PhRMA PISC Rolling Dose Studies Working Group

Preliminary Summary Results for Simulation Study — Version 3

February 13, 2006

Background

- Team decided to evaluate and quantify benefit of Rolling Dose Designs via simulation studies
- Different scenarios of interest identified; focus on trials in patient population; assume MTD has been previously determined
- Start with simple scenario and evaluation criteria; move to more complex cases as results are analyzed and understood
- Ultimate goal is to be able to make recommendations on the potential benefits of rolling dose studies over more traditional designs and methods, under different practical scenarios

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 to bring to confirmatory phase and how well dose response (DR) curve is estimated
- Primary endpoint: change from baseline in VAS at Week 6
- Weekly measurements available, only last and baseline used in analysis
- Assumed model:

$$\text{VAS}_{ij} = f(d_i, t_j, \boldsymbol{\theta}) + b_i + \epsilon_{ij},\ b_i \overset{\text{ind}}{\sim} \mathcal{N}(0, 2.5^2),\ \epsilon_{ij} \overset{\text{ind}}{\sim} \mathcal{N}(0, 1.5^2)$$

$$\Rightarrow \Delta\text{VAS}_i = \text{VAS}_{i6} - \text{VAS}_{i0} = g(d_i, \theta) + \eta_i,\ \eta_i \overset{\text{ind}}{\sim} \mathcal{N}(0, 2 \times 1.5^2)$$

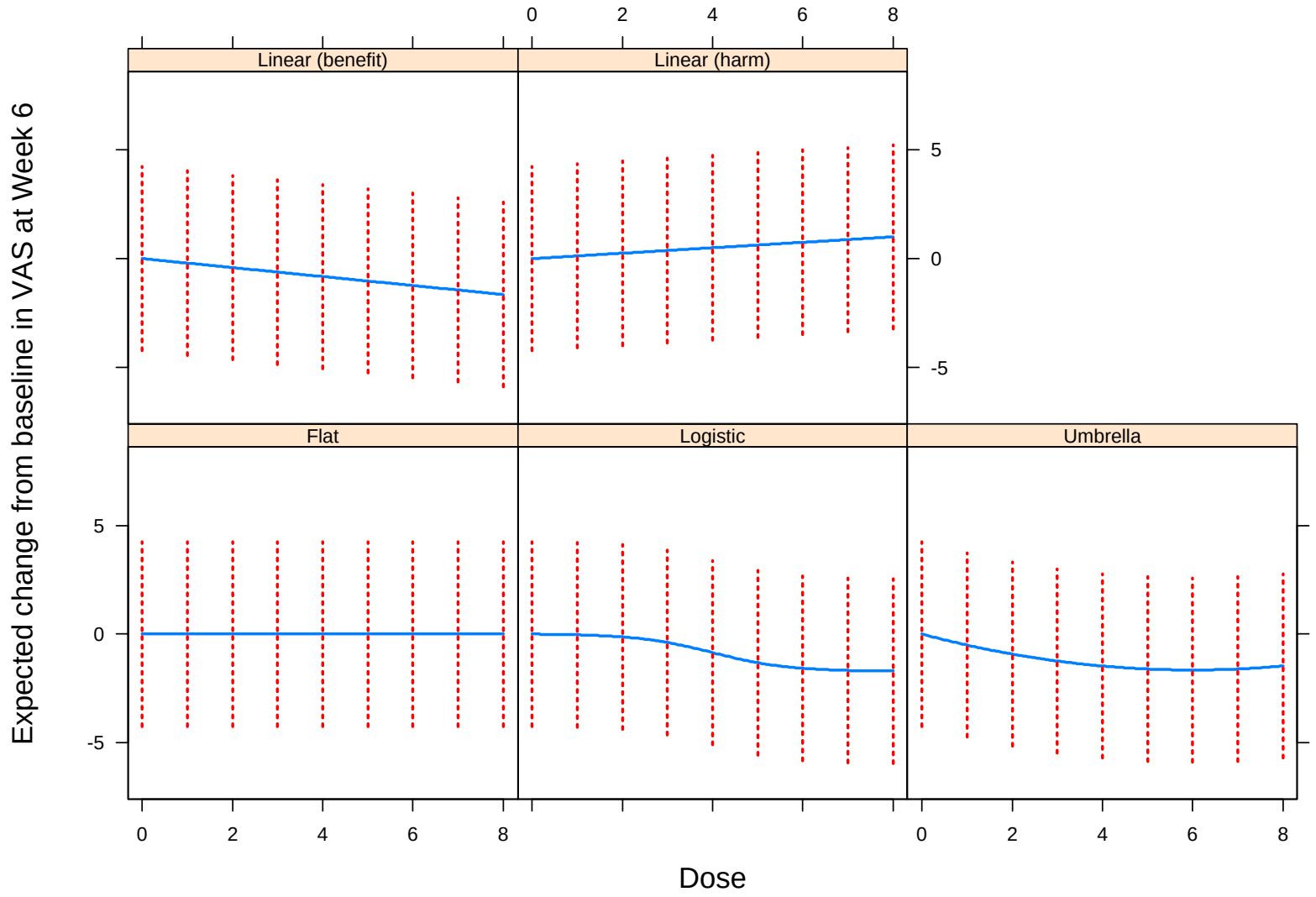
Simulation study (cont.)

- Accrual rates: 16, 48, and 72 weeks (only relevant for GADA)
- Dose design scenarios:
  - 5 equally spaced doses: 0, 2, 4, 6, 8
  - 7 unequally spaced doses: 0, 2, 3, 4, 5, 6, 8
  - 9 equally spaced doses: 0, 1, . . . , 8
- Significance level: one-sided FWER $\alpha = 0.05$ (not for all methods)
- Number of simulations: between 1K and 10K, depending on method
- Evaluation: power to identify dose response, accuracy of target dose estimates and DR estimation
- Interim analysis scenarios:
  - No interim analysis
  - One interim analysis when 50% of patients expected to have endpoint observed ($\alpha_1 = 0.015,\ \alpha_2 = 0.035$)

Design scenarios

- Clinically relevant effect: $\Delta = -1.3$ units; maximum effect for observed dose range: $\Delta_{\max} = -1.65$ units
- Sample sizes: 250 patients – 80% power at Δ and 95% power at $\Delta_{\max}$ for pairwise comparisons under 5 dose level design (Dunnett procedure) and 150 patients – 56% power at Δ and 78% power at $\Delta_{\max}$
- Dose response profiles
  - Flat: $g(d, \boldsymbol{\theta}) = 0$
  - Logistic: $g(d, \boldsymbol{\theta}) = 0.015 - 1.73/(1 + \exp(1.2(4 - d)))$
  - Umbrella: $g(d, \boldsymbol{\theta}) = (1.65/3)\left(-d + d^2/12\right)$
  - Linear I: $g(d, \boldsymbol{\theta}) = -1.65d/8$ (beneficial)
  - Linear II: $g(d, \boldsymbol{\theta}) = d/8$ (harmful)

Dose response profiles



Methods utilized in simulations

- Fixed-dose methods for benchmarking
  - ANOVA based on pairwise comparisons and multiplicity adjustment (Dunnett) – Amit Roy and Frank Shen
  - MCP-Mod approach combining multiple comparisons and modeling – José Pinheiro and Frank Bretz
- Adaptive methods
  - Bayesian dynamic dose allocation based on non-parametric model – Tom Parke and Michael Krams
  - D-optimality adaptive allocation based on parametric model – Alex Dmitrienko
- Non-adaptive, novel method (can potentially be made adaptive) based on Multiple Trend Tests (MTT) – Qing Liu

Simulation scenarios currently available

- ANOVA: $N = 150, 250$, all models and doses, without early termination (ET), 1K simulations
- D-opt: $N = 150, 250$, all models but Linear II and all doses, without ET, 3K simulations
- GADA: $N = 150, 250$, all doses and models, with and without ET
- MCP-Mod: $N = 150, 250$, all doses and models, with and without ET, 10K simulations
- MTT: $N = 150, 250$, all doses and models, without ET, 10K simulations

Measuring performance

- Probability of identifying dose response: $Pr(DR)$
- Probability of selecting a dose for Phase III: $Pr(dose)$
- Dose selection
  - Distribution of selected doses (rounded to nearest integer, if continuous estimate possible)
  - Summary statistics (mean and standard deviation) for *percentage difference from target*
    pDiff $= 100(\widehat{d} - d_{\text{targ}})/d_{\text{targ}}$
- DR estimation: summary statistics for *average prediction error* (PE): $100|\widehat{DR} - DR|/DR$

Measuring performance (cont.)

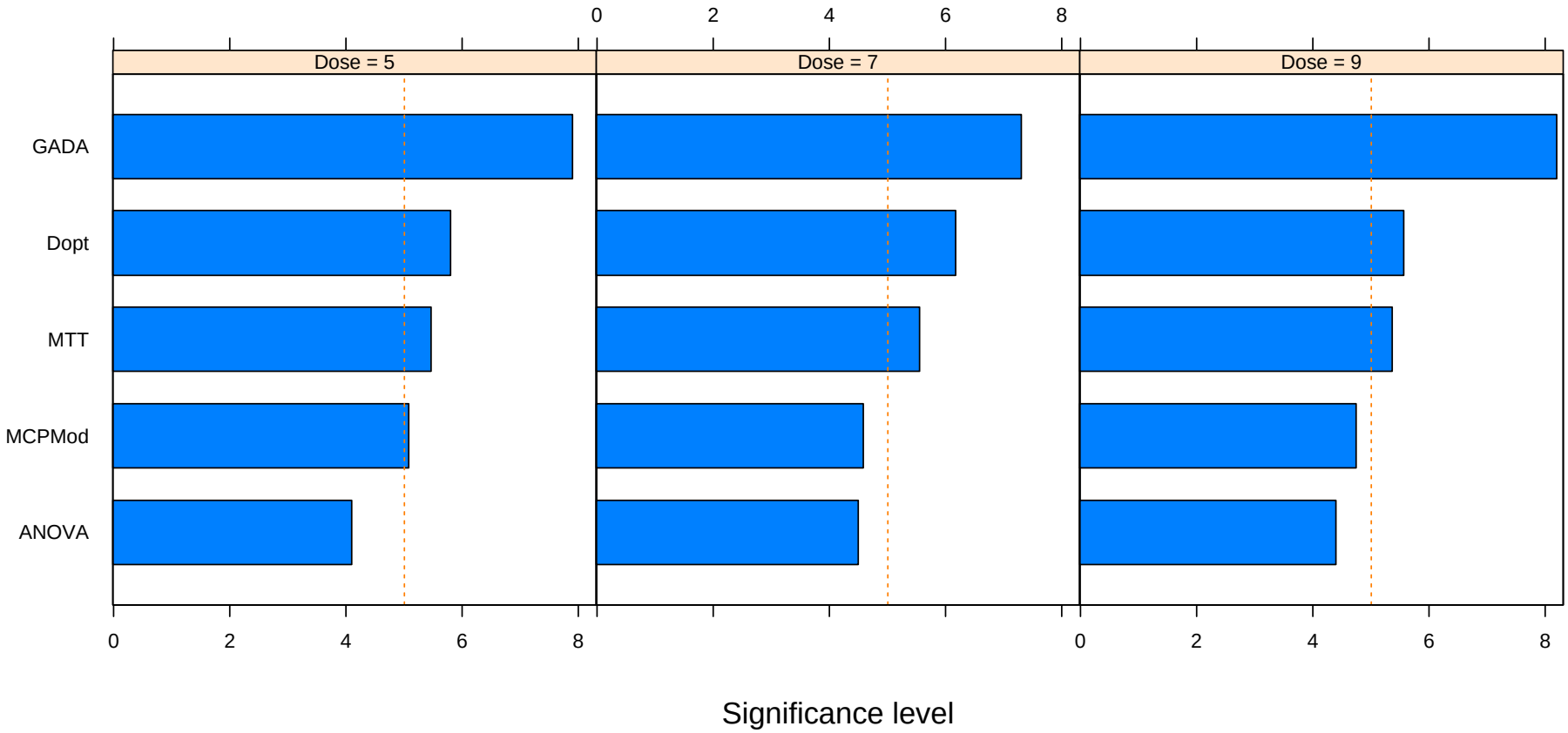
- Linear II model (harm) not utilized in this preliminary summary
- Flat model not utilized for dose selection and DR estimation summaries
- Target doses: Logistic = 4.96 (rounded to 5), Umbrella = 3.24 (3), and Linear I = 6.3 (6)
- Doses utilized for calculating average prediction errors: Logistic = $3, \ldots, 8$, Umbrella = $2, \ldots, 8$, and Linear = $1, \ldots, 8$

