Improving Dose-Finding Methods in Clinical Development: Design, Adaptation, and Modeling

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On behalf of the PhRMA Adaptive Dose-Ranging Studies WG

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DAEW03 – Cambridge, UK – Aug 16, 2011
Isaac Newton Institute of Mathematical Statistics

Outline

- Motivation: need to improve drug development
- Improving dose-finding: a multifaceted problem
- PhRMA ADRS: goals, conclusions, recommendations
- Further thoughts

Motivation

- Pharmaceutical industry pipeline problem: fewer approvals, escalating development costs, high late phase attrition, tougher regulatory environment
- Traditional development paradigm not sustainable
- Innovative design and analysis methods are key priority for improving clinical development practice
  - How to make best use of available information
  - Integrate knowledge across trials, phases, programs
  - Designs to optimize information value per patient

Need to improve dose-finding

- Poor understanding of dose response (DR) indicated by both FDA and industry as one of root causes of late phase attrition and post-marketing problems with approved drugs
- FDA reported that 20% of drugs approved between 1980 and 1999 had initial dose changed by $> 33\%$ (80% decreased)
- Most commonly used dose finding designs and methods today still focus on selection of target dose out of a fixed, generally small number of dose levels, via pairwise hypothesis testing $\Longrightarrow$ typically inefficient

How to improve dose-finding?

- Need to move away from "Phase 3 view" – hypothesis testing vs. estimation (modeling)
- Better exploration of dose-range: more doses and regimens than typically used in Phase 2 – not an easy task to convince clinical teams/management
- Recognize exploratory nature of dose finding, avoid "potentially pivotal" hope often underlying design
- Allocate proper resources (sample size, time, planning, etc) to Phase 2: evaluate better balance between Phase 2 and 3 resource allocation

Improving dose-finding (cont.)

Combination of design and analysis methods:

- Adaptive designs
- Optimal designs (fixed and adaptive)
- Model-based approaches: dose-response, exposure-response, longitudinal models, PK/PD, etc
- Bayesian methods and models

⇨Evaluation of operating characteristics of proposed design/methods critical to proper planning: simulations play a key role (proper software needed)

Challenges to improving DF

- Industry mindset favoring conventional development approaches, intuition-driven decisions ⇨ need for change management
- Need adequate operational infrastructure: drug supply, recruitment, data management, etc, especially in context of adaptive designs
- Resource needs: increased planning, people with proper expertise; adequate software for design and implementation; hardware for intensive computing
- Speed-focused environment often not conducive to innovation: moving quickly in short term does not imply later success (program level thinking)

Overcoming mindset hurdle: Making the case for innovative DF

- Need to establish operating characteristics (OC) of competitor designs and methods – show value
- Statistical as well as operational aspects need to be included in OC evaluation – overall view
- Range of plausible scenarios should be used to evaluate sensitivity of OC to changes
- Quantification of benefit/cost of competitor designs and methods is critical to convince clinical teams, management, and self of potential value of innovative approaches

Adaptive Dose Ranging Studies WG

- Main goals: investigate and develop designs and methods for efficient learning about Dose Response (DR) $\Rightarrow$ better and faster decision making on dose selection and improved labeling
- How: evaluate statistical OC of alternative designs and methods via comprehensive simulation studies
- Focus: adaptive and model-based dose-ranging designs and methods
- Adaptive Designs WG: another PhRMA WG, focusing on higher level recommendations and advocacy of adaptive designs in general

First evaluation round

- Simulation study comparing different dose finding (DF) methods under variety of scenarios (e.g., dose-response models, number of doses)
- Evaluated operational characteristics of methods with regard to:
  - detecting dose-response signal
  - dose selection for Phase 3
  - estimation of dose-response profile
- Key conclusions & recommendations published in white paper and presented to Health Auth., with positive feedback

ADRS WG White Paper – first round

Journal of Biopharmaceutical Statistics, 17: 965–995, 2007

ISSN: 1054-3406 print/1520-5711 online
DOI: 10.1080/10543400701643848

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INNOVATIVE APPROACHES FOR DESIGNING AND ANALYZING ADAPTIVE DOSE-RANGING TRIALS

Björn Bornkamp
University of Dortmund, Dortmund, Germany

Frank Bretz
Novartis Pharma AG, Basel, Switzerland

Alex Dmitrienko
Eli Lilly and Company, Indianapolis, Indiana, USA

with discussion, including regulators (FDA and CHMP)

