

Adaptive Dose-Ranging Studies: An Update from the PhRMA WG

José Pinheiro

Novartis Pharmaceuticals

on behalf of the PhRMA ADRS WG

Adaptive Designs WG KOL series

November 13, 2009

- **Motivation and background**
- **Recommendations from 1st evaluation round**
- **2nd evaluation round: key results & conclusions**
- **Overall conclusions and recommendations**

Motivation

- **Pharmaceutical industry pipeline problem:** fewer approvals, at higher development costs [Bornkamp et al., 2007]
- **Stakeholders reaction:** FDA's **Critical Path Initiative**; PhRMA Pharmaceutical Innovation Steering Committee (**PISC**) working groups (WG)
- **Inadequate dose selection for confirmatory trials identified as key driver** of poor performance
- **Adaptive Dose-Ranging Studies (ADRS) WG** formed by PISC to evaluate and address the problem

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 **operational characteristics** of alternative designs and methods via comprehensive simulation studies
- Focus: **adaptive** and **model-based** dose-ranging designs and methods
- Adaptive Designs WG: another PISC group, focusing on **higher level** recommendations and **advocacy of adaptive designs in general**

ADRS WG Membership

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

Current 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

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 III
 - 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
Copyright © Taylor & Francis Group, LLC
ISSN: 1054-3406 print/1520-5711 online
DOI: 10.1080/10543400701643848



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)

Key Conclusions – first round

- Detecting DR is much **easier** than estimating it
- Sample sizes for DF studies are typically not large enough for **accurate** dose selection and estimation of DR
- Adaptive dose ranging methods and other innovative DF methods can lead to substantial **gains** over traditional pairwise testing approaches (especially for estimating DR and selecting dose)

Recommendations – first round

- Adaptive, model-based dose ranging methods should be **routinely considered** in Phase II
- Sample size calculations for DF studies should take into account **precision** of estimated dose
- When resulting N is not feasible, should consider selecting **more than one** dose for Phase III – preferably coupled with adaptive design
- PoC and dose selection should, when feasible, be **combined** in one seamless trial
- Simulations should be used for protocol design