Probabilities

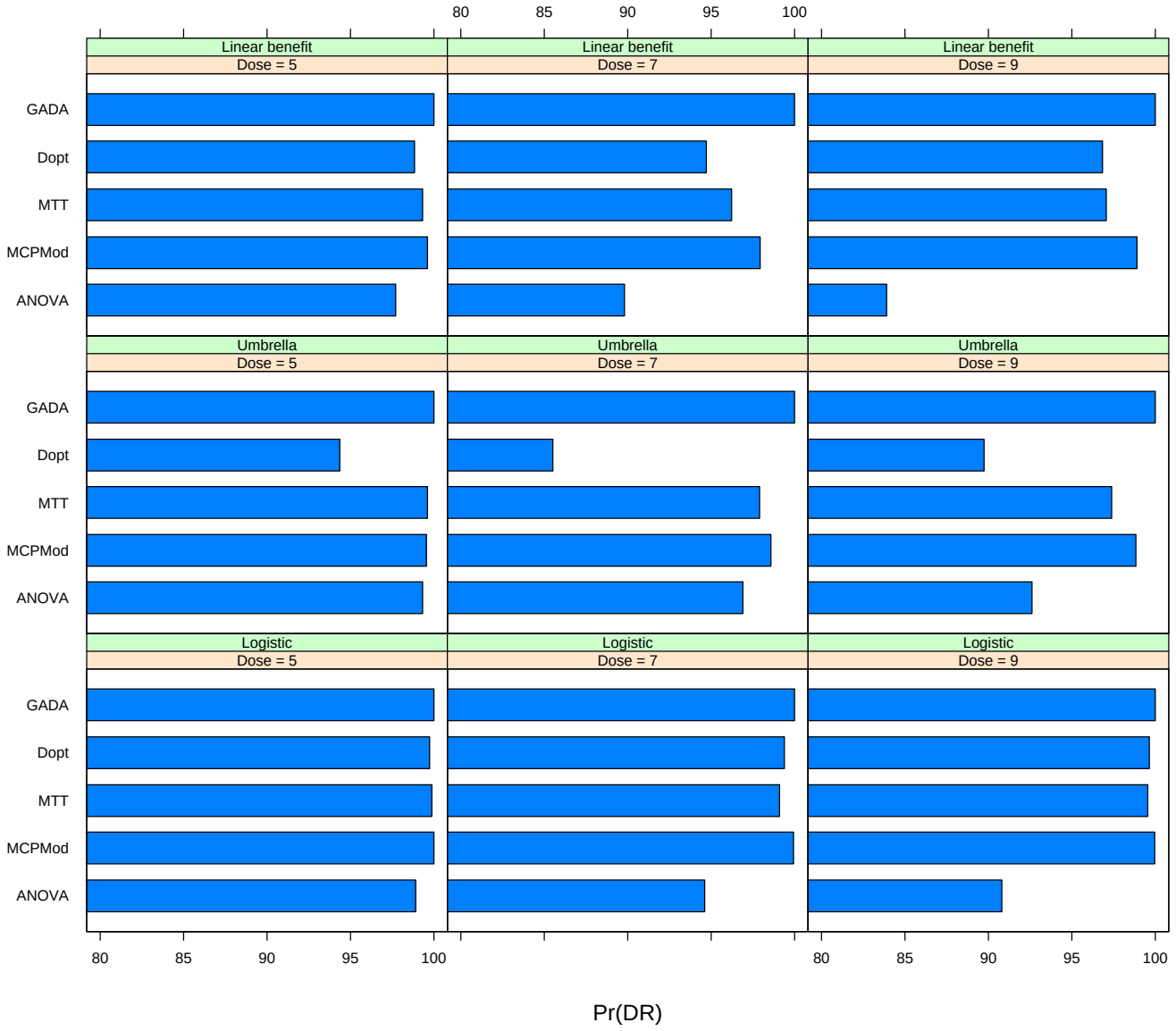
Pr(DR), N=250, no ET

		Method				
Model	Doses	ANOVA	D-Opt	GADA	MCP-Mod	MTT
Flat	5	4.1	5.8	7.9	5.1	5.4
	7	4.5	6.2	7.3	4.6	5.5
	9	4.4	5.6	8.2	4.7	5.3
Logistic	5	98.9	99.7	100.0	100.0	99.9
	7	94.6	99.4	100.0	99.9	99.1
	9	90.8	99.6	100.0	100.0	99.5
Umbrella	5	99.3	94.3	100.0	99.5	99.6
	7	96.9	85.5	100.0	98.6	97.9
	9	92.6	89.7	100.0	98.8	97.4
Linear I	5	97.7	98.8	100.0	99.6	99.3
	7	89.8	94.7	100.0	97.9	96.2
	9	83.9	96.8	100.0	98.9	97.0

Significance level, N=250, no ET



Pr(DR), N=250, no ET



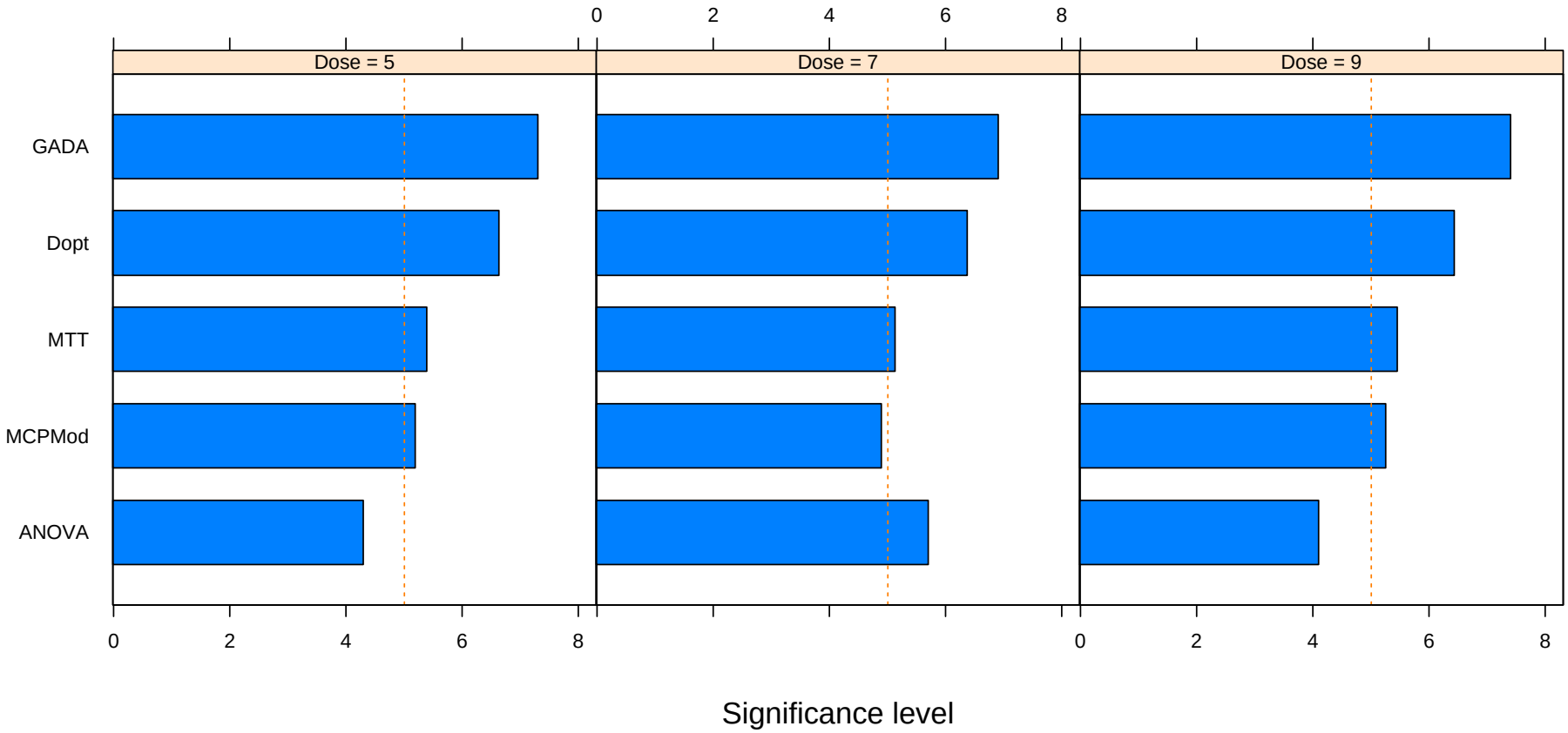
Pr(DR), N=250, with ET

		Method	
Model	Doses	GADA	MCP-Mod
Flat	5	6.2	4.3
	7	6.8	4.3
	9	7.7	4.1
Logistic	5	100.0	100.0
	7	100.0	99.8
	9	100.0	100.0
Umbrella	5	100.0	99.7
	7	100.0	99.5
	9	99.7	98.2
Linear I	5	98.6	99.2
	7	99.7	96.9
	9	99.8	98.2