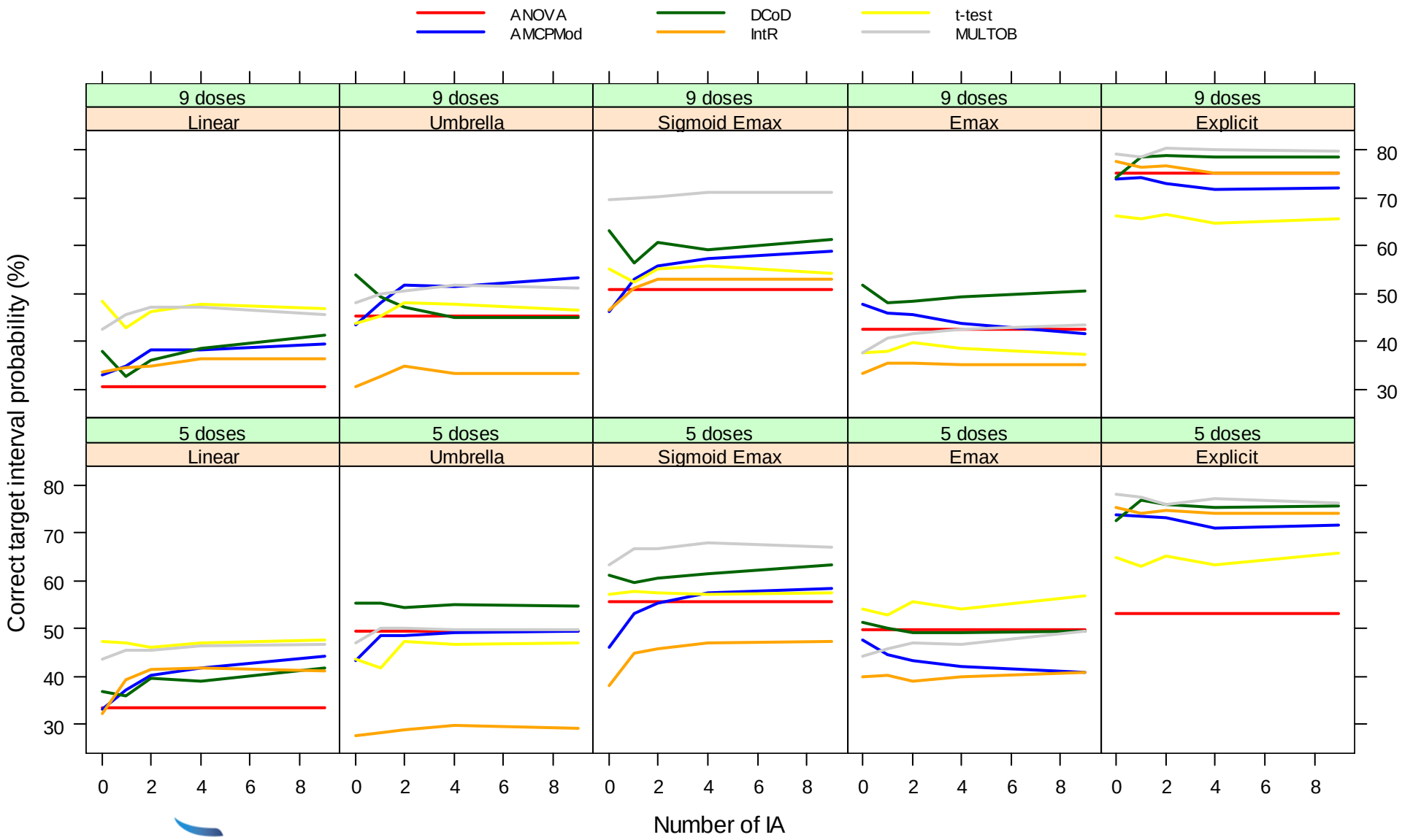
Second evaluation round

Three work streams (WKS) :