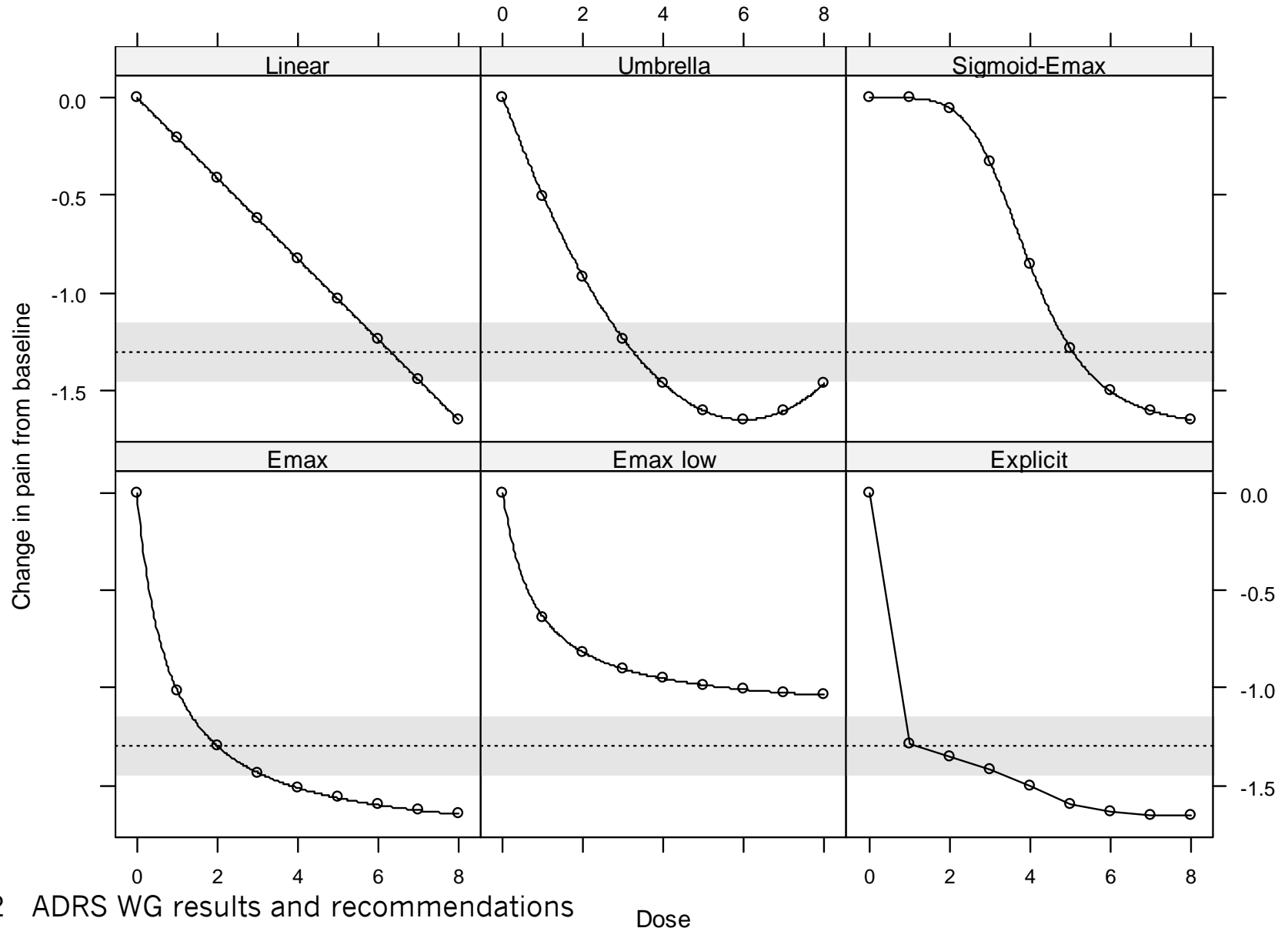
Second evaluation round

Three work streams (WKS) :

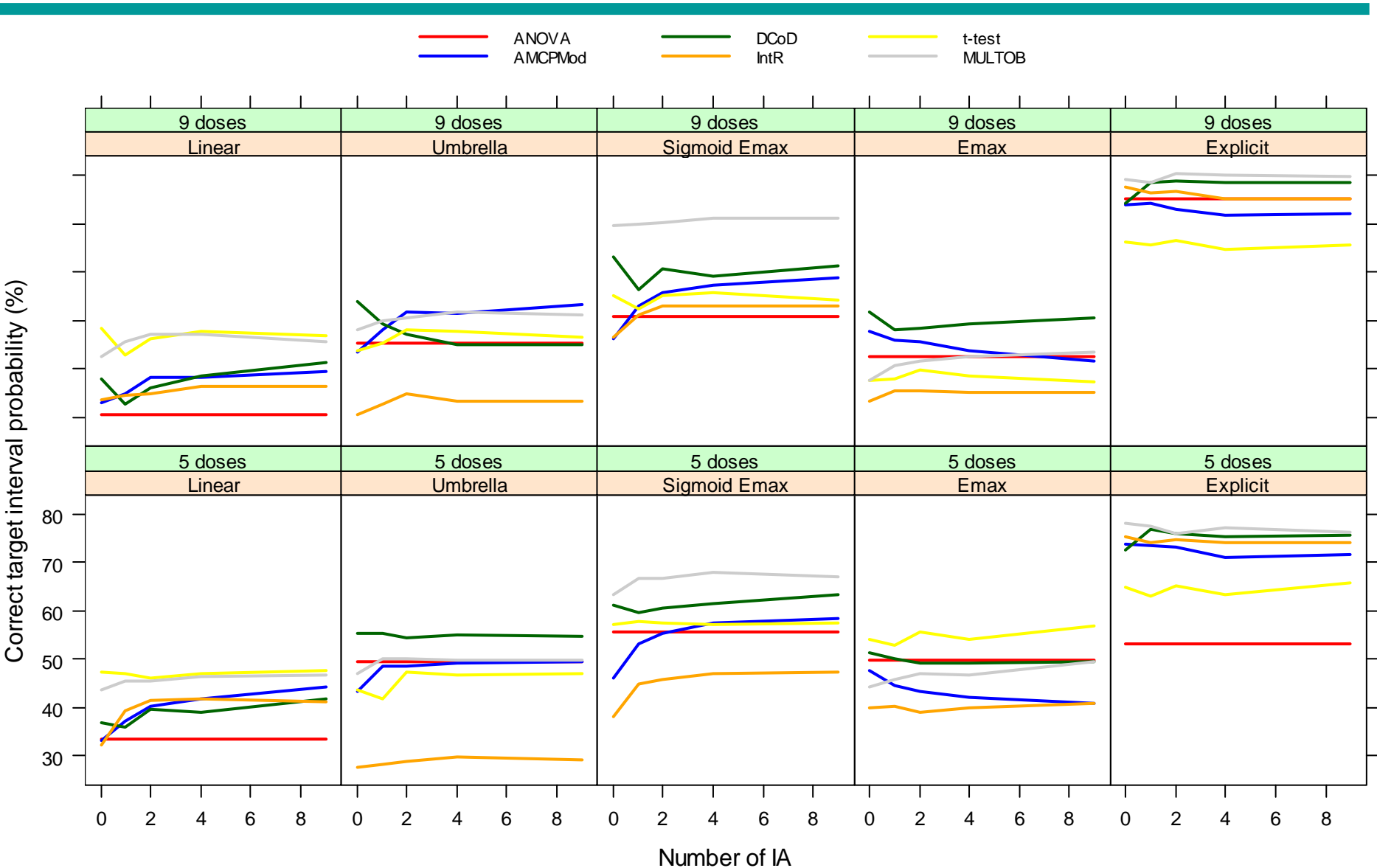
- **New Adaptive Methods**: first round evaluation included only 2 ADR approaches – 5 new ones evaluated by WKS (similar simulation design as in first round)
 - ❖ Chair: Vlad Dragalin
- **Impact of dose selection** (in Phase II) on likelihood of success of Phase III program and net present value (NPV) 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 WKS simulations I – New Methods WKS

