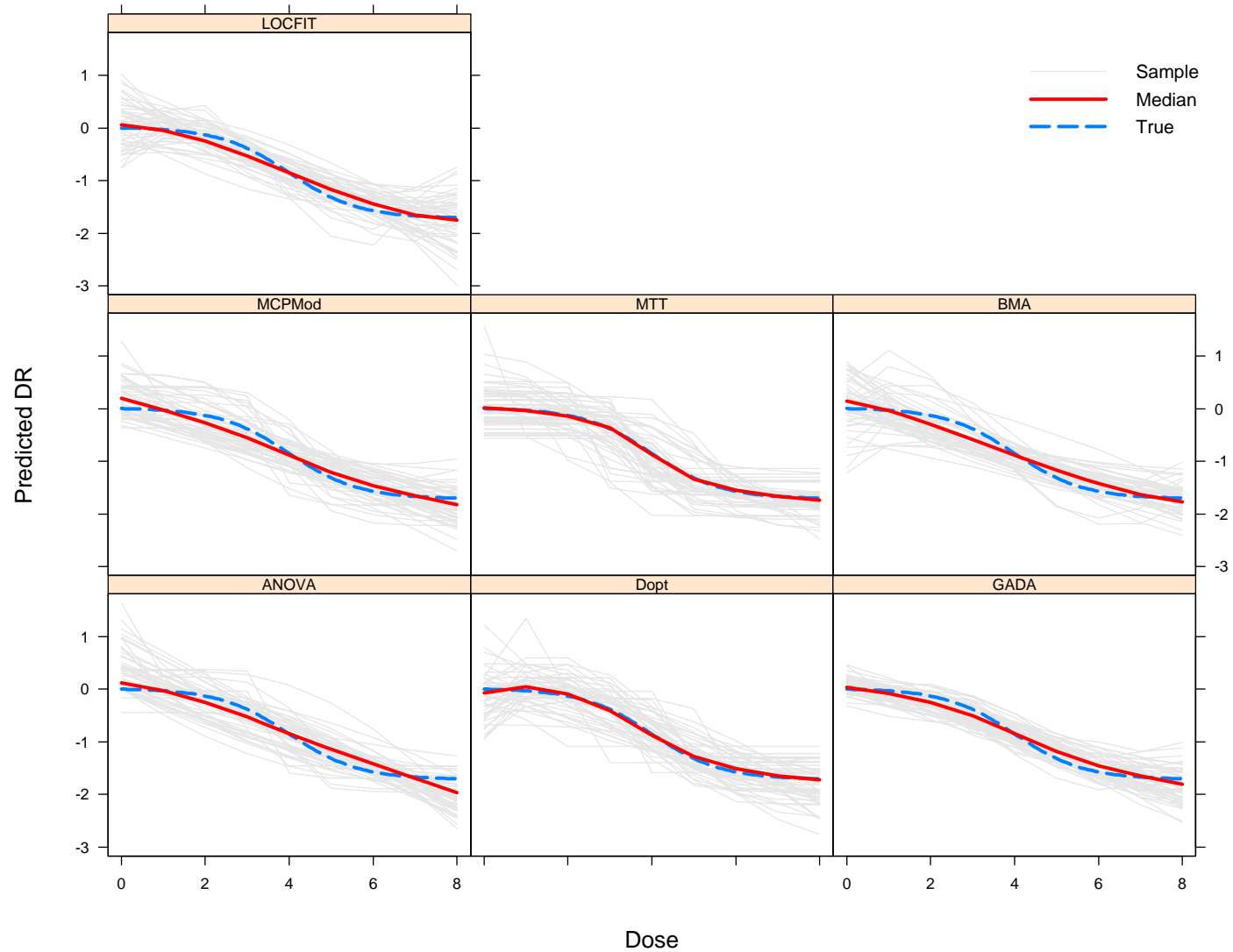
Probability dose selection under active DR