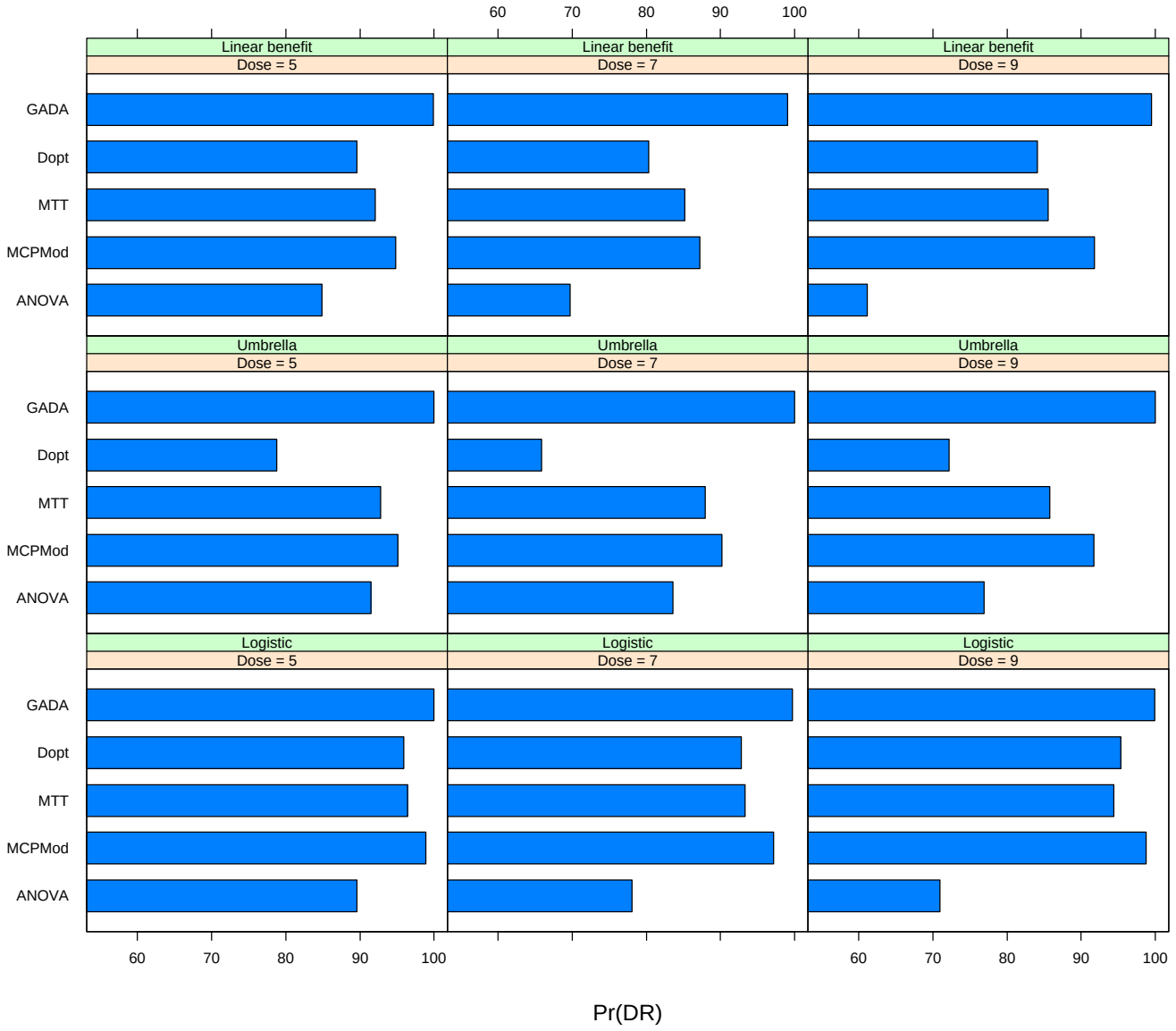
Pr(DR), N=150, no ET

		Method				
Model	Doses	ANOVA	D-Opt	GADA	MCP-Mod	MTT
Flat	5	4.3	6.6	7.3	5.2	5.4
	7	5.7	6.4	6.9	4.9	5.1
	9	4.1	6.4	7.4	5.3	5.5
Logistic	5	89.6	95.9	100.0	98.9	96.4
	7	78.1	92.8	99.7	97.2	93.3
	9	71.0	95.4	99.9	98.8	94.4
Umbrella	5	91.5	78.8	100.0	95.1	92.8
	7	83.6	65.9	100.0	90.2	87.9
	9	76.9	72.2	100.0	91.7	85.7
Linear I	5	84.9	89.6	99.9	94.8	92.1
	7	69.7	80.3	99.0	87.2	85.2
	9	61.2	84.1	99.5	91.8	85.6

Significance level, N=150, no ET



Pr(DR), N=150, no ET



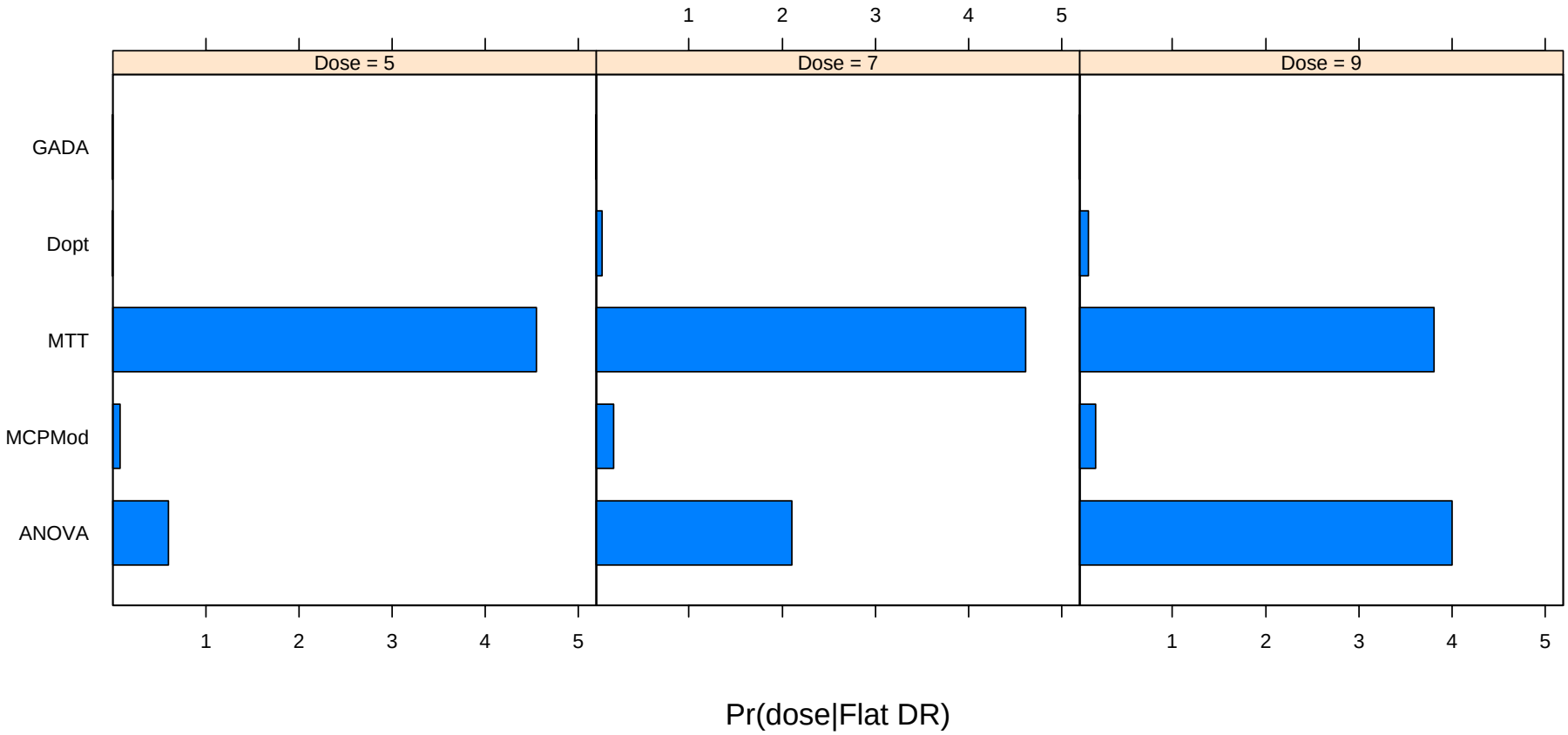
Pr(DR), N=150, with ET

		Method	
Model	Doses	GADA	MCP-Mod
Flat	5	7.7	4.4
	7	6.1	5.0
	9	6.8	4.9
Logistic	5	99.9	98.6
	7	99.9	95.9
	9	100.0	98.3
Umbrella	5	100.0	94.0
	7	99.9	87.1
	9	99.8	89.6
Linear I	5	100.0	93.0
	7	99.2	84.0
	9	99.3	89.1