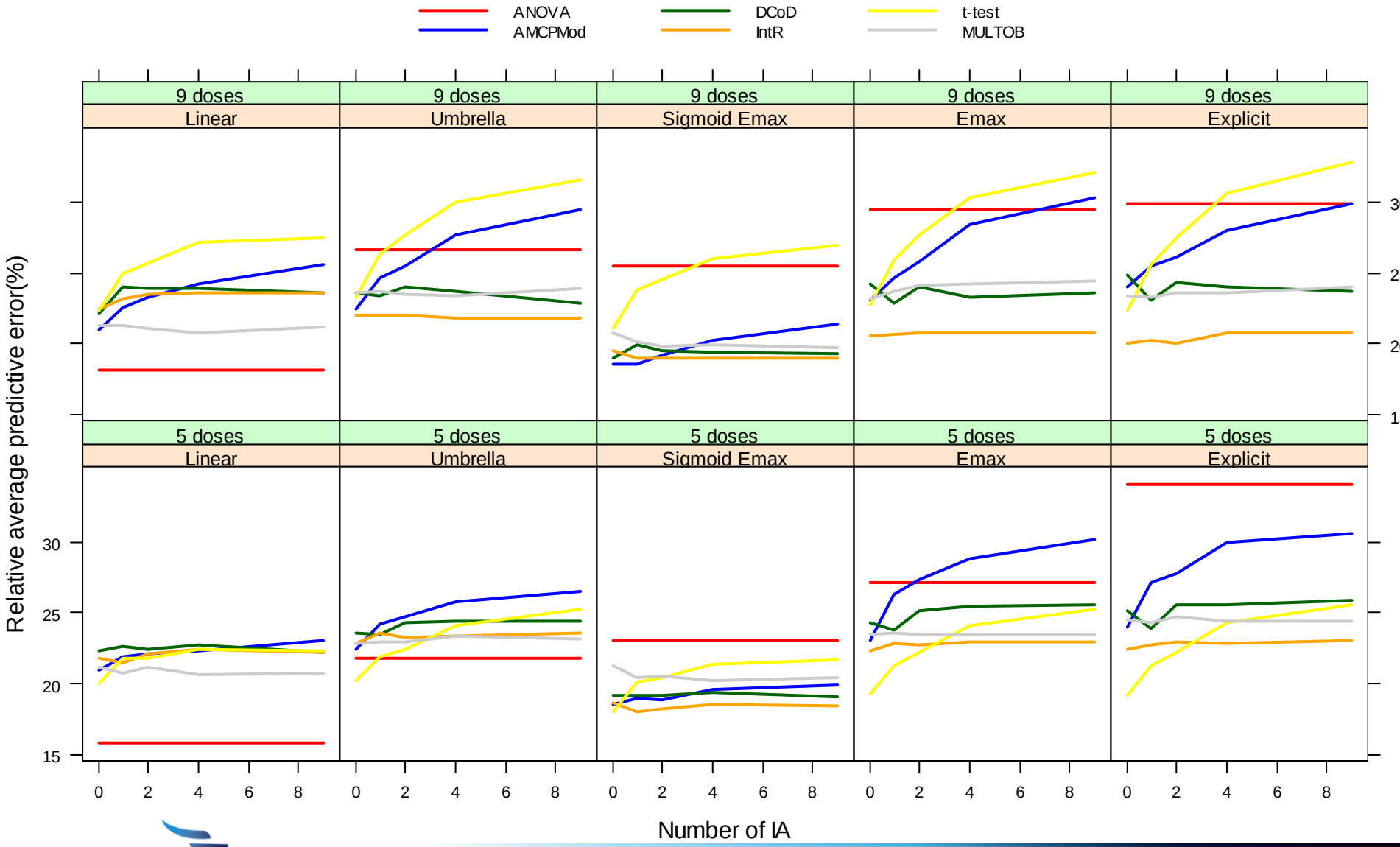
- New Adaptive Methods: first round evaluation included only 2 ADR approaches – 5 new ones evaluated by WKS (similar simulation design as in first round)
  - ❖ Chair: Vlad Dragalin
- Impact of dose selection (in Phase II) on likelihood of success of Phase III program and net present value (NPV) for compound in indication
  - ❖ Chair: Zoran Antonijevic
- Value of exposure-response modeling in dose response characterization and dose selection
  - ❖ Chair: Amit Roy