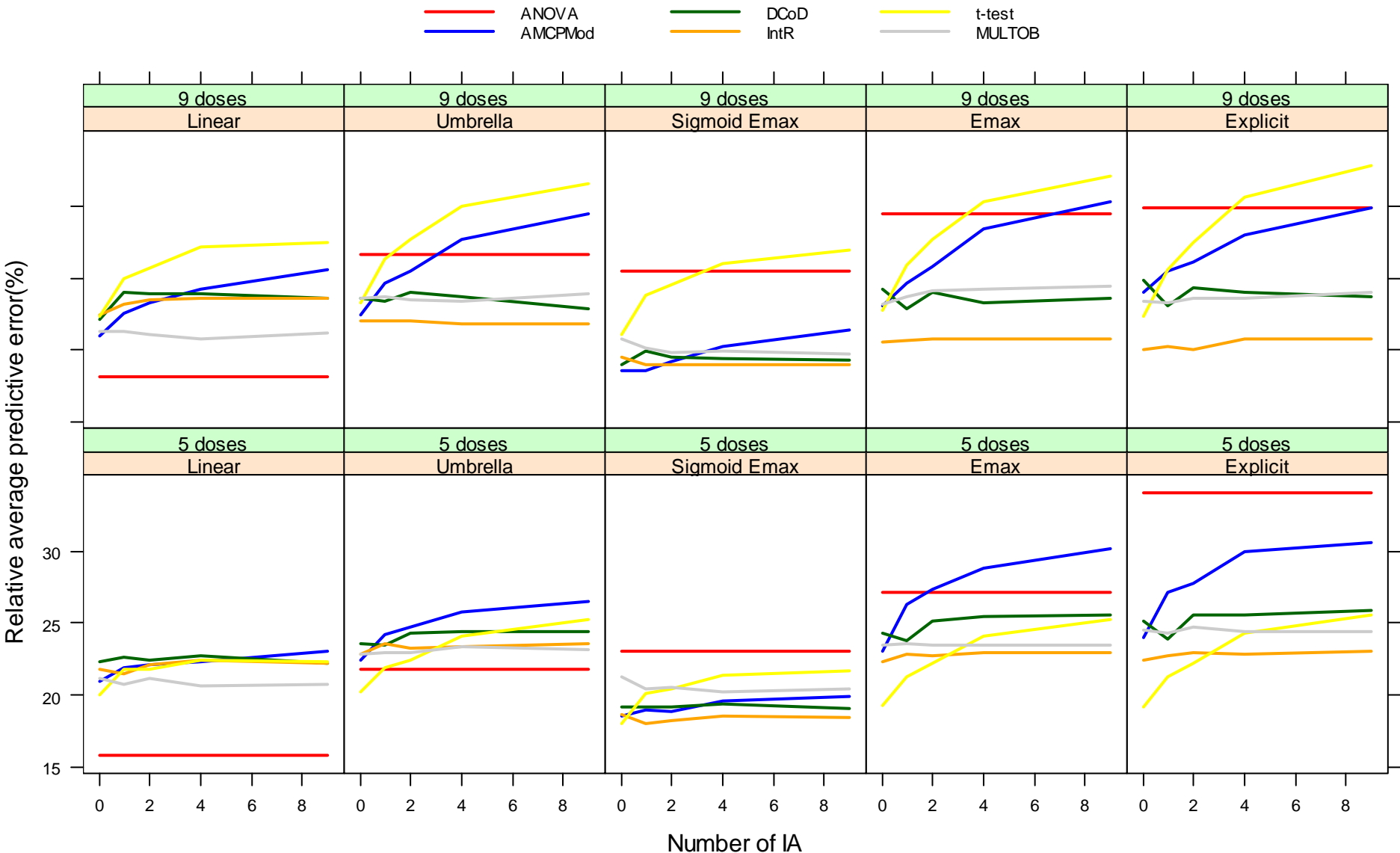
Simulation models



Pr(dose right)

