

**Scenario Planning: Comparing Methods,
Quantifying Potential Gains from
Adaptive Dose-Finding Designs**

José Pinheiro, *Novartis Pharmaceuticals*

on behalf of the

PhRMA PISC WG on Adaptive Dose-Ranging Studies

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- Adaptive dose-ranging studies WG
- Evaluating dose finding methods: simulation study and sample of results
- Conclusions
- Preliminary recommendations from WG

Adaptive Dose-Ranging Studies core WG members

- Alex Dmitrienko, Eli Lilly
- Amit Roy, BMS
- Brenda Gaydos, Eli Lilly
- Frank Bretz, Novartis
- Frank Shen, BMS
- Greg Enas, Eli Lilly
- José Pinheiro, Novartis
- Michael Krams, Wyeth
- Qing Liu, J & J
- Rick Sax, Astra Zeneca
- Tom Parke, Tessella

ADRS additional WG members

- Björn Bornkamp, University of Dortmund
- Beat Neuenschwander, Novartis
- Chyi-Hung Hsu, Pfizer
- Franz König, Med. Univ. Vienna

ADRS initiative – Motivation

- 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 target dose (e.g., minimum effective dose) out of fixed, generally small number of dose levels, via pairwise hypothesis testing \implies **inefficient**

ADRS initiative – Goals

- Investigate and develop designs and methods for efficiently **learning** about safety and efficacy DR profile \implies benefit/risk profile
- Emphasis on modeling/estimation (**learning**) as opposed to hypothesis testing (**confirming**)
- More accurate and faster **decision making** on dose selection and improved labeling
- Evaluate statistical operational characteristics of alternative designs and methods via simulation study to make recommendations on their use in practice

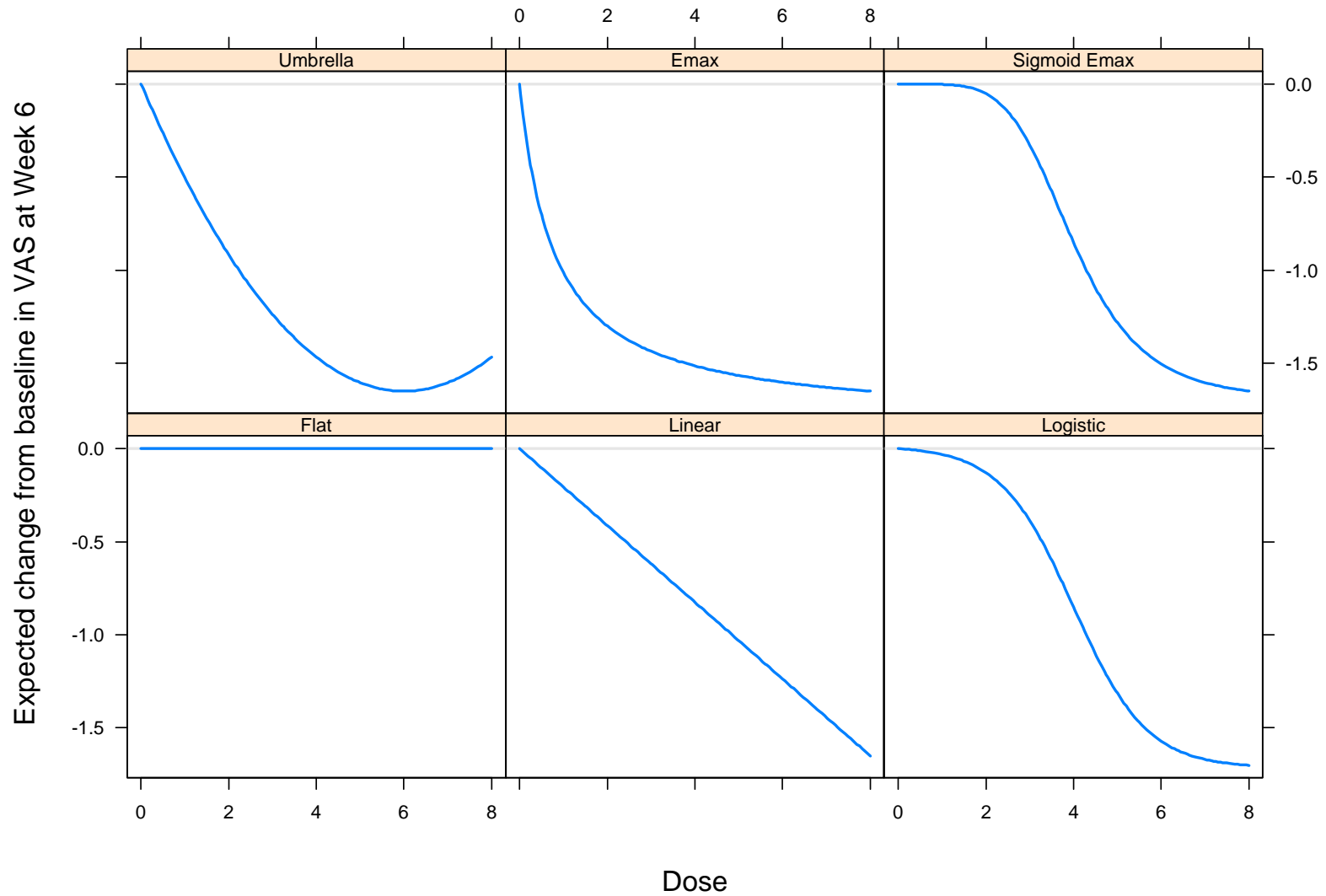
Simulation study: design and assumptions