Selected results from ADRS WG 2nd round simulations

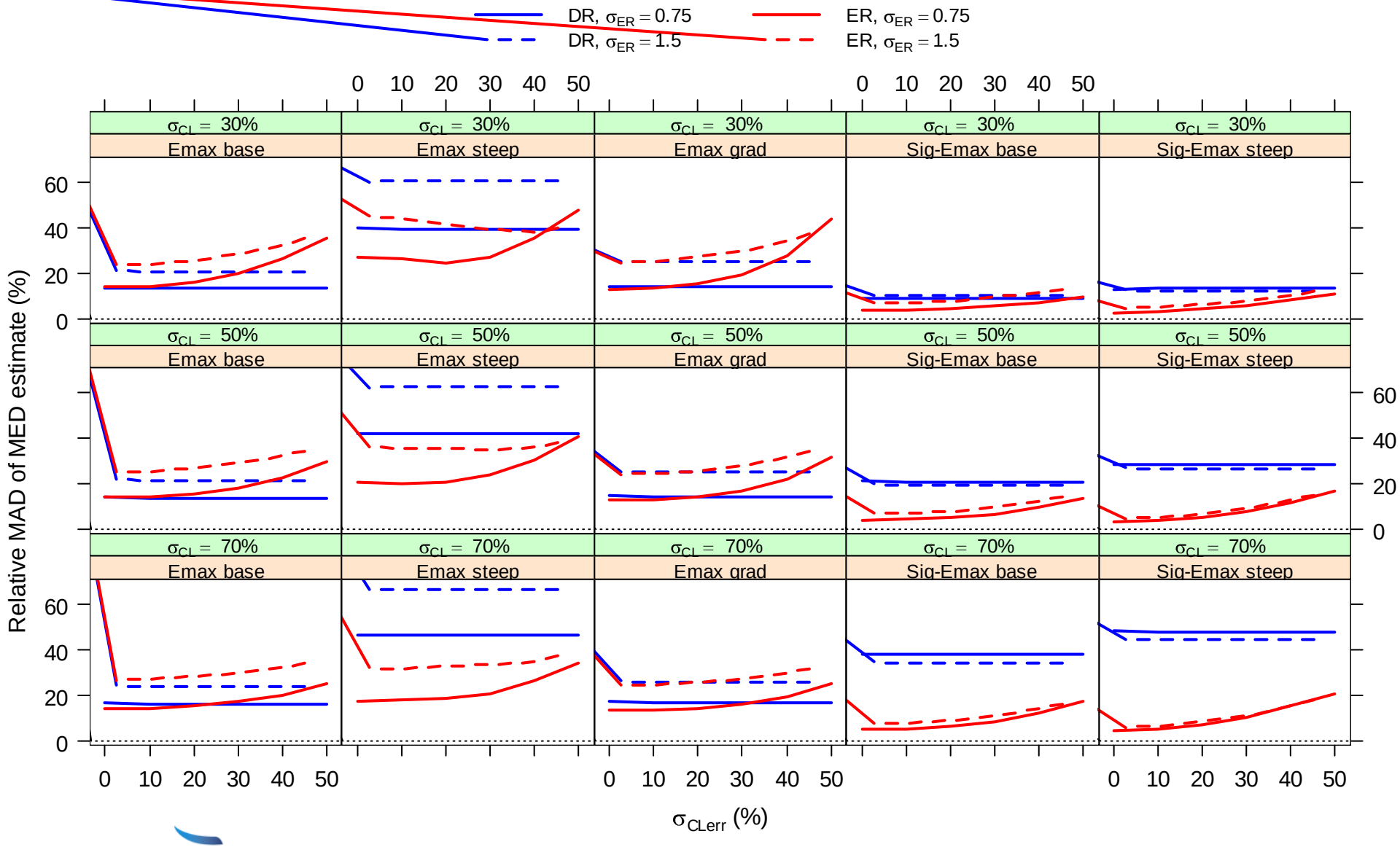
New Methods WKS: Pr(dose right)