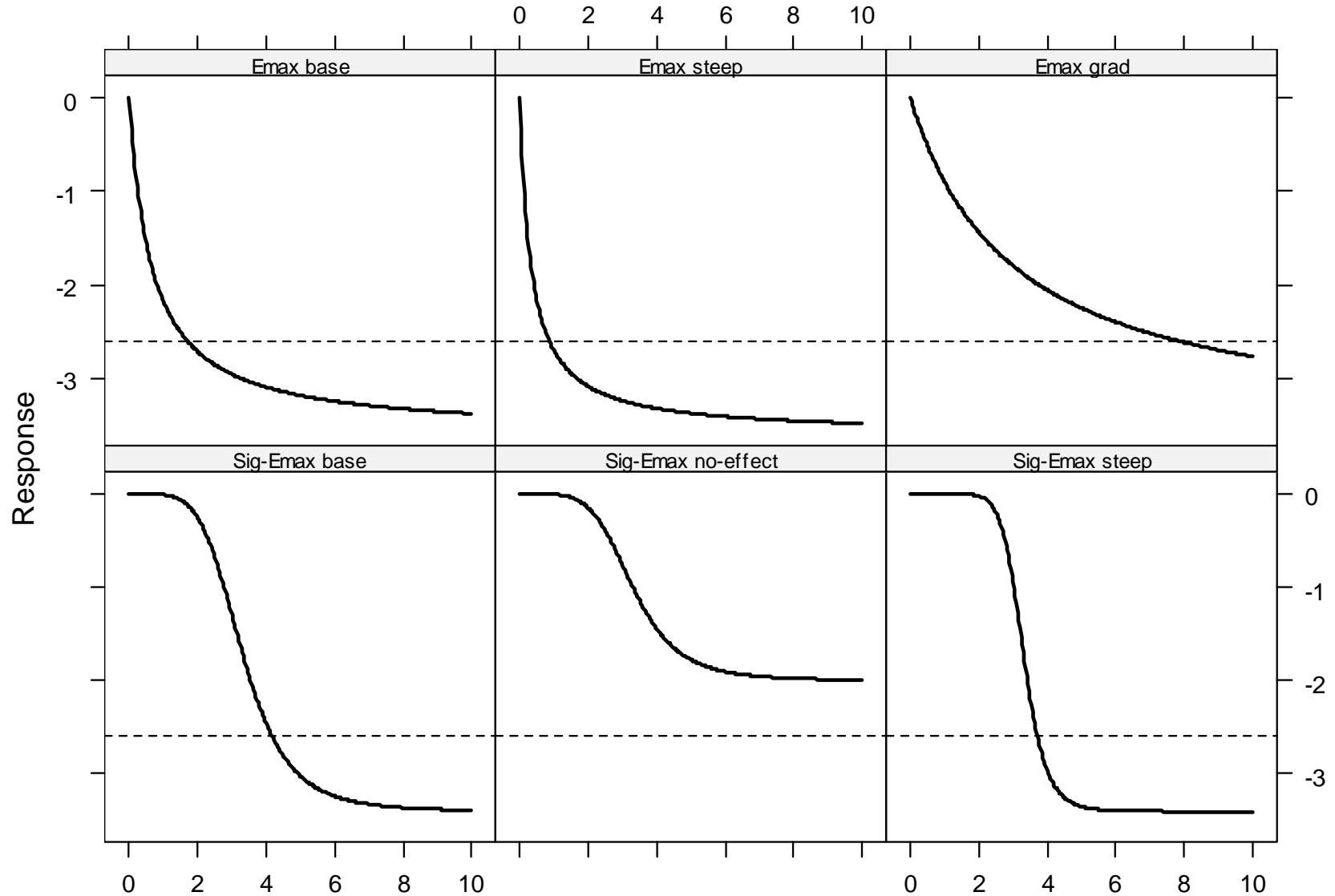


Average prediction error

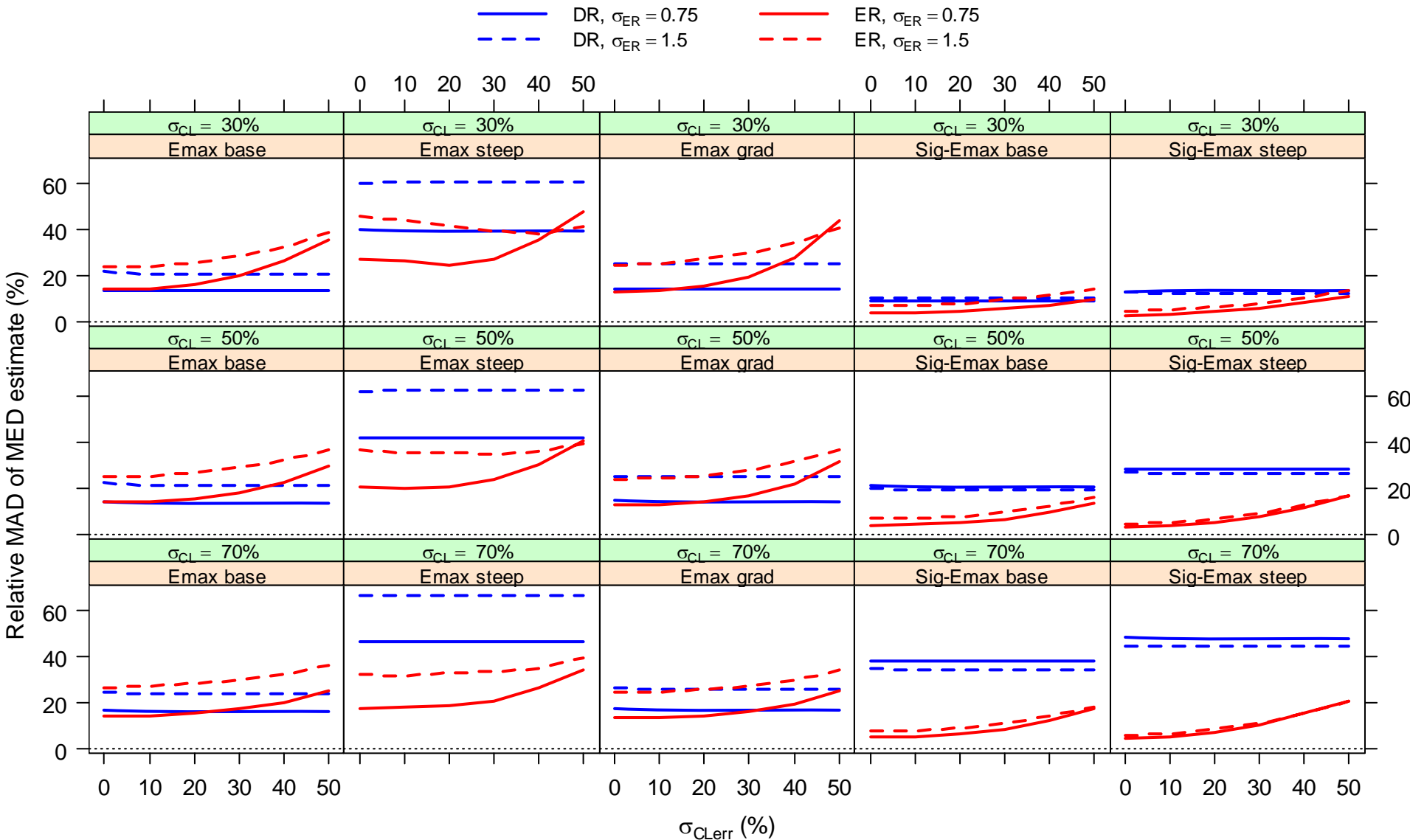


Selected results from WKS simulations II – Exposure Response WKS

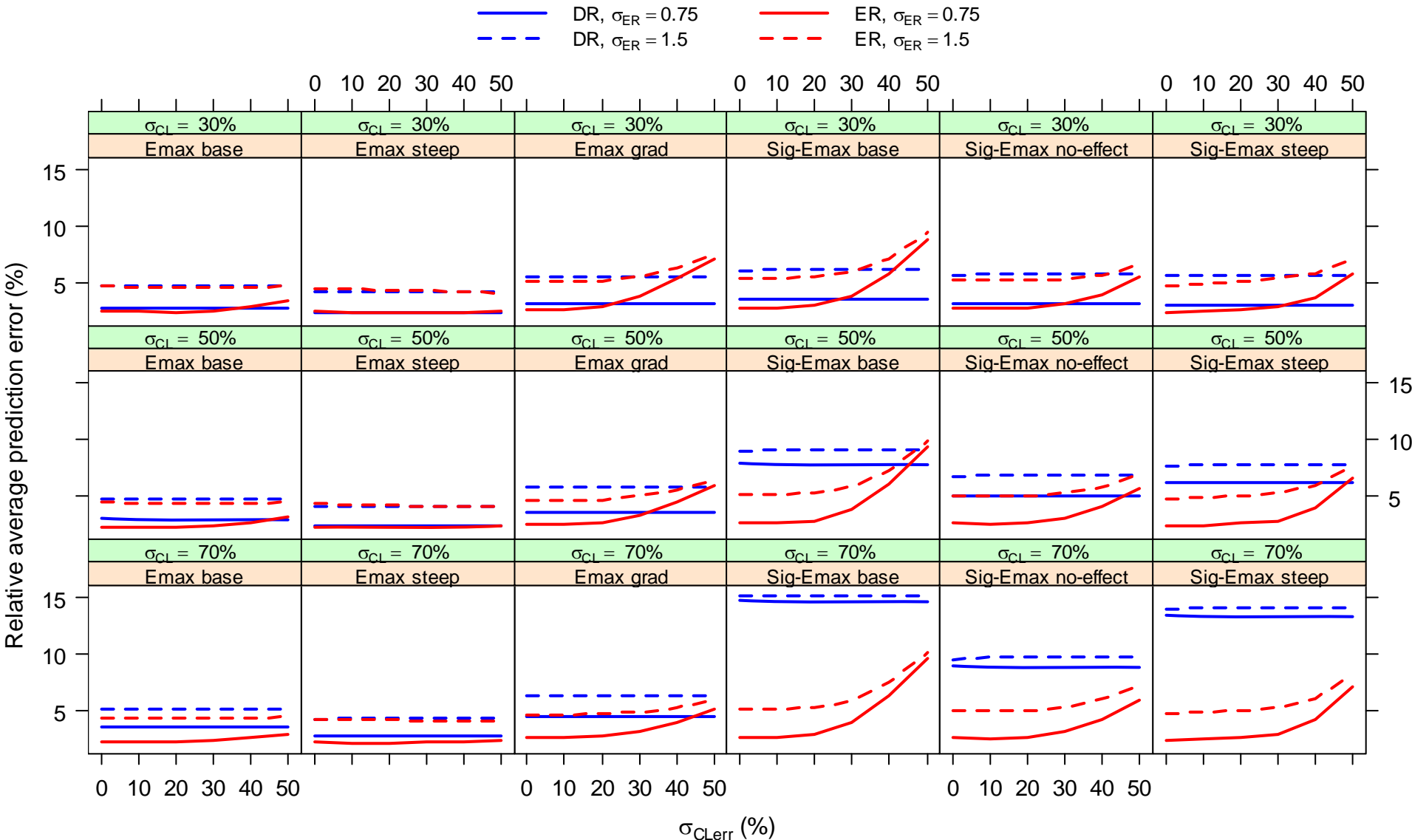
Simulation models



MED Precision

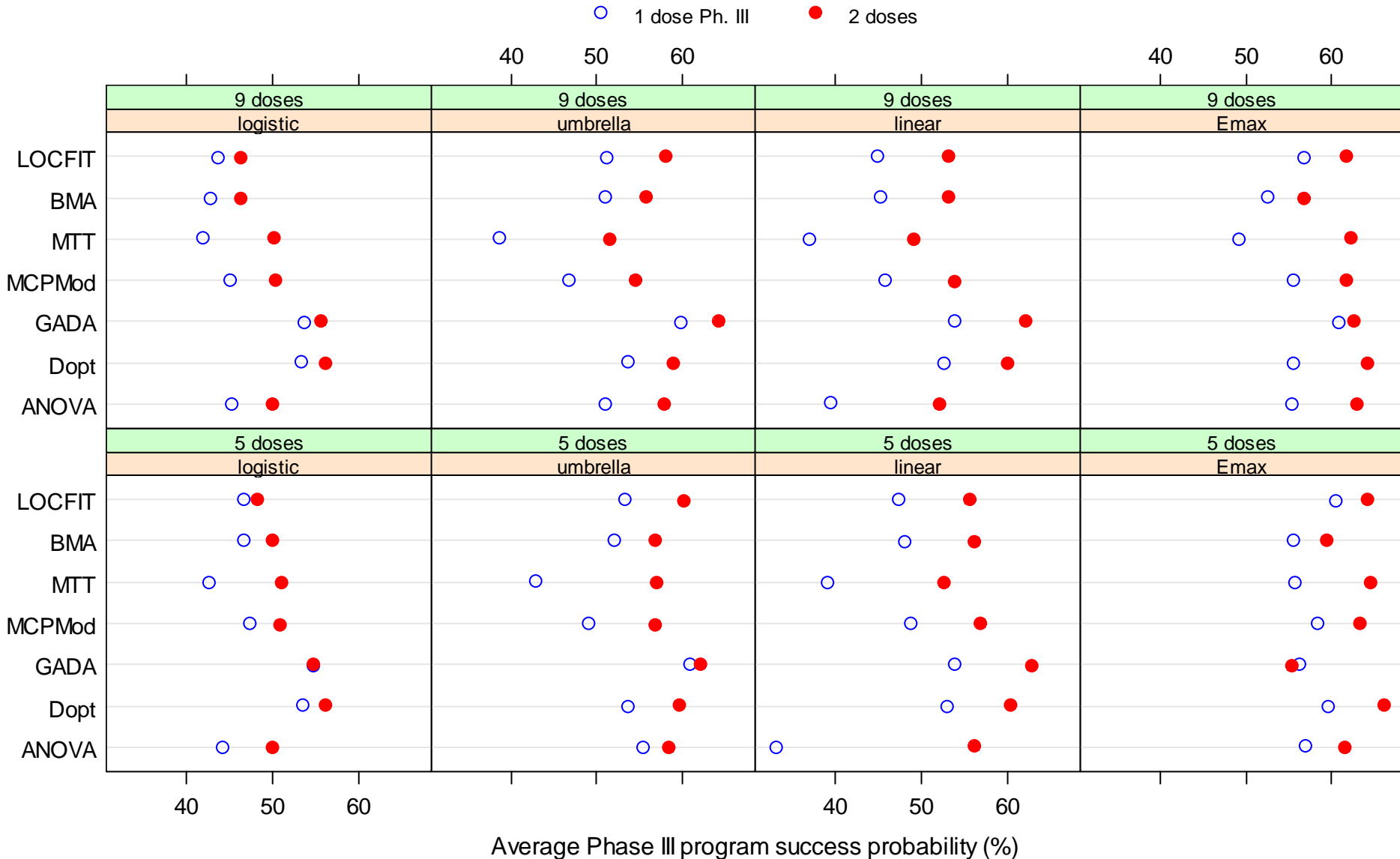