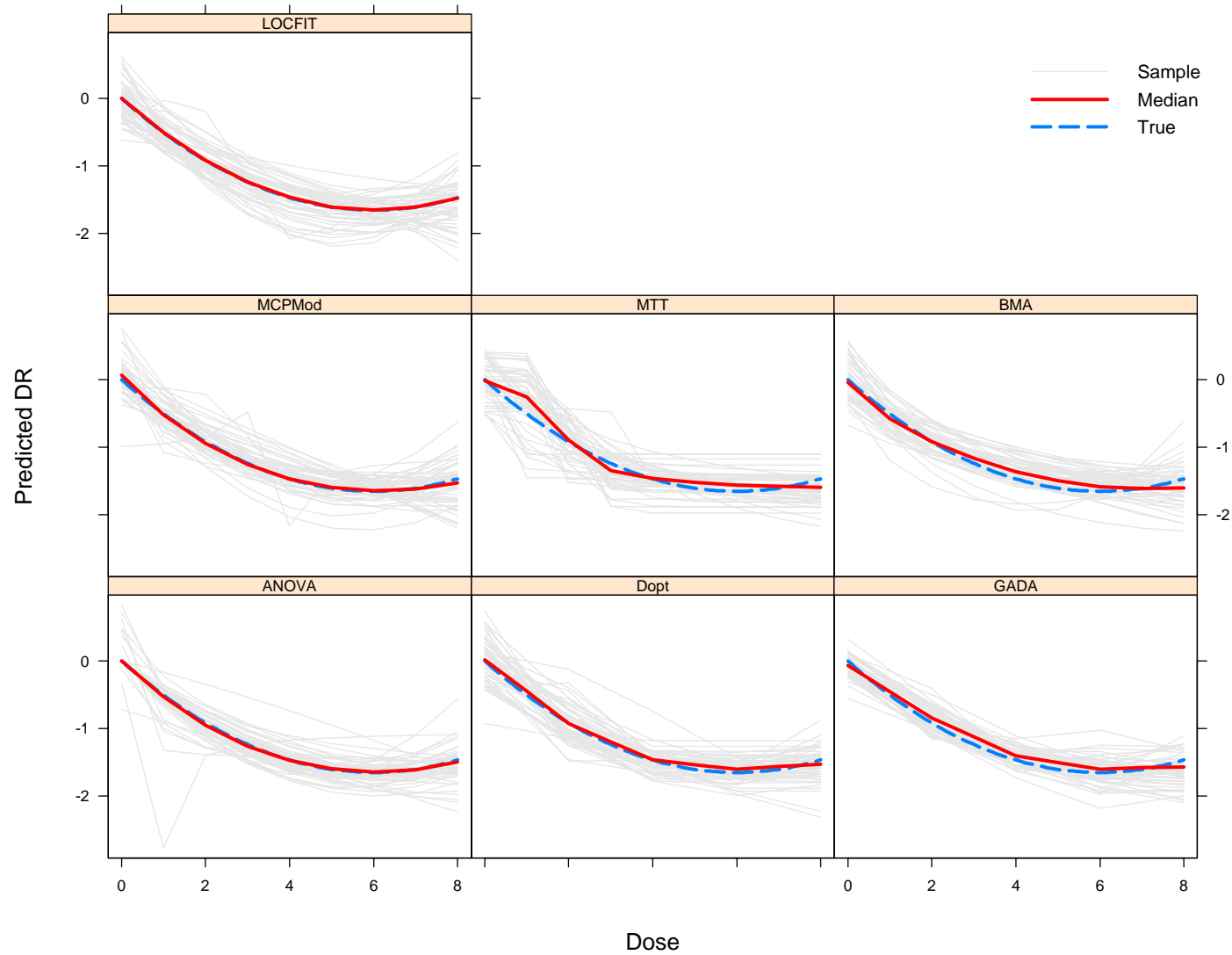
Probability of correct interval dose selection



Sample predicted curves: Logistic, 9 doses and N = 150



Sample predicted curves: Umbrella, 5 doses and N = 250



Conclusions

- Detecting DR is considerably easier than estimating it
- Current sample sizes for DF studies, based on power to detect DR, are inappropriate for dose selection and DR estimation
- None of methods had good performance in estimating dose in the correct target interval: maximum observed percentage of correct interval selection – 60% \implies larger N needed
- Adaptive dose-ranging methods (i.e., ADRS) lead to gains in power to detect DR, precision to select target dose, and to estimate DR – greatest potential in the latter two

Conclusions (cont.)

- Model-based methods have superior performance compared to methods based on hypothesis testing
- Number of doses larger than 5 does not seem to produce significant gains (provided overall N is fixed) \implies trade-off between more detail about DR and less precision at each dose
- In practice, need to balance gains associated with adaptive dose ranging designs approach against greater methodological and operational complexity

Recommendations

- Adaptive, model-based dose-ranging designs should be used routinely in drug development, as they can lead to substantial gains in performance over traditional DF methods
- Sample size calculations for Phase II studies should take into account desired precision of estimated target dose and possibly also estimated DR (current methods are not appropriate)
- When resulting sample size is not feasible, should consider selecting two or three doses for confirmatory phase to increase likelihood of including “correct” dose – adaptive designs could be used in confirmatory phase for greater efficiency (e.g., dropping less efficient doses earlier)

Recommendations (cont.)

- Proof-of-concept (PoC) and dose selection should be combined, when feasible, into one seamless trial
- Early stopping rules, for both efficacy and futility, should be used when feasible to allow greater efficiency in adaptive designs – Bayesian methods are particularly well-suited for this purpose
- Trial simulations should be used to determine appropriate sample sizes, as well as for estimating operational characteristics of designs/methods under consideration
- Explore pre-competitive consortium for Adaptive Designs software, including ADRS

References

Bretz, F., Pinheiro, J. and Branson, M. (2005). Combining multiple comparisons and modeling techniques in dose-response studies, *Biometrics* **61**(3): 738–748.

Krams, M., Lees, K. R. and Berry, D. A. (2005). The past is the future: Innovative designs in acute stroke therapy trials, *Stroke* **36**(6): 1341–7.