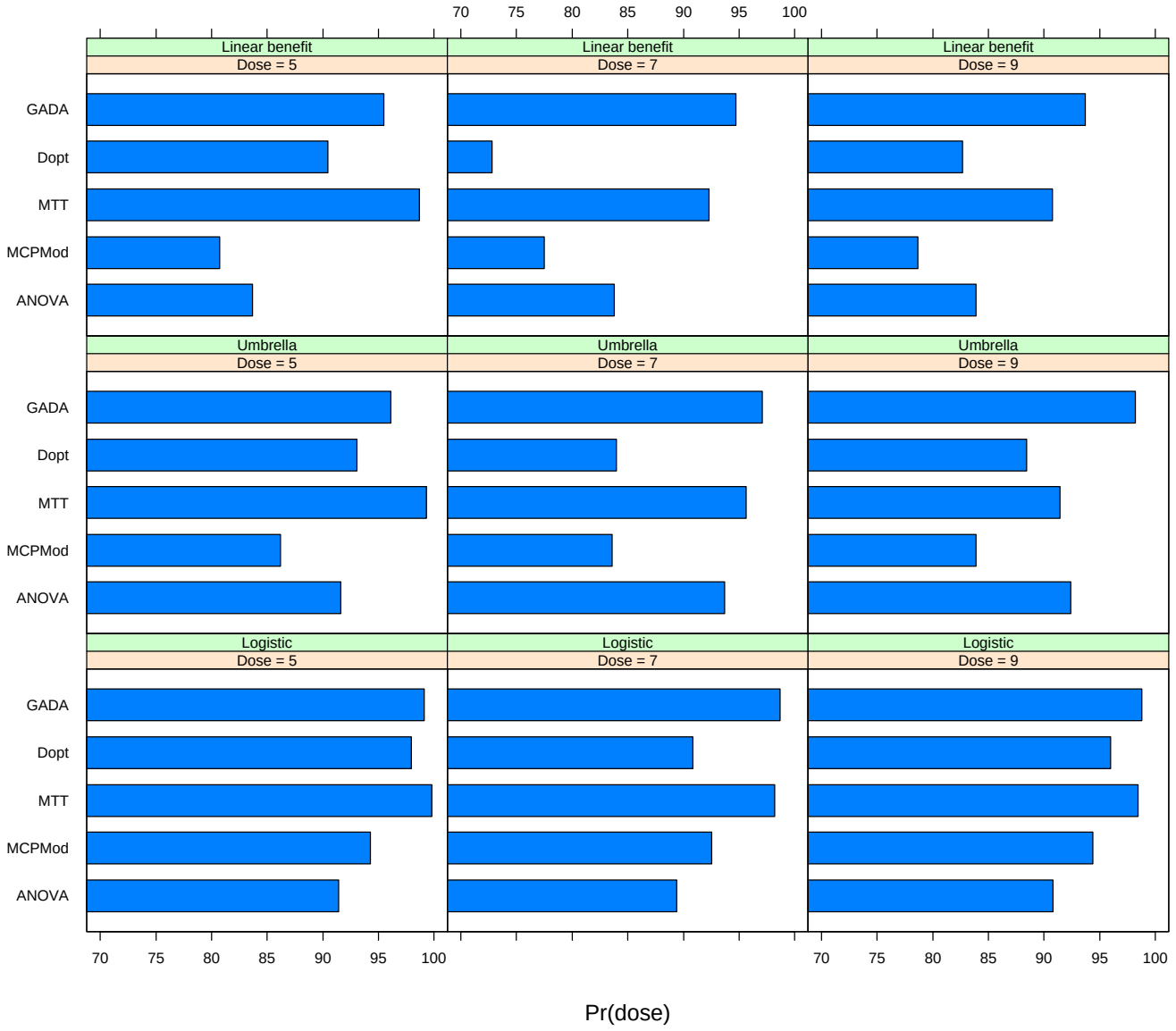
Pr(dose), N=250, no ET

		Method				
Model	Doses	ANOVA	D-Opt	GADA	MCP-Mod	MTT
Flat	5	0.6	0.0	0.0	0.1	4.6
	7	2.1	0.0	0.0	0.2	4.6
	9	4.0	0.1	0.0	0.2	3.8
Logistic	5	91.4	97.9	99.1	94.3	99.8
	7	89.4	90.8	98.7	92.6	98.2
	9	90.8	96.0	98.8	94.4	98.4
Umbrella	5	91.6	93.1	96.1	86.2	99.3
	7	93.7	84.0	97.1	83.6	95.6
	9	92.4	88.4	98.2	83.9	91.4
Linear I	5	83.7	90.4	95.5	80.8	98.7
	7	83.8	72.8	94.7	77.5	92.3
	9	83.9	82.7	93.7	78.7	90.8

Pr(dose—Flat DR), N=250, no ET



Pr(dose), N=250, no ET



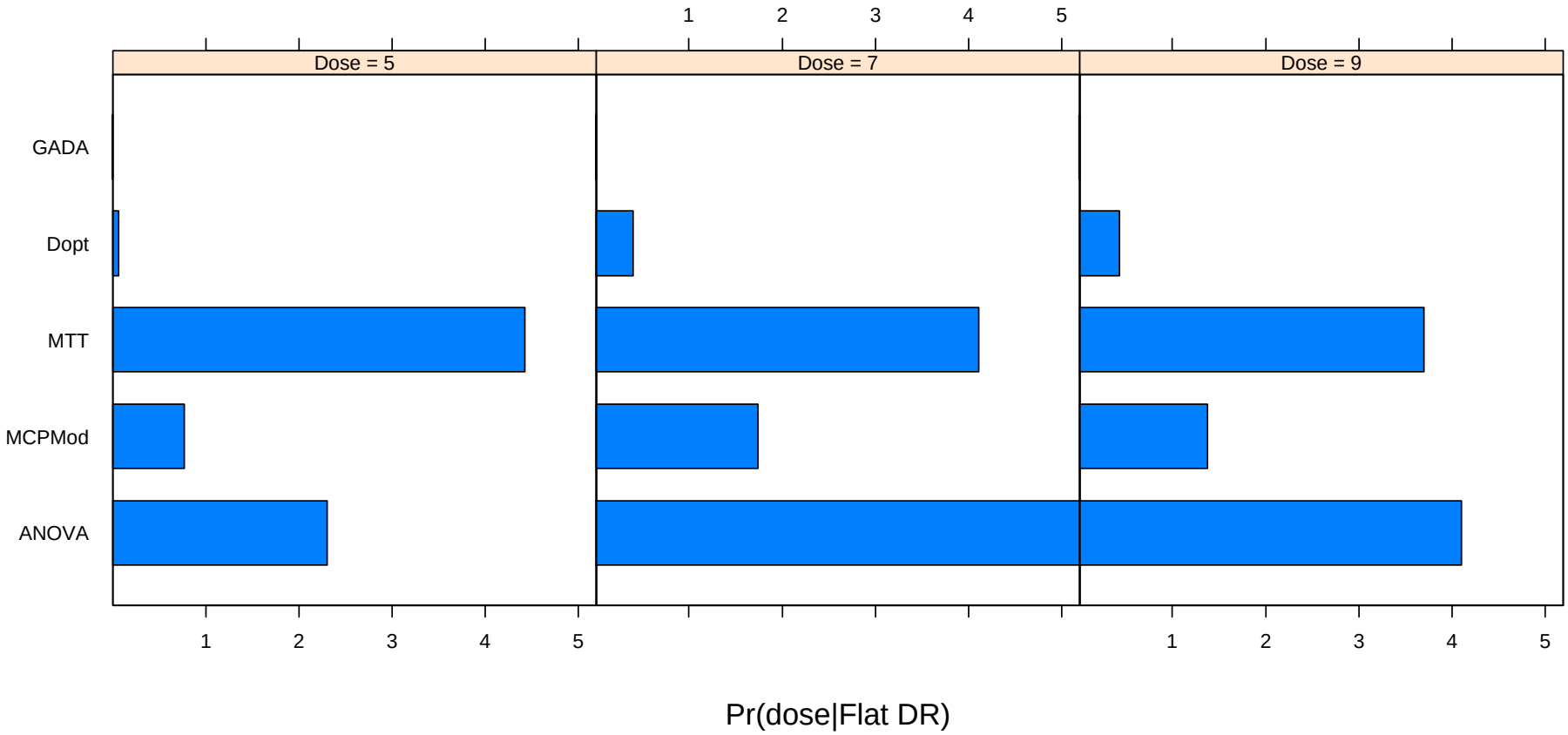
Pr(dose), N=250, with ET

		Method	
Model	Doses	GADA	MCP-Mod
Flat	5	0.0	0.9
	7	0.1	1.3
	9	0.0	1.3
Logistic	5	100.0	100.0
	7	100.0	99.8
	9	100.0	100.0
Umbrella	5	100.0	99.7
	7	100.0	99.5
	9	99.7	98.2
Linear I	5	99.7	99.2
	7	99.8	96.9
	9	99.5	98.2

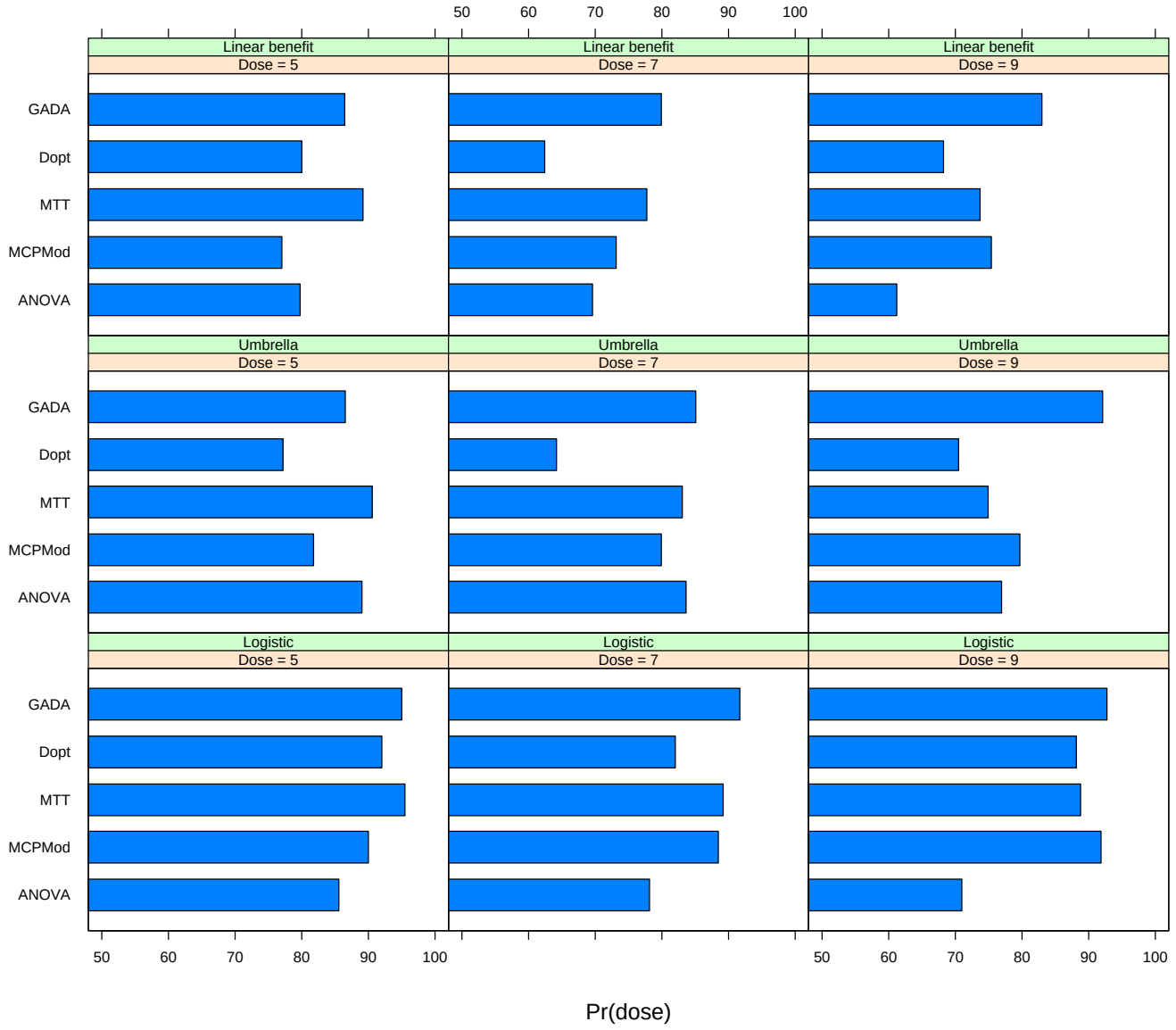
Pr(dose), N=150, no ET

		Method				
Model	Doses	ANOVA	D-Opt	GADA	MCP-Mod	MTT
Flat	5	2.3	0.1	0.0	0.8	4.4
	7	5.7	0.4	0.0	1.7	4.1
	9	4.1	0.4	0.0	1.4	3.7
Logistic	5	89.6	92.0	95.0	90.0	95.4
	7	78.1	82.0	91.7	88.4	89.1
	9	71.0	88.1	92.7	91.9	88.8
Umbrella	5	91.5	77.1	86.5	81.8	90.5
	7	83.6	64.2	85.1	79.9	83.0
	9	76.9	70.5	92.1	79.7	74.9
Linear I	5	84.9	80.0	86.4	77.0	89.1
	7	69.7	62.4	79.9	73.1	77.7
	9	61.2	68.2	83.0	75.4	73.7