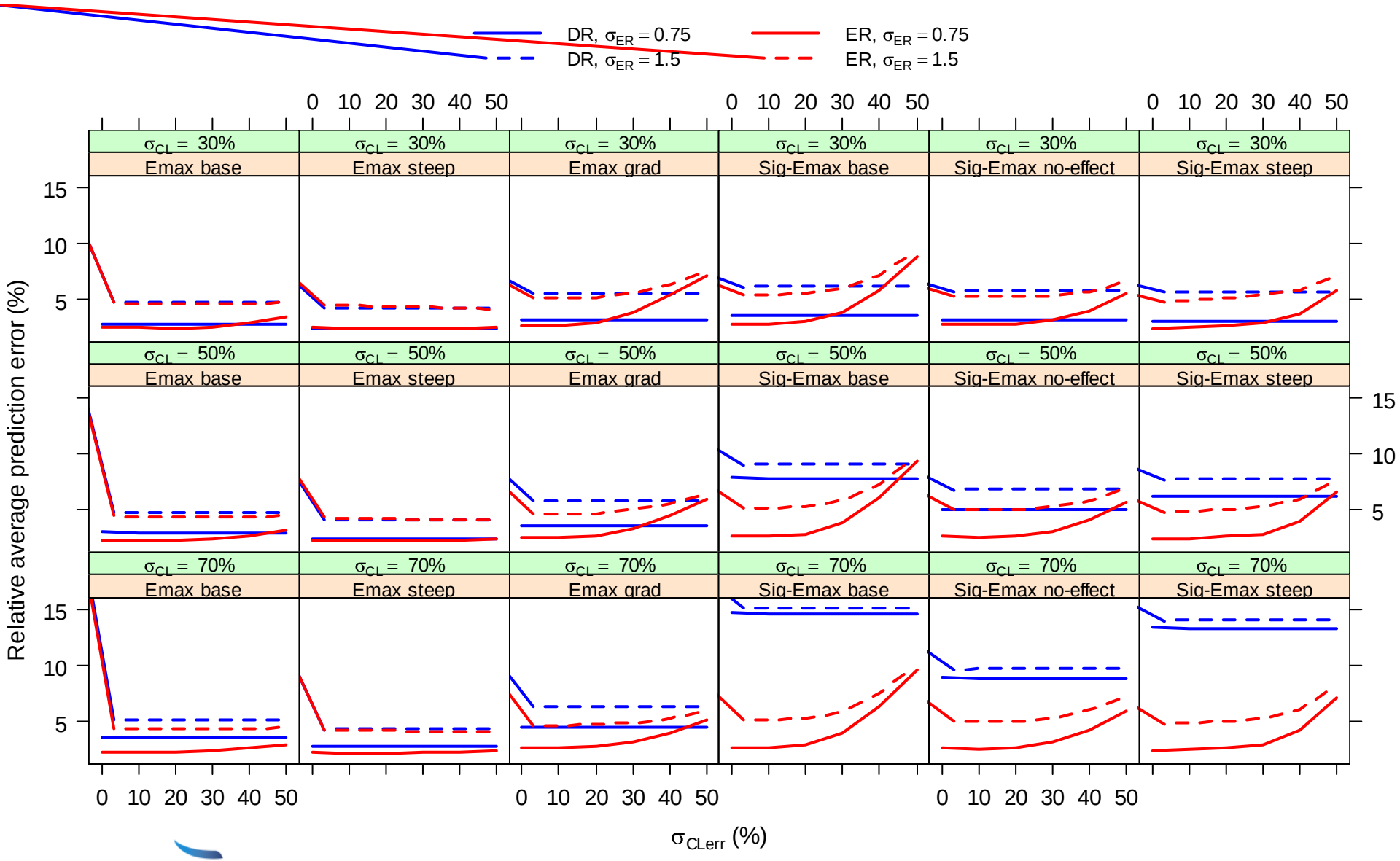
New Methods WKS: Avg. prediction error



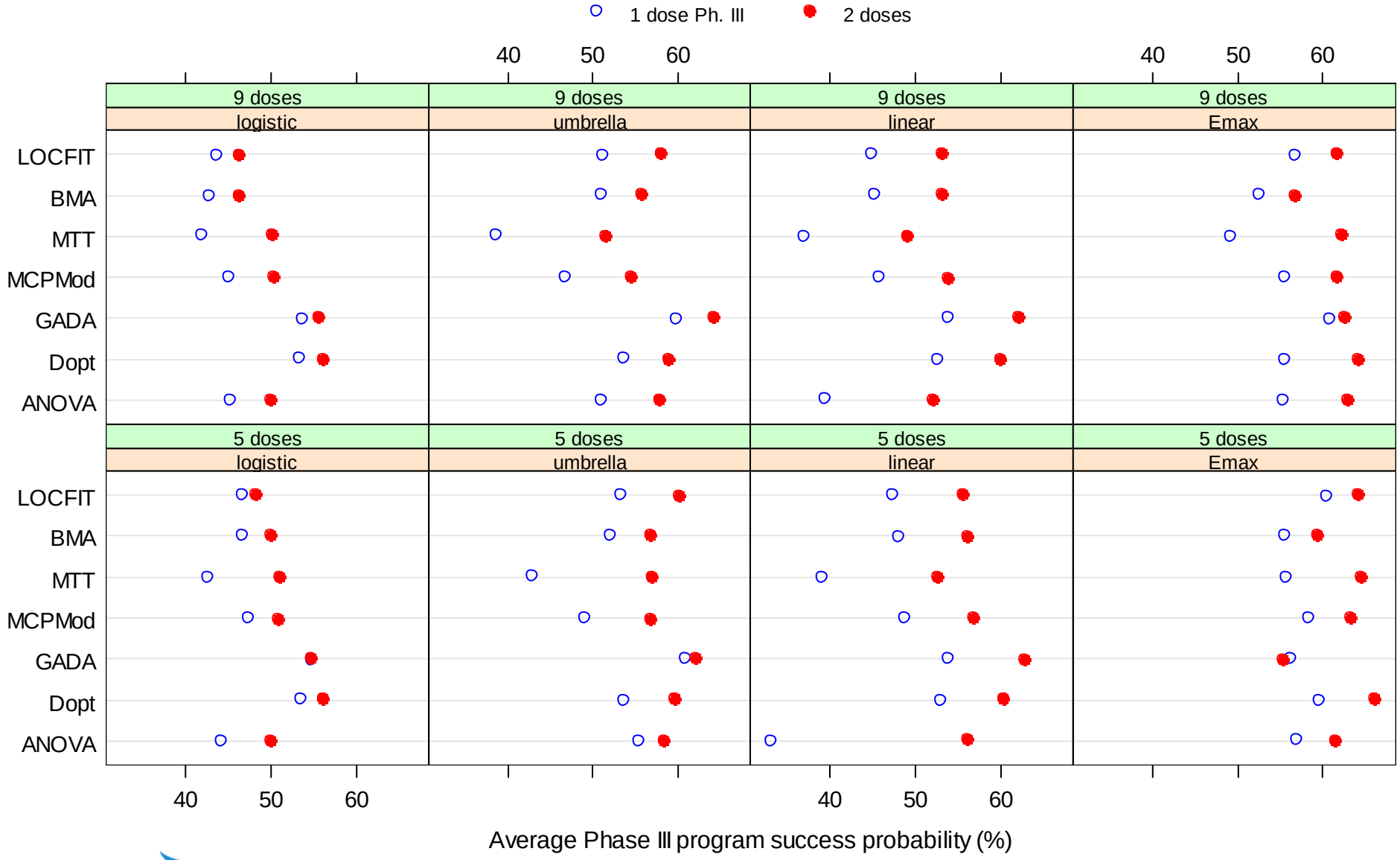
Exp. response WKS: MED Precision



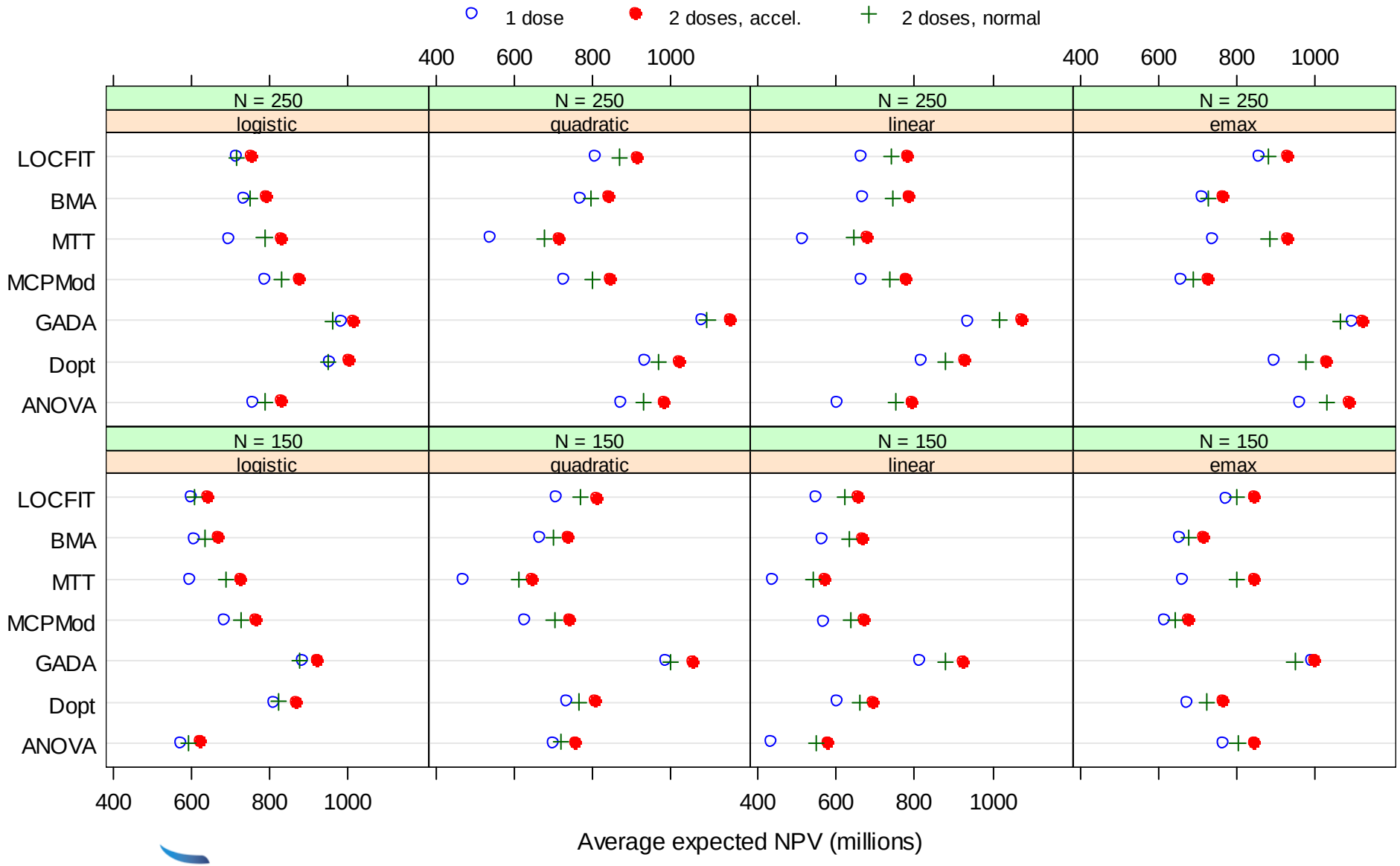
Exp. response WKS: Avg. prediction error



Impact dose sel. WKS: Pr(Success Ph 3)



Impact dose sel. WKS: E(NPV)



Key conclusions

- No silver bullet approach to DF problem
- No design/method uniformly best: relative performance depends on scenario, assumptions
- Approaches are multifaceted: e.g., adaptive, model-based, Bayesian, optimal design, etc
- Factored view of individual components: e.g., frequent adaptations not always add value
- Learning priorities in trial lead to different operational characteristics: e.g., dose selection vs. DR characterization
- Better DR learning approaches exist and can produce substantial knowledge gains

Recommendations

- Implement Toolbox approach: comprehensive set of useful, practical designs and methods, such as:
  - ✓response-adaptive allocation
  - ✓model-based estimation
  - ✓optimal designs
  - ✓Bayesian methods
  - ✓Exposure-response modeling
- Revisit resource allocation balance between DR learning and confirmatory phases, to optimize likelihood of program success and E(NPV)
- Toolbox should be implemented in software, with good simulation and reporting capabilities; open-source strategy would be most efficient

Recommendations (cont.)

- Comprehensive, simulation-based evaluations of proposed designs and methods to guide modern protocol design
- Reinforce 1st round recommendation to bring 2 or 3 doses into Phase 3, when uncertain at end of Ph. 2
- More program-level planning should be used, instead of focusing on individual trials

⇨ White papers from ADRS WG and its WKS published in special issue of Statistics in Biopharmaceutical Research, Volume 2, Number 4, November 2010.