- 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)

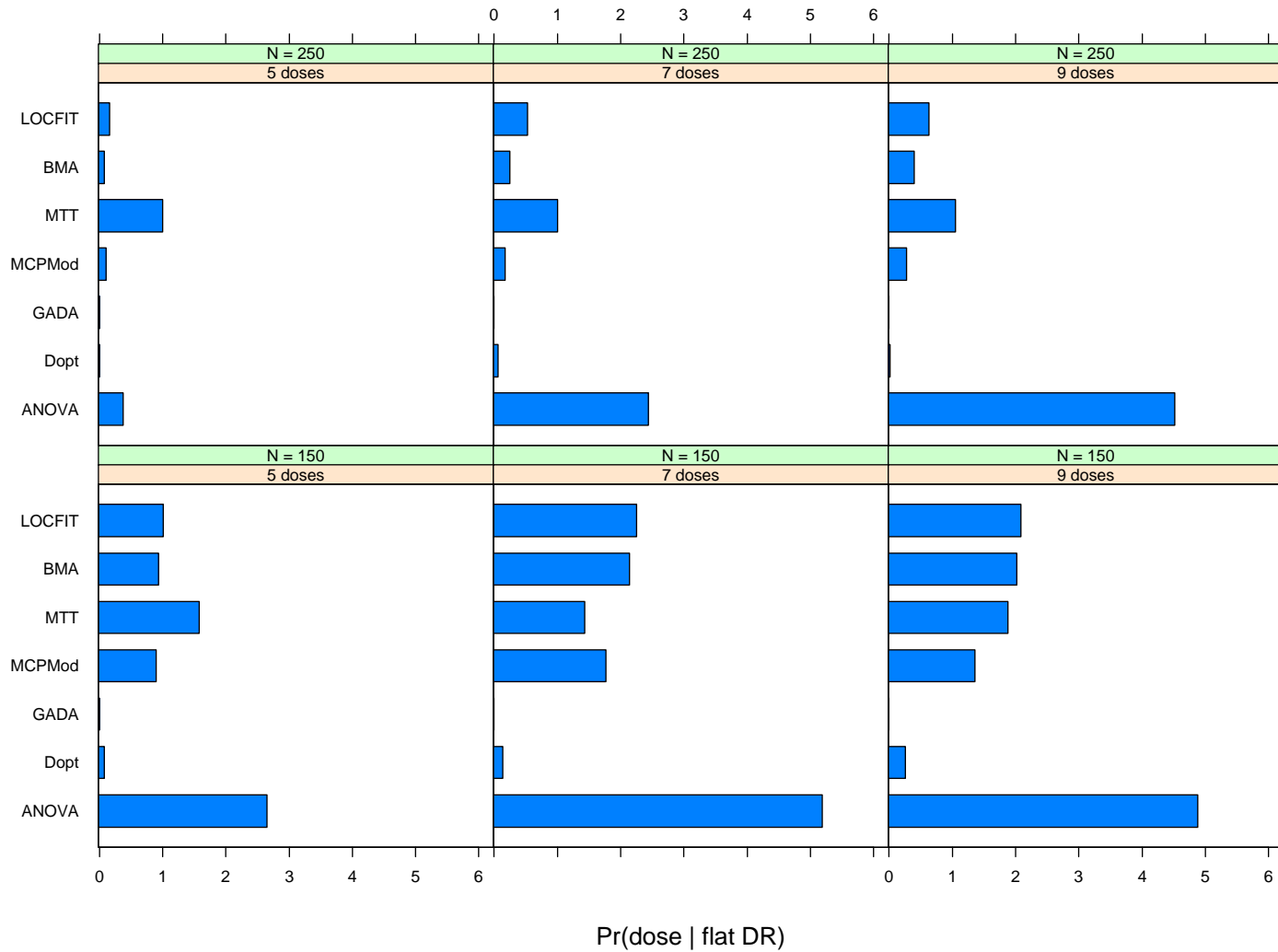