Pr(dose—Flat DR), N=150, no ET



Pr(dose), N=150, no ET

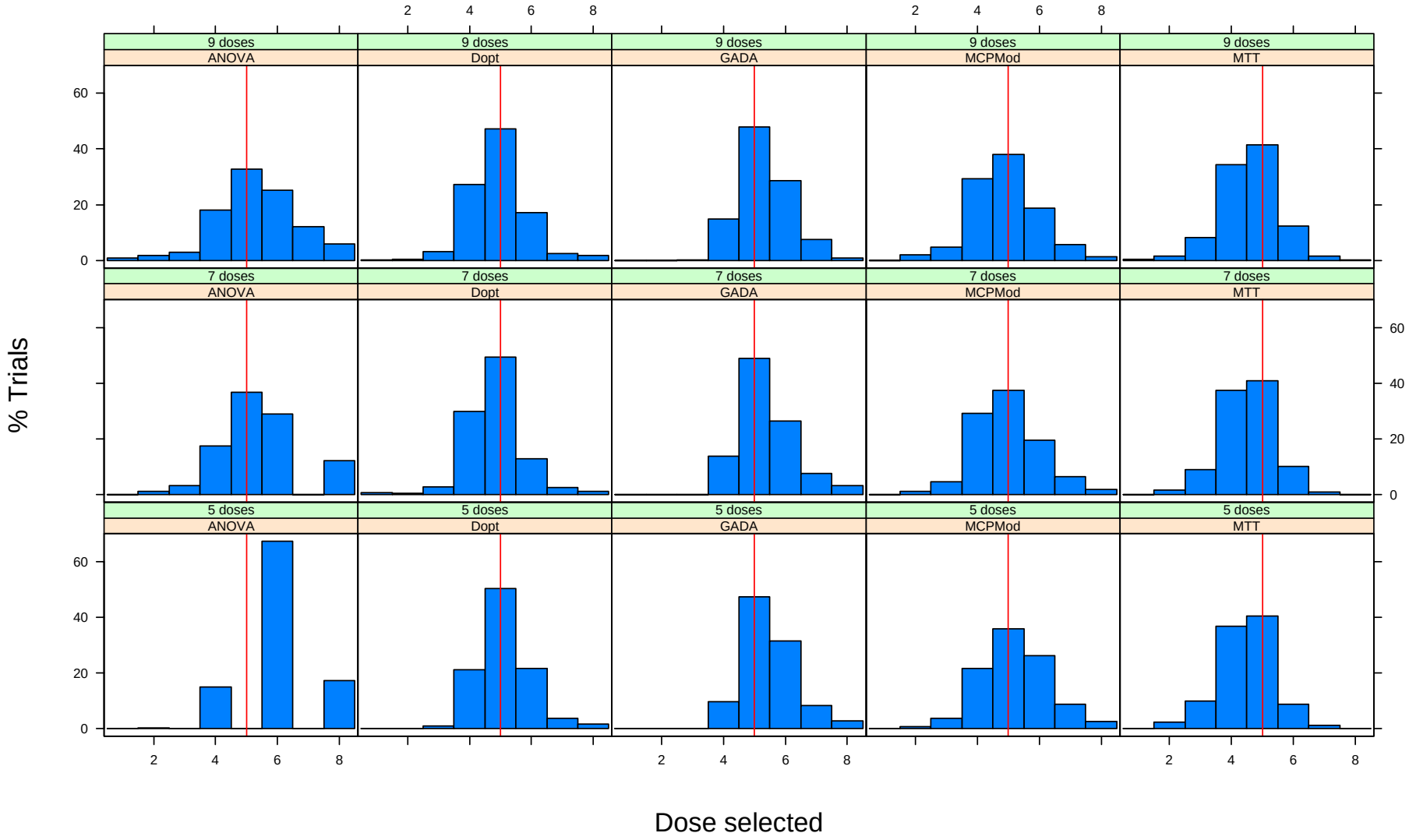


Pr(dose), N=150, with ET

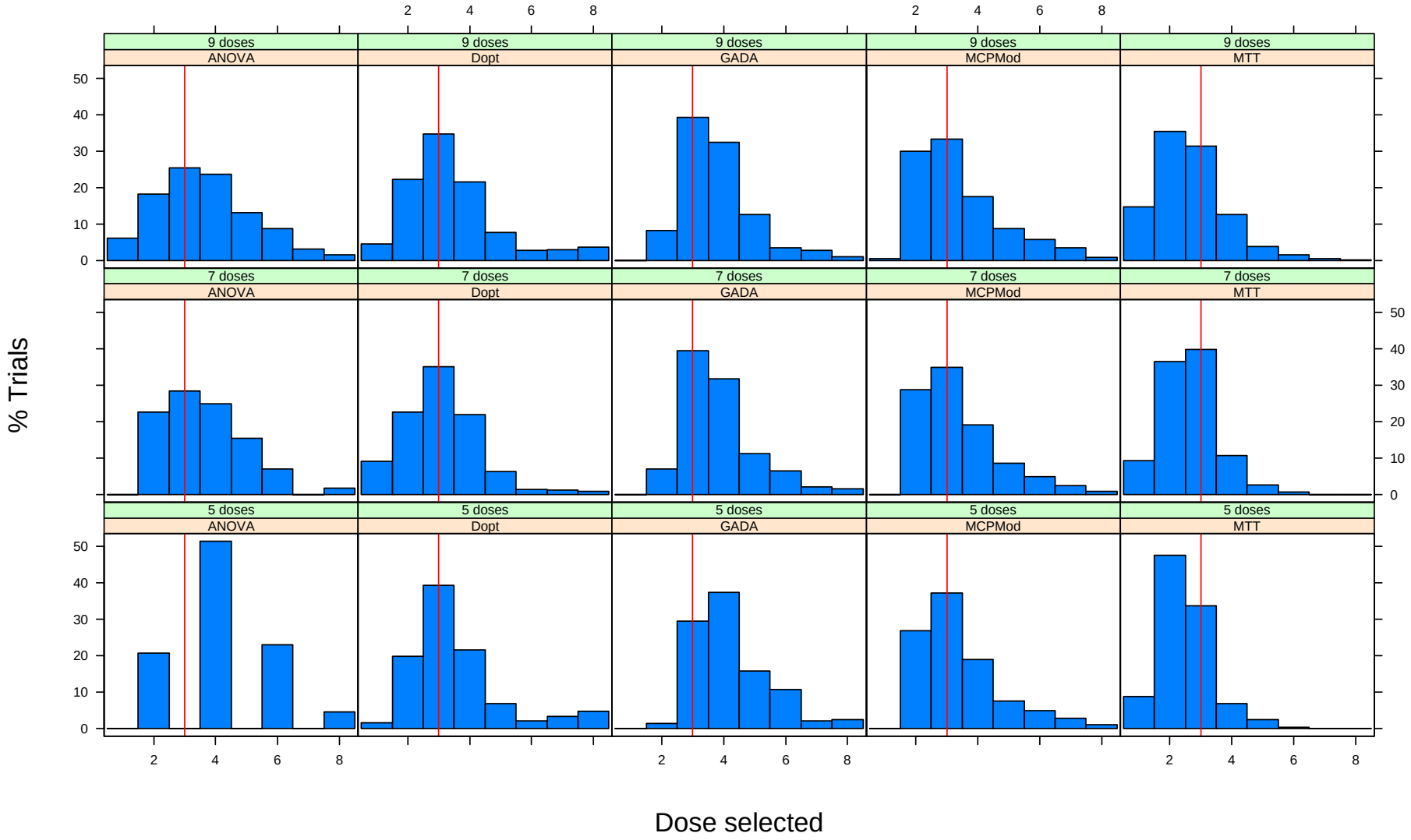
		Method	
Model	Doses	GADA	MCP-Mod
Flat	5	0.0	1.9
	7	0.0	3.1
	9	0.0	2.7
Logistic	5	94.5	89.0
	7	94.1	85.6
	9	95.6	89.6
Umbrella	5	85.2	84.1
	7	89.8	80.2
	9	91.7	80.8
Linear I	5	86.6	79.0
	7	83.1	74.3
	9	83.4	76.1