Further thoughts

- Detecting DR is much easier than estimating it; designing DF studies based on power to detect DR is misleading and leads to inaccurate dose selection
- Sample sizes for DF studies typically not large enough for accurate dose selection and estimation of DR; should take into account precision of estimated dose
- Adaptive, model-based dose ranging methods should be routinely considered in Phase 2
- Changing the prevailing mindset of "Phase 2 on the cheap" will require combined efforts from different stakeholders in drug development (industry, regulators, and academia), and strong upper-management support

Back Up

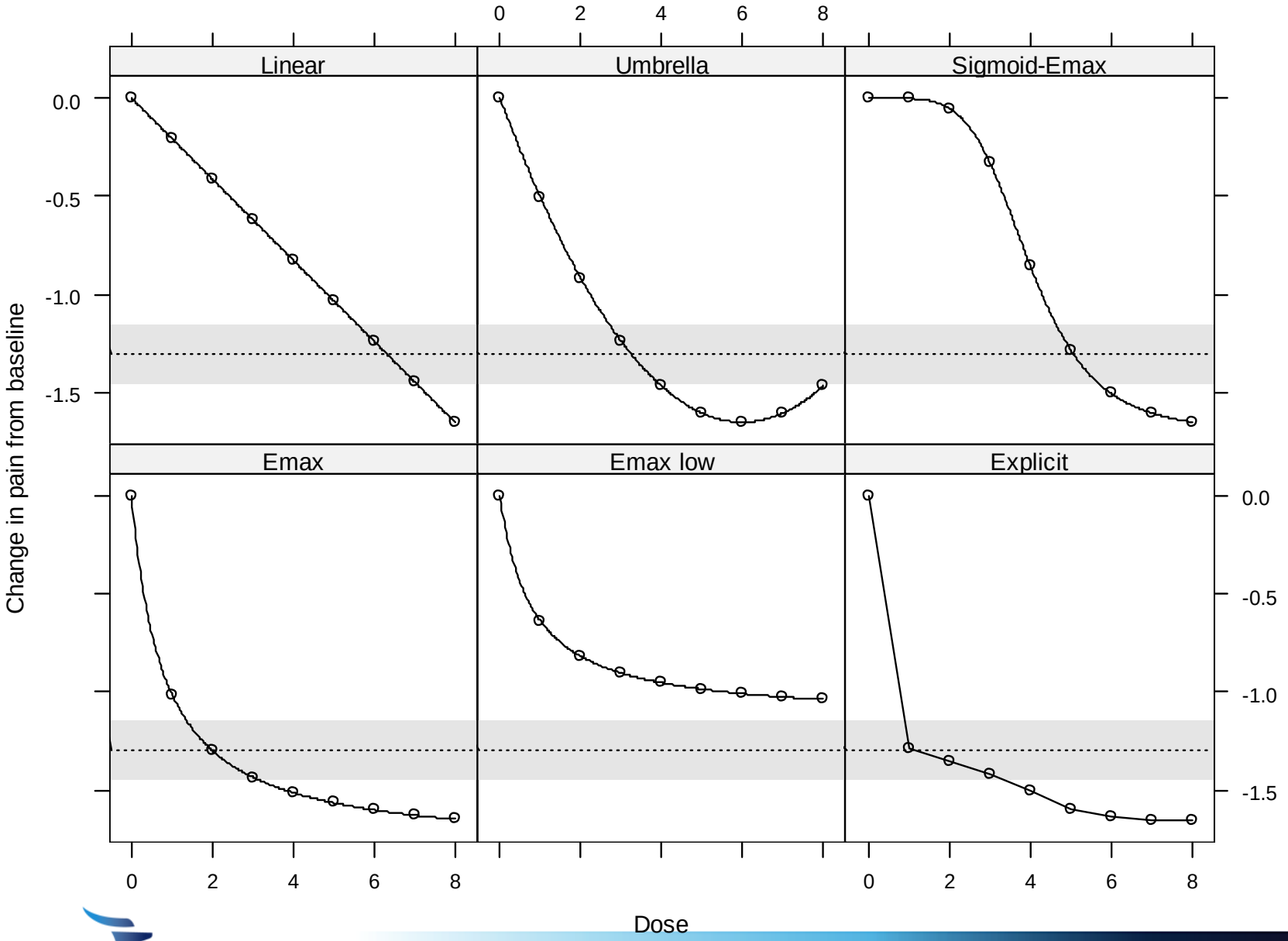
ADRS WG Membership – 2nd round

Co-Chairs: **José Pinheiro, Rick Sax**

Members:

Zoran Antonijevic
Björn Bornkamp
Frank Bretz
Christy Chuang-Stein
Vlad Dragalin
Parvin Fardipour
Bill Gillespie
Chyi-Hung Hsu
Frank Miller
Krishna Padmanabhan
Tom Parke
Nitin Patel
Inna Perevozskaya
Amit Roy
Ashish Sanil
Jonathan Smith

Simulation models – New Meth.WKS



Sim. models – Exposure-response WKS