Dose finding methods used in simulation

- 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

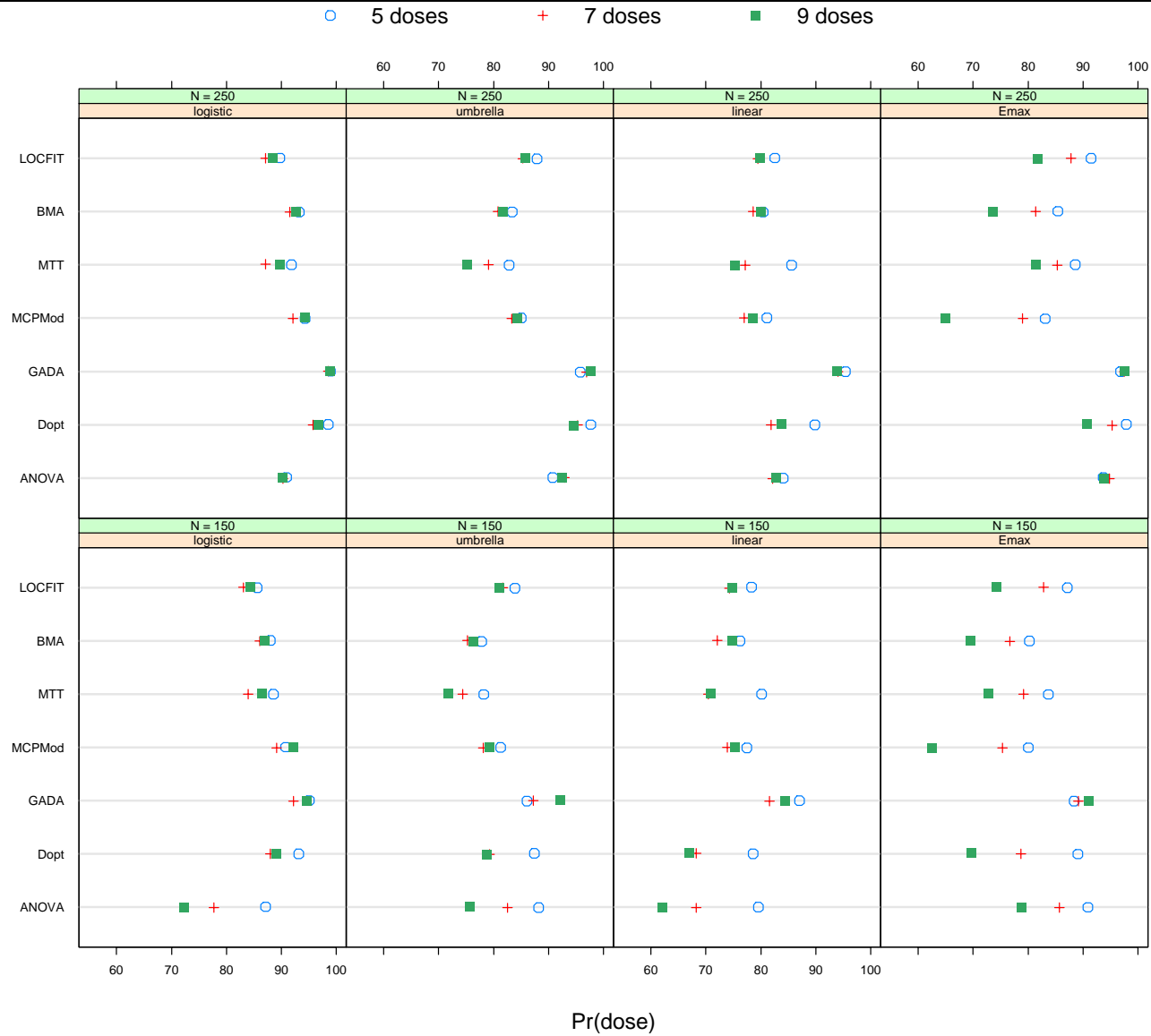