Dose Selection

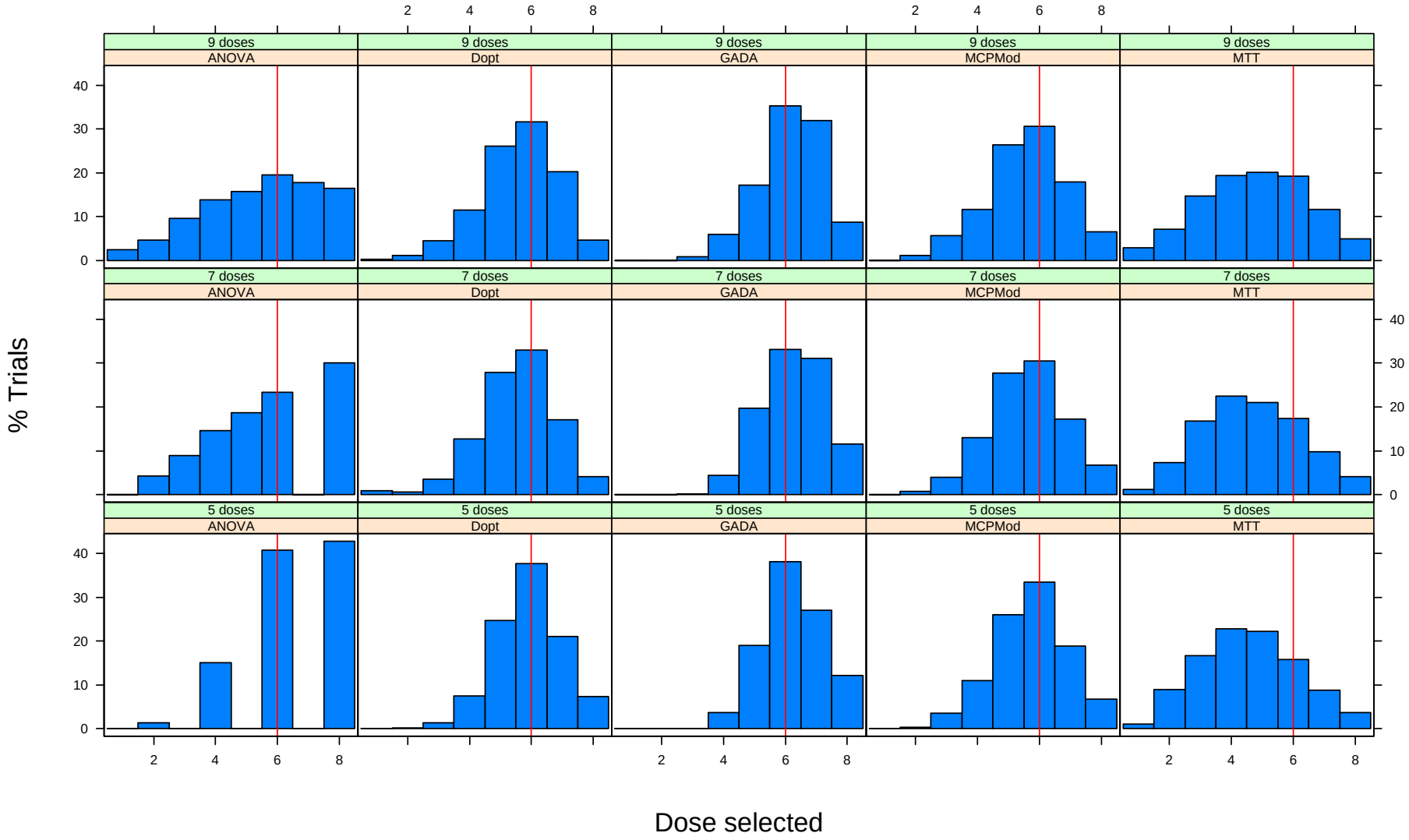
Logistic, N=250, no ET



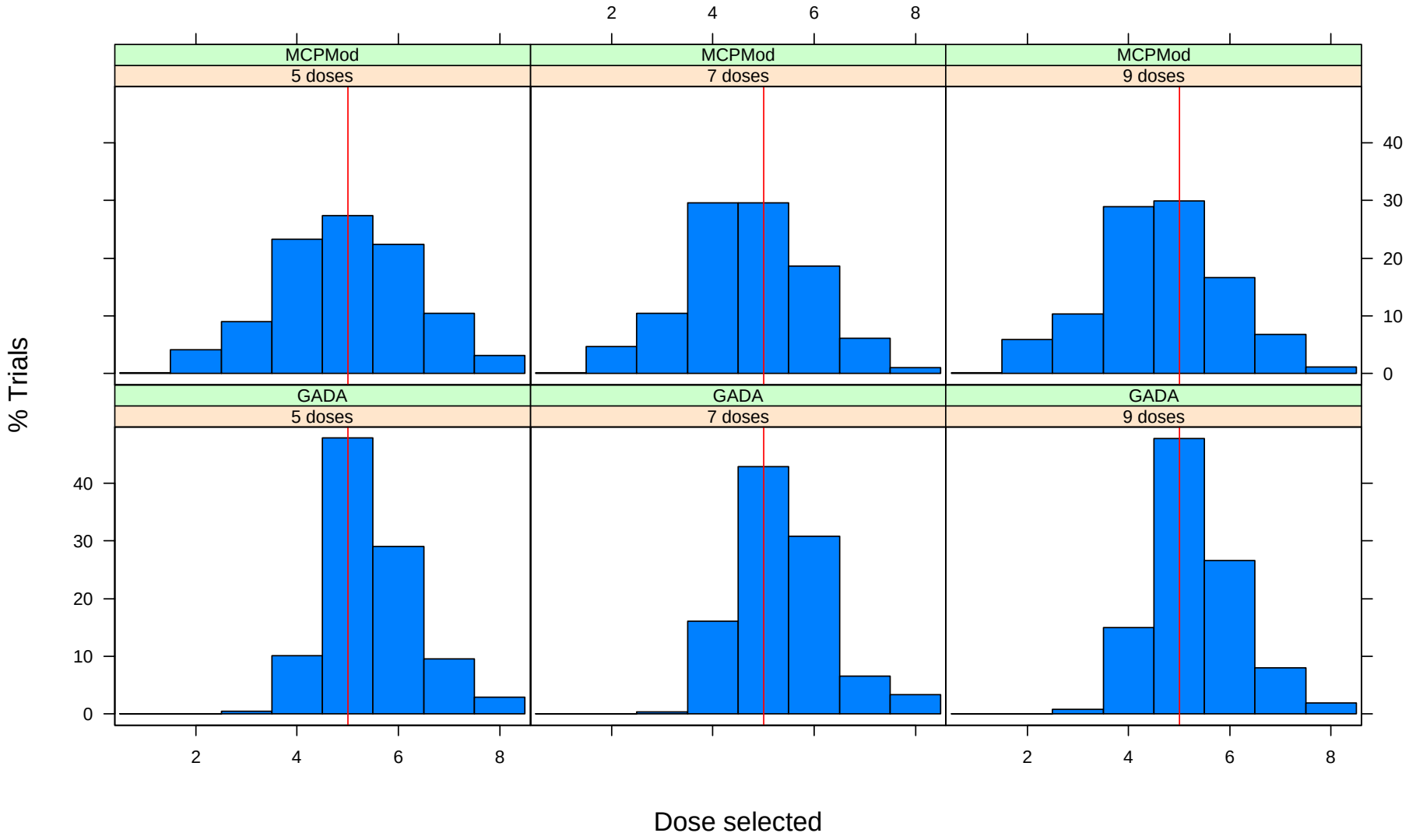
Umbrella, N=250, no ET



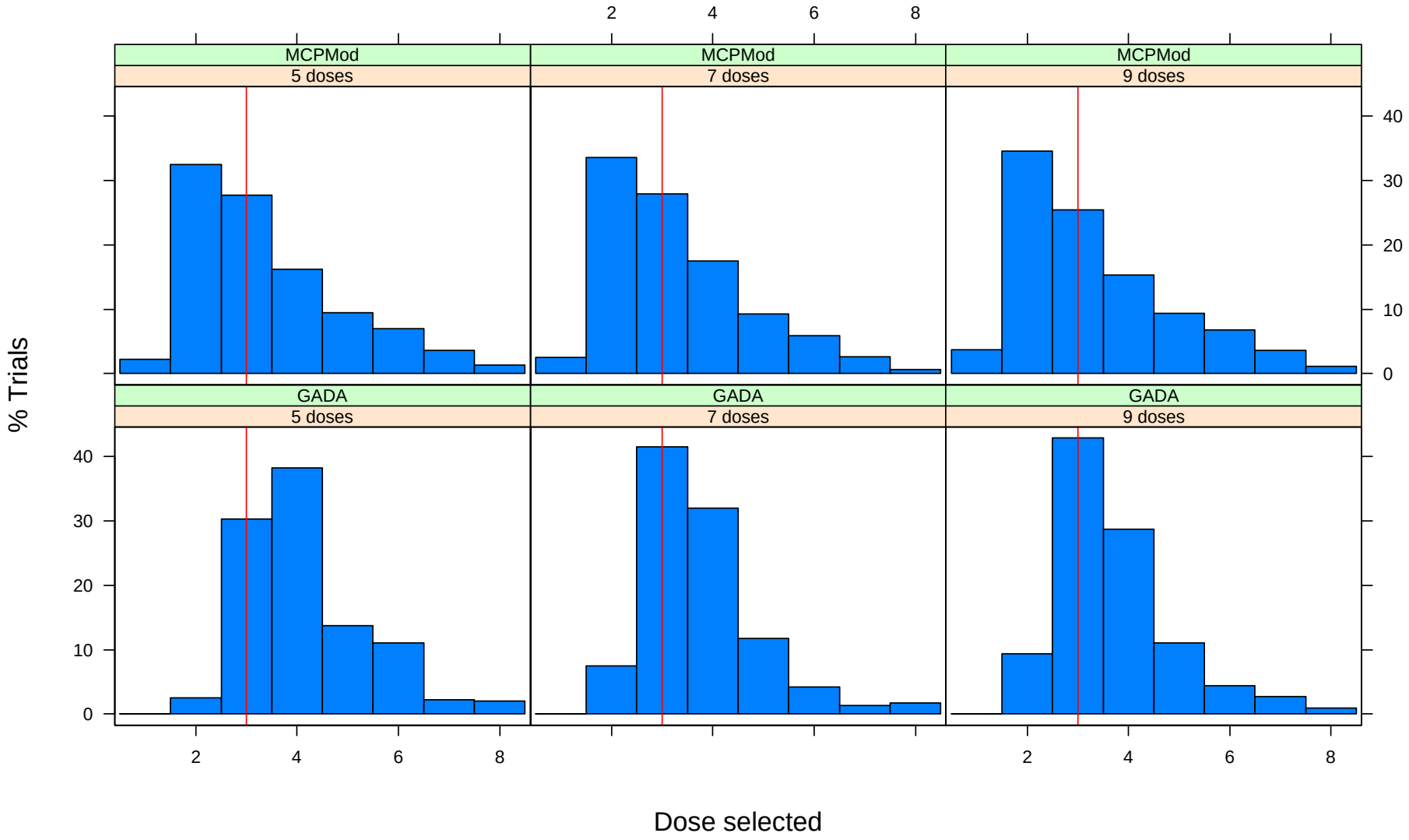
Linear benefit, N=250, no ET