Average prediction error

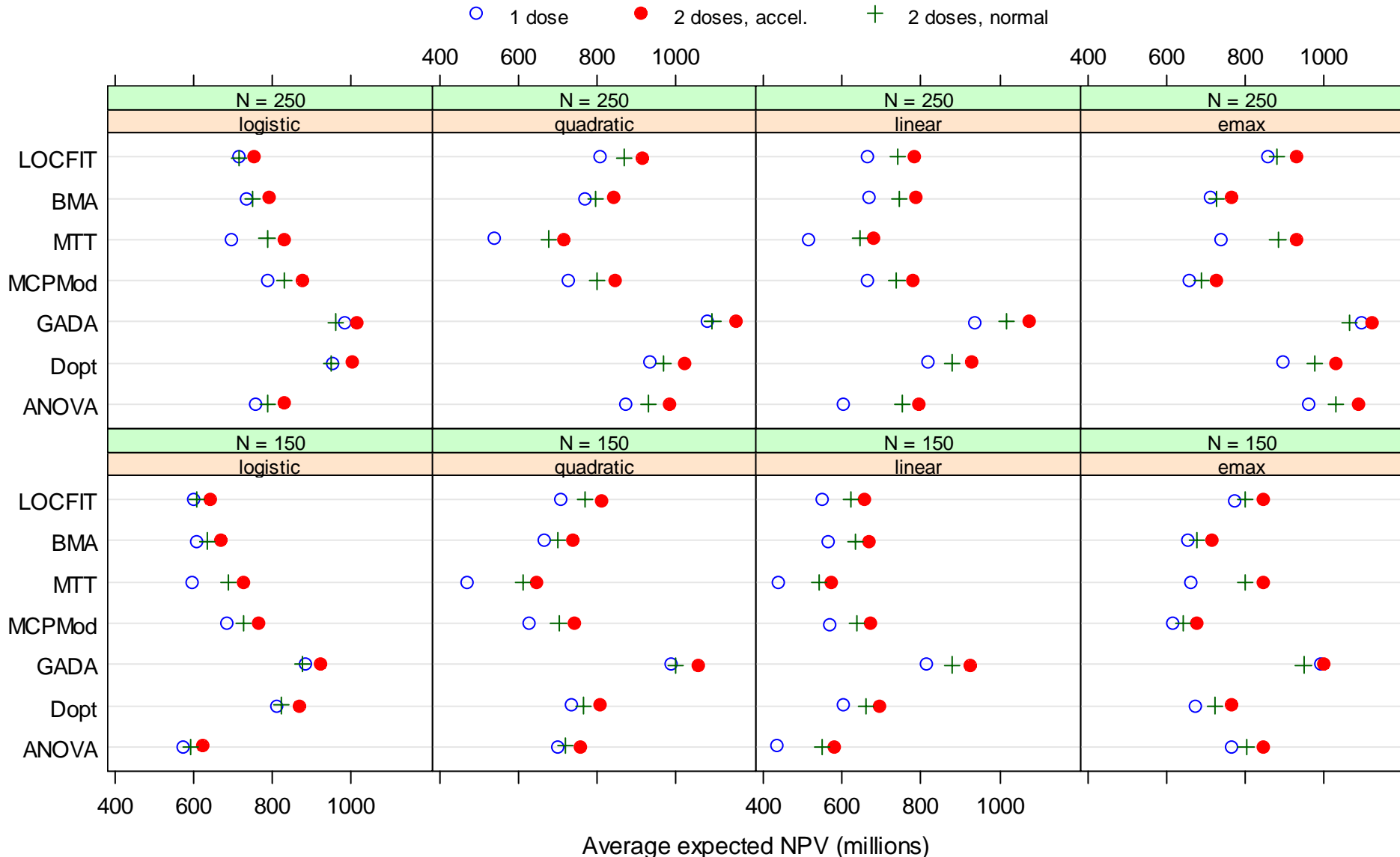


Selected results from WKS simulations III – Impact on Phase 3 WKS

Pr(Success Ph III)



Expected Net Present Value (NPV)



Key conclusions: second round

- No **silver bullet** approach to DF conundrum
- 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: 2nd round

- Recommendations from 1st round remain **valid**
- **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)**

Recommendations: 2nd round (cont.)

- Toolbox should be implemented in **software**, with good **simulation** and **reporting** capabilities; **open-source** strategy would be most efficient
- Comprehensive, simulation-based evaluations to guide modern protocol design
- **Reinforce** 1st round recomm. to bring 2 or 3 doses into Ph. 3, when **uncertain** at end of Ph. 2
- More program-level planning should be used, instead of focusing on individual trials