Dose response profiles



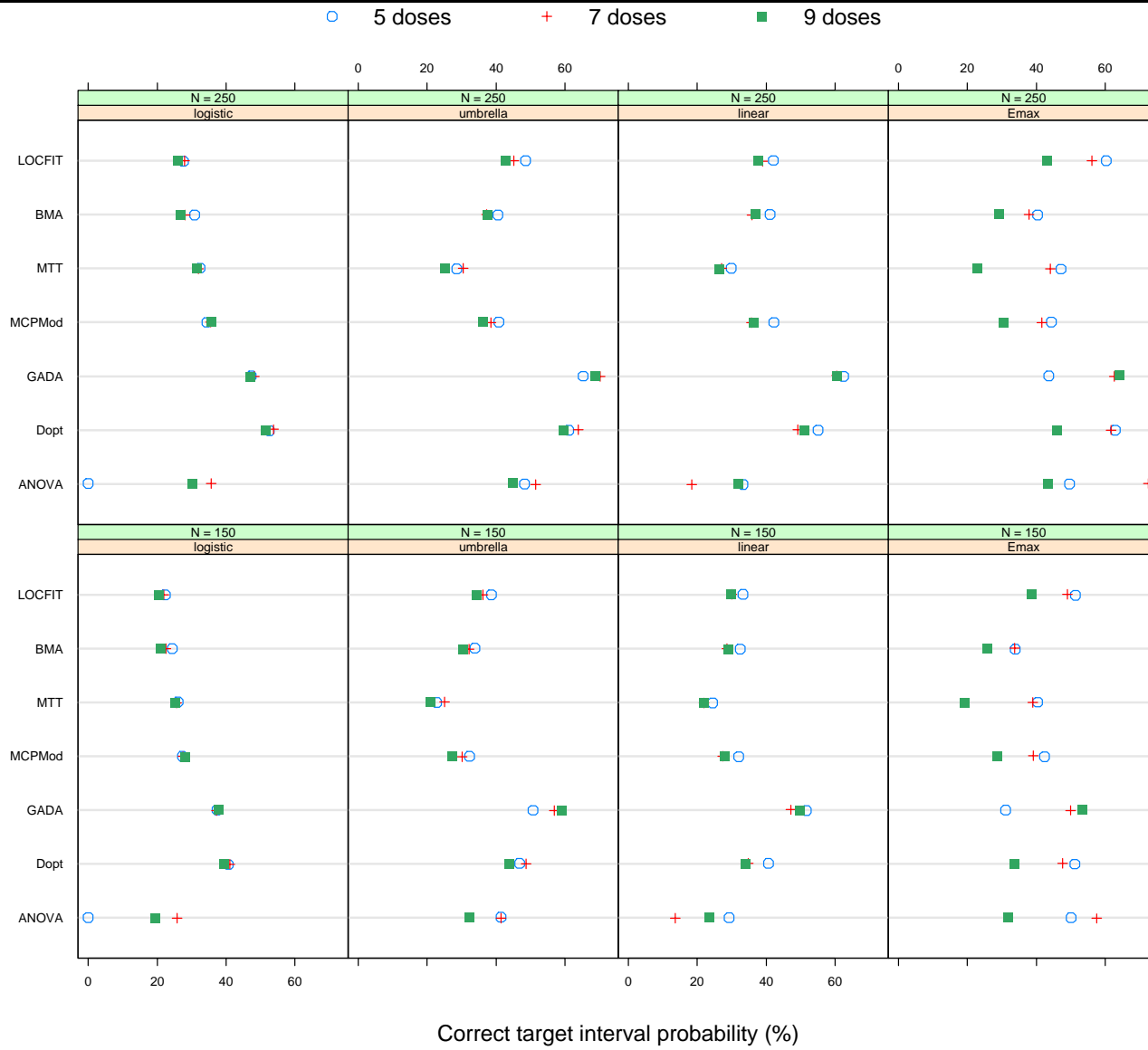
Probability dose selection under flat DR