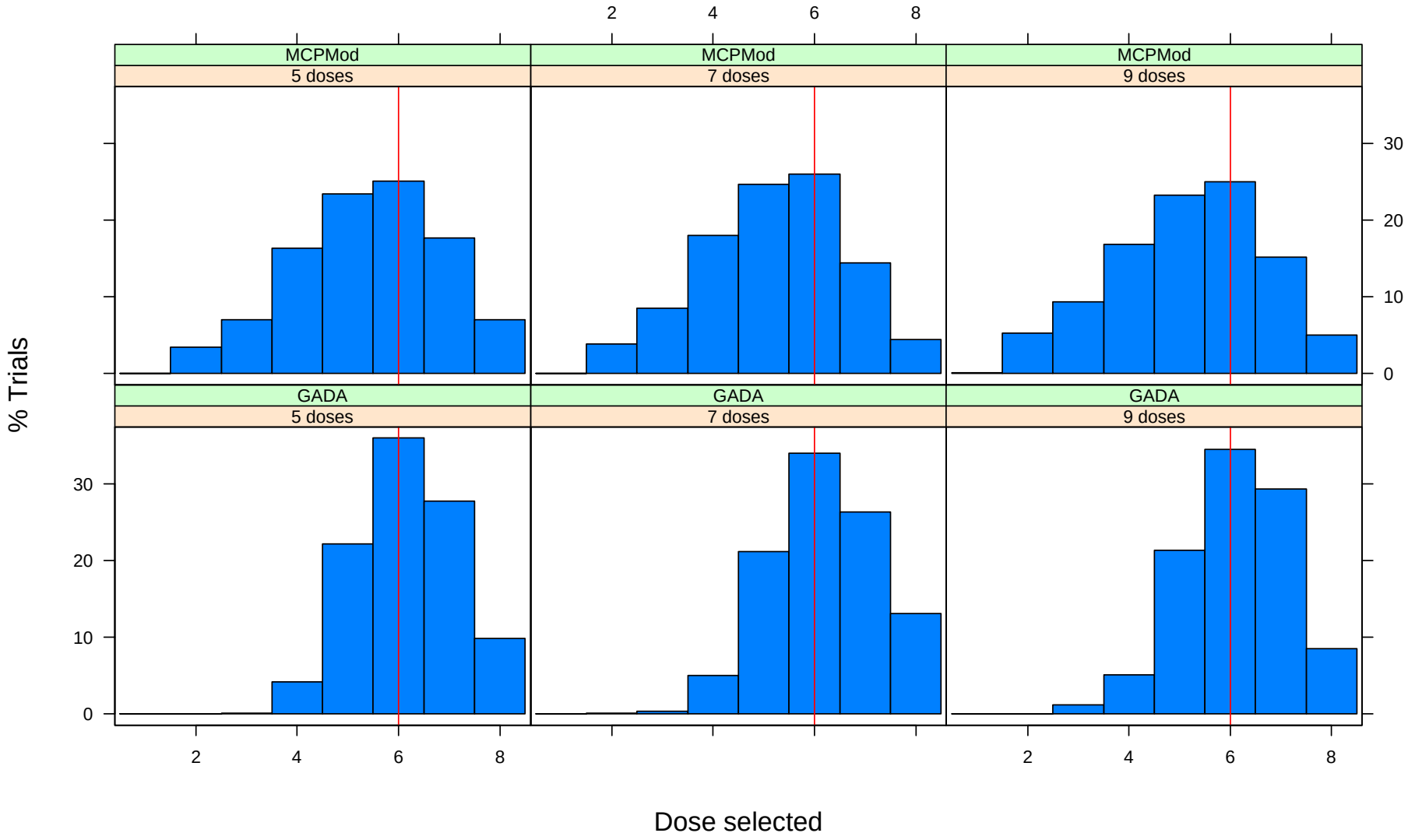
Logistic, N=250, with ET



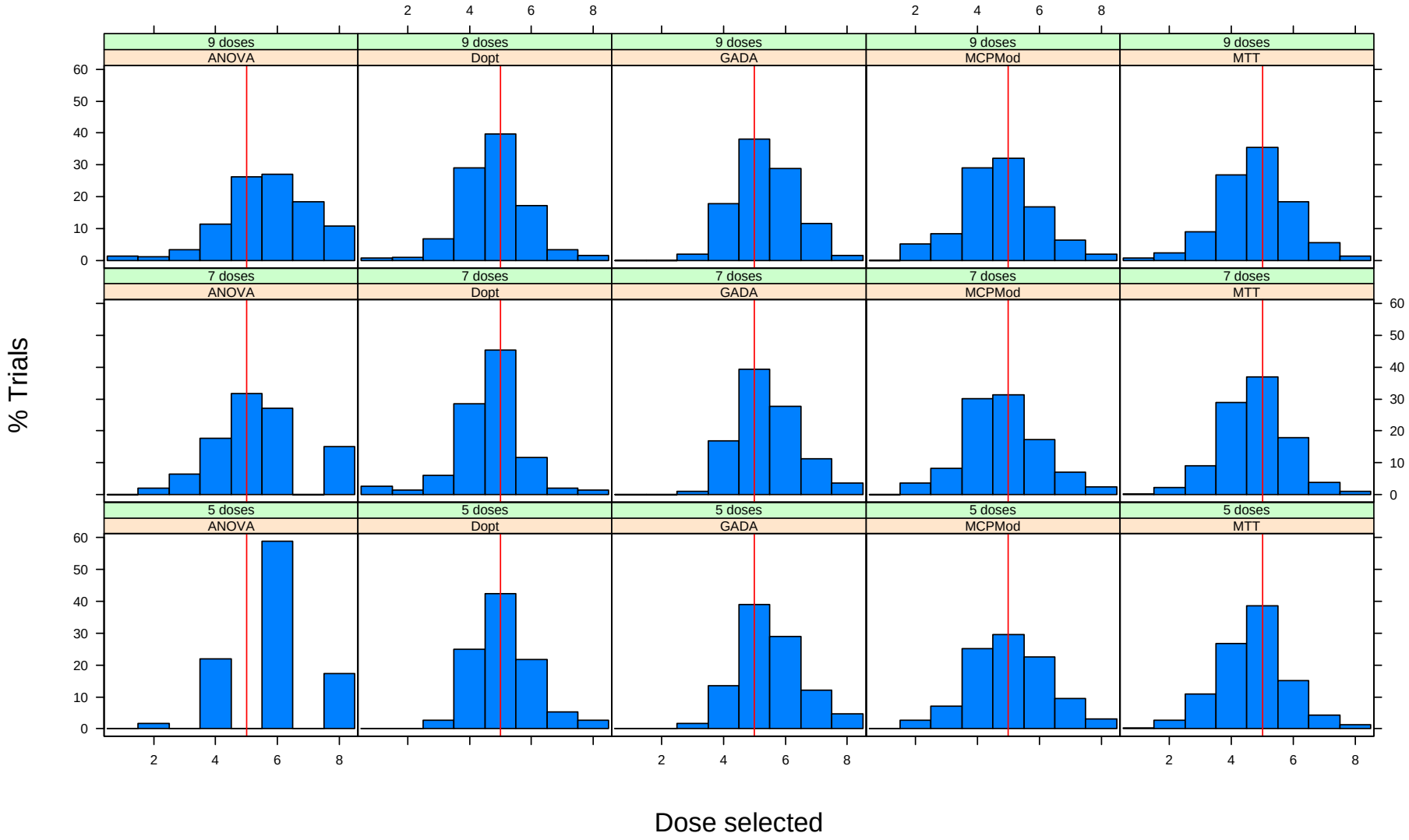
Umbrella, N=250, with ET



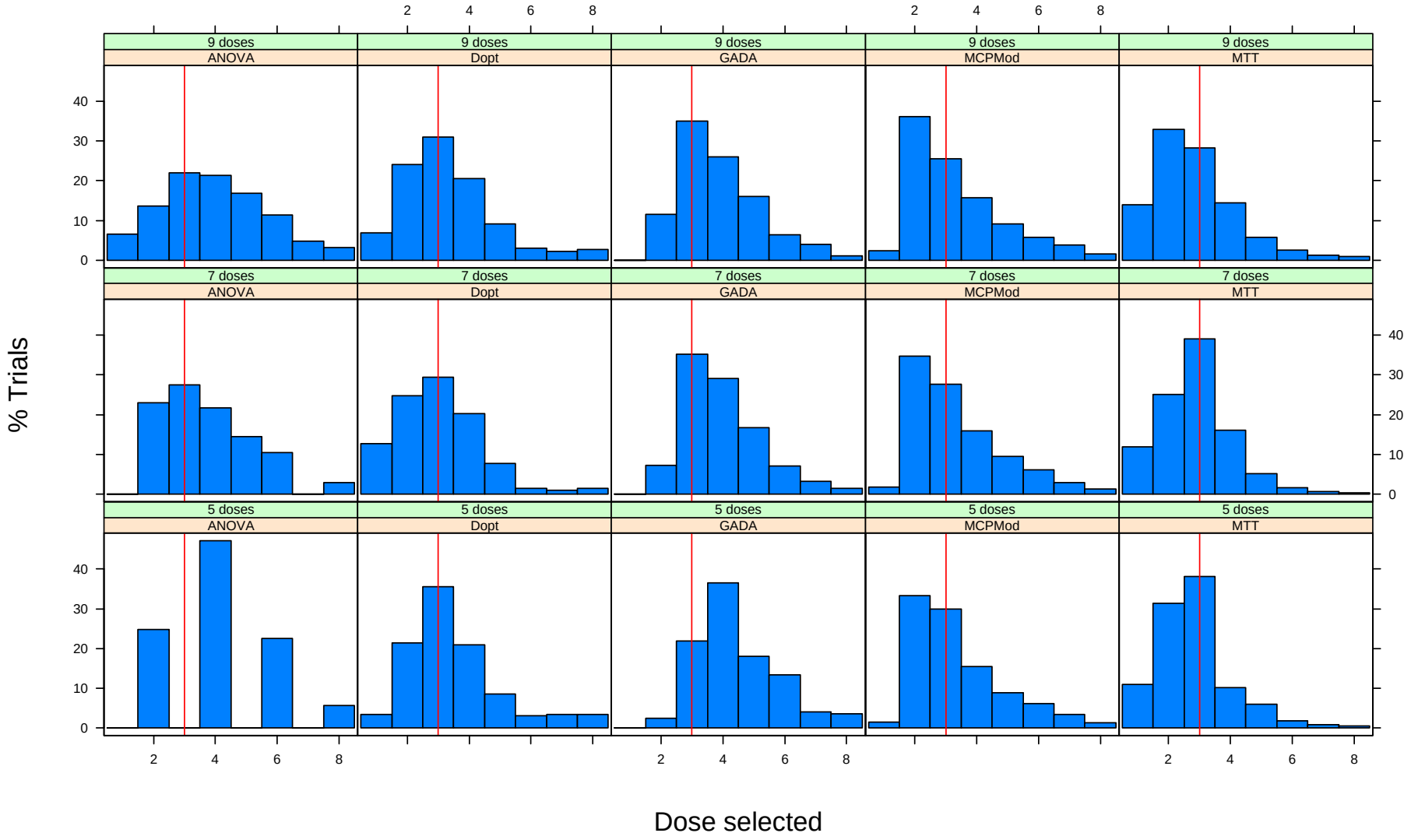
Linear benefit, N=250, with ET



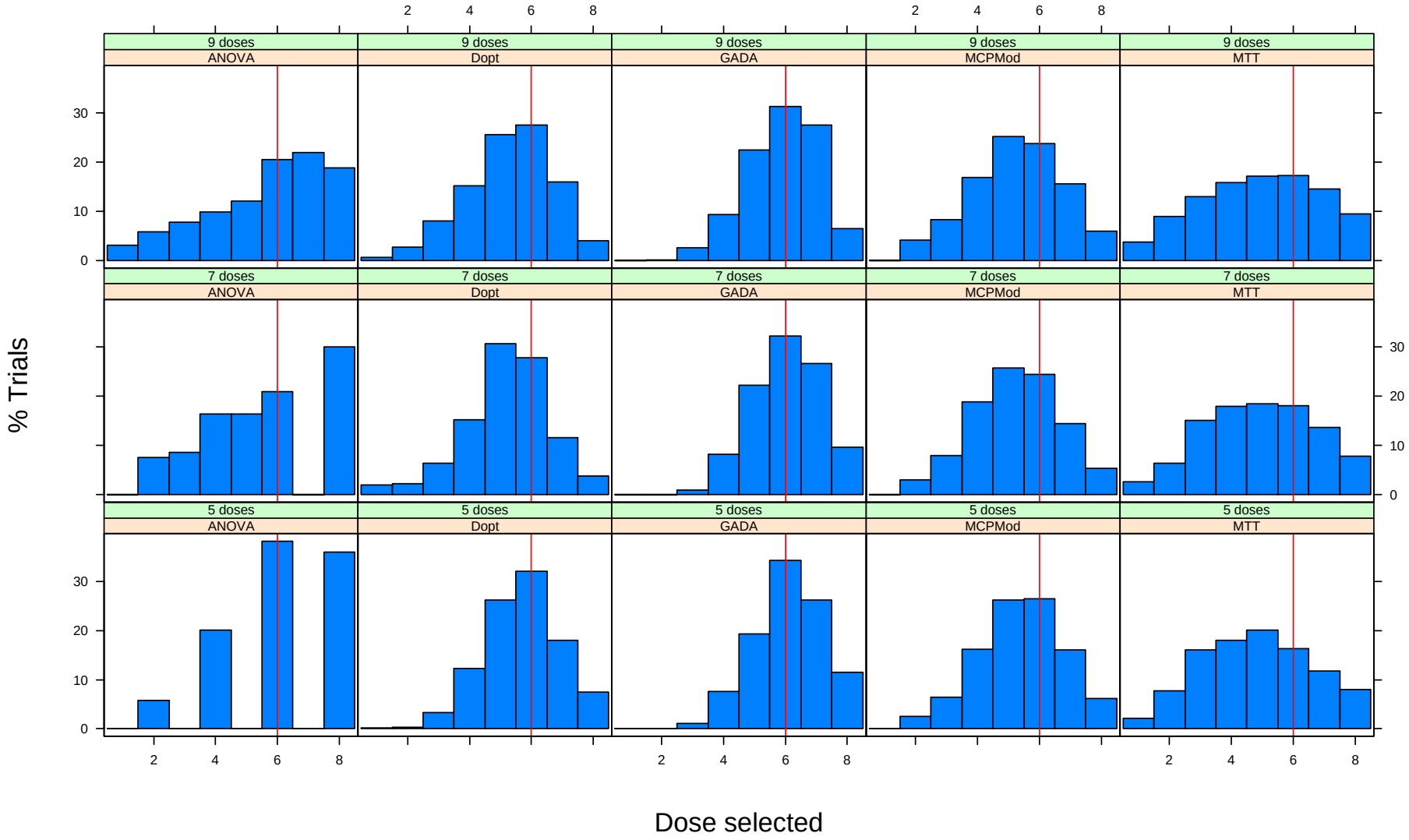
Logistic, N=150, no ET



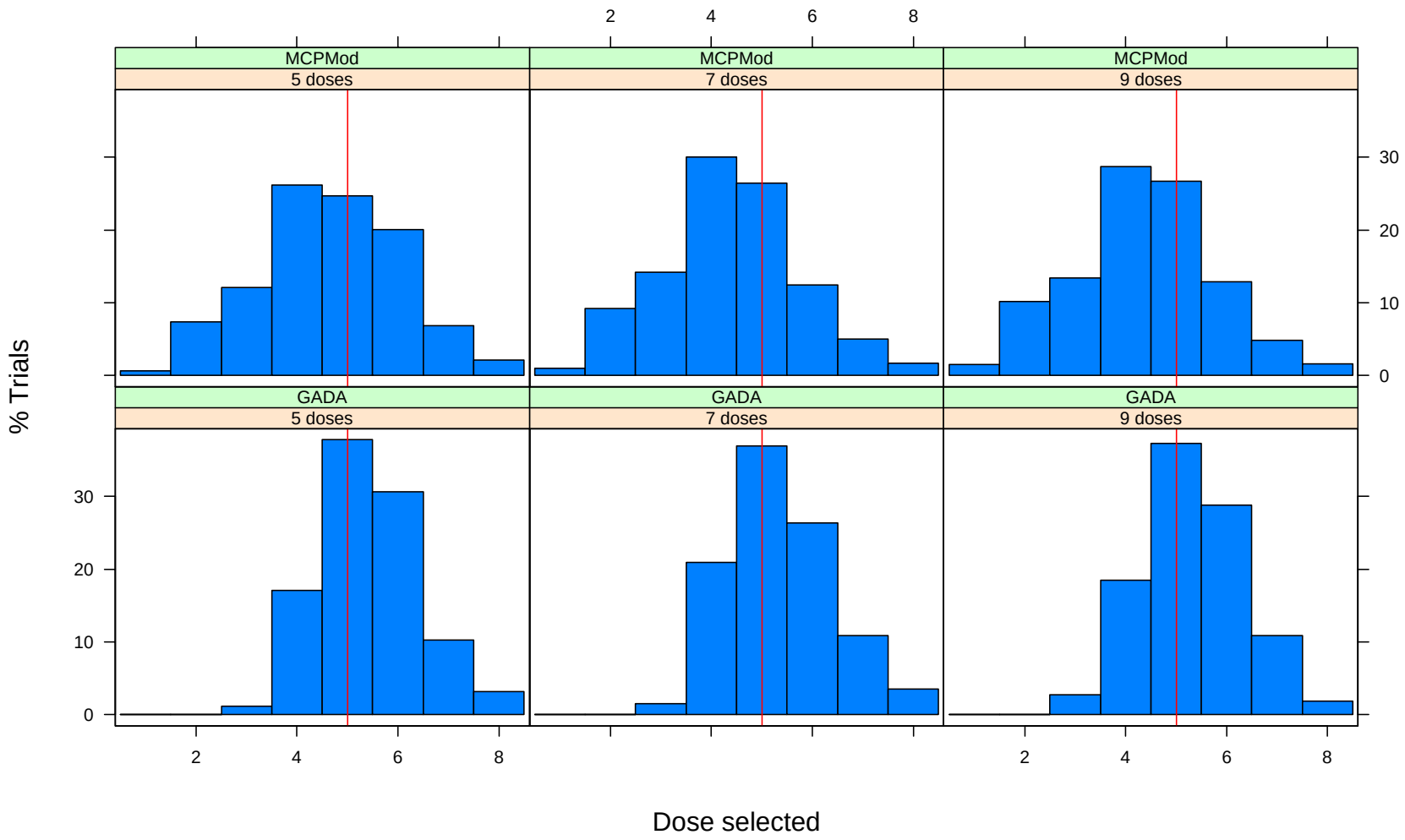
Umbrella, N=150, no ET



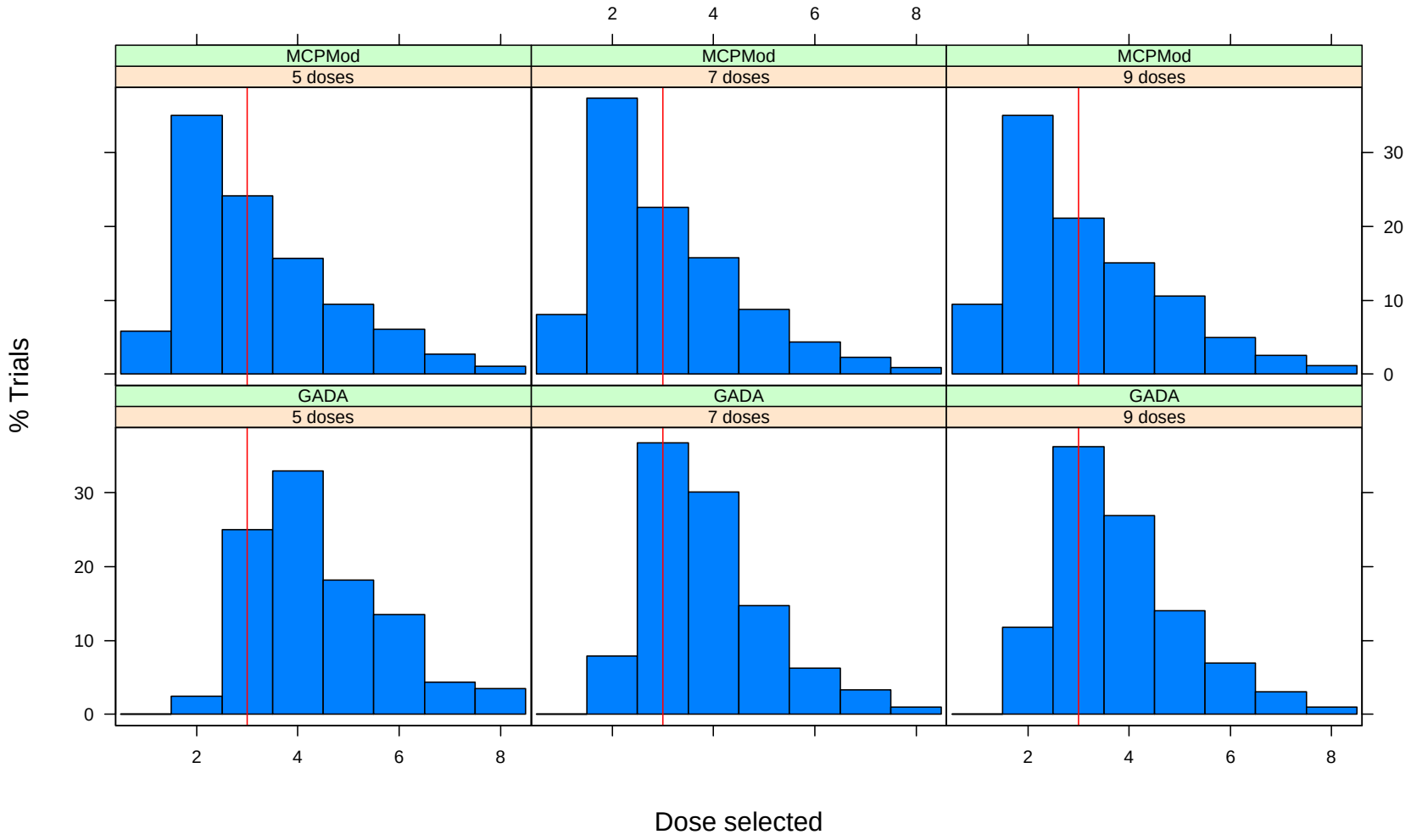
Linear benefit, N=150, no ET