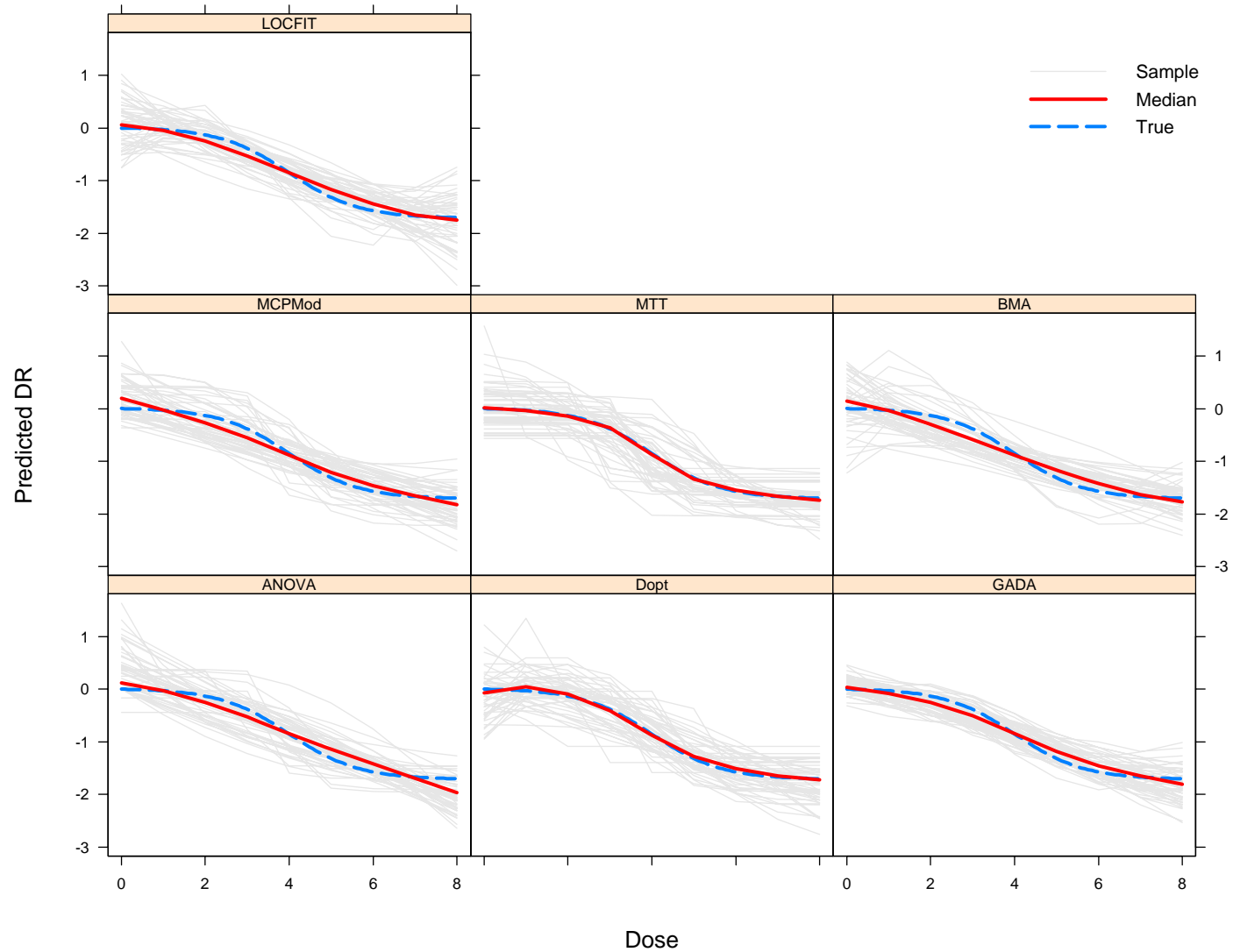
Probability dose selection under active DR



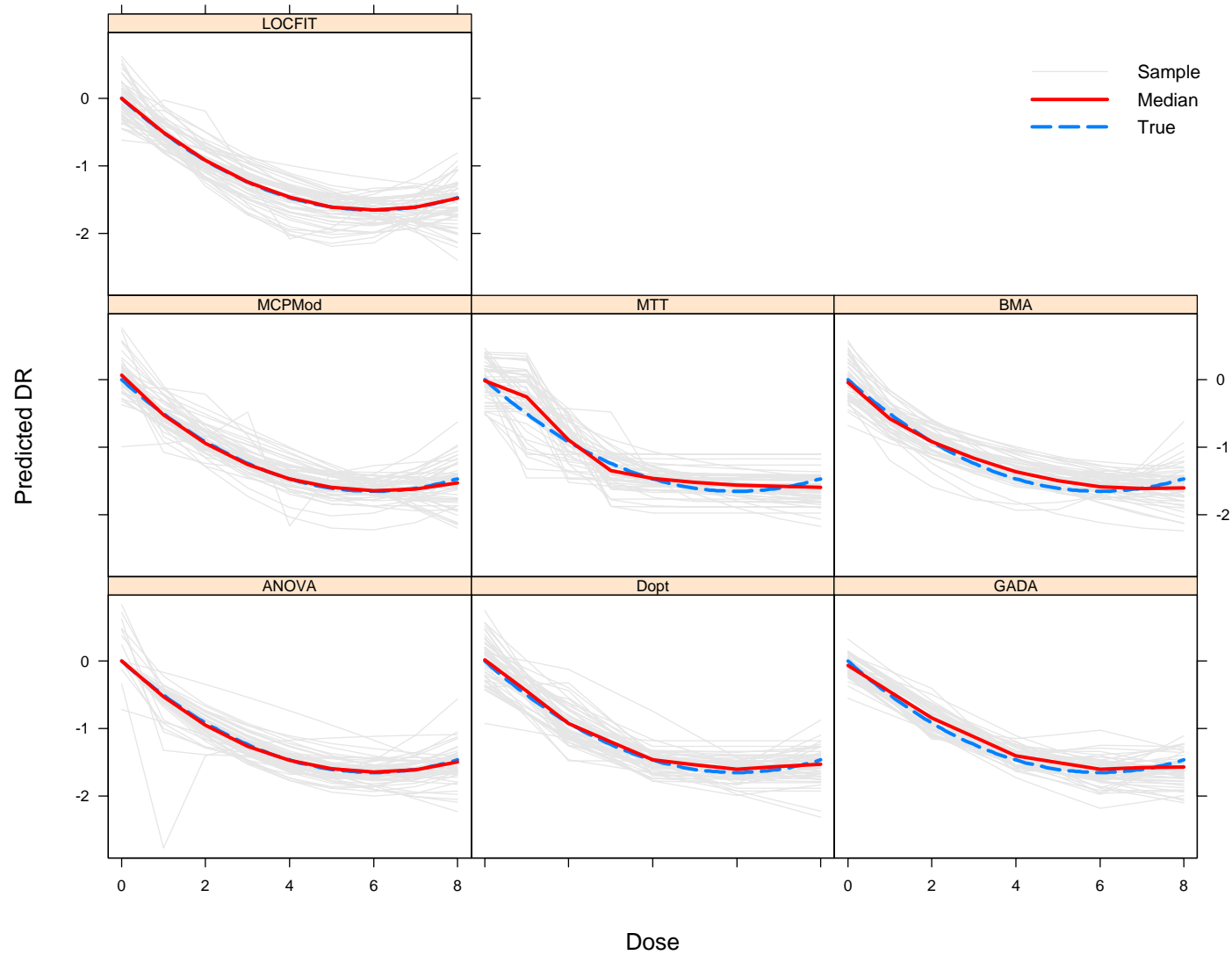
Prob. of correct interval dose selection



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 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

Preliminary 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)

Preliminary 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 (scenario planning)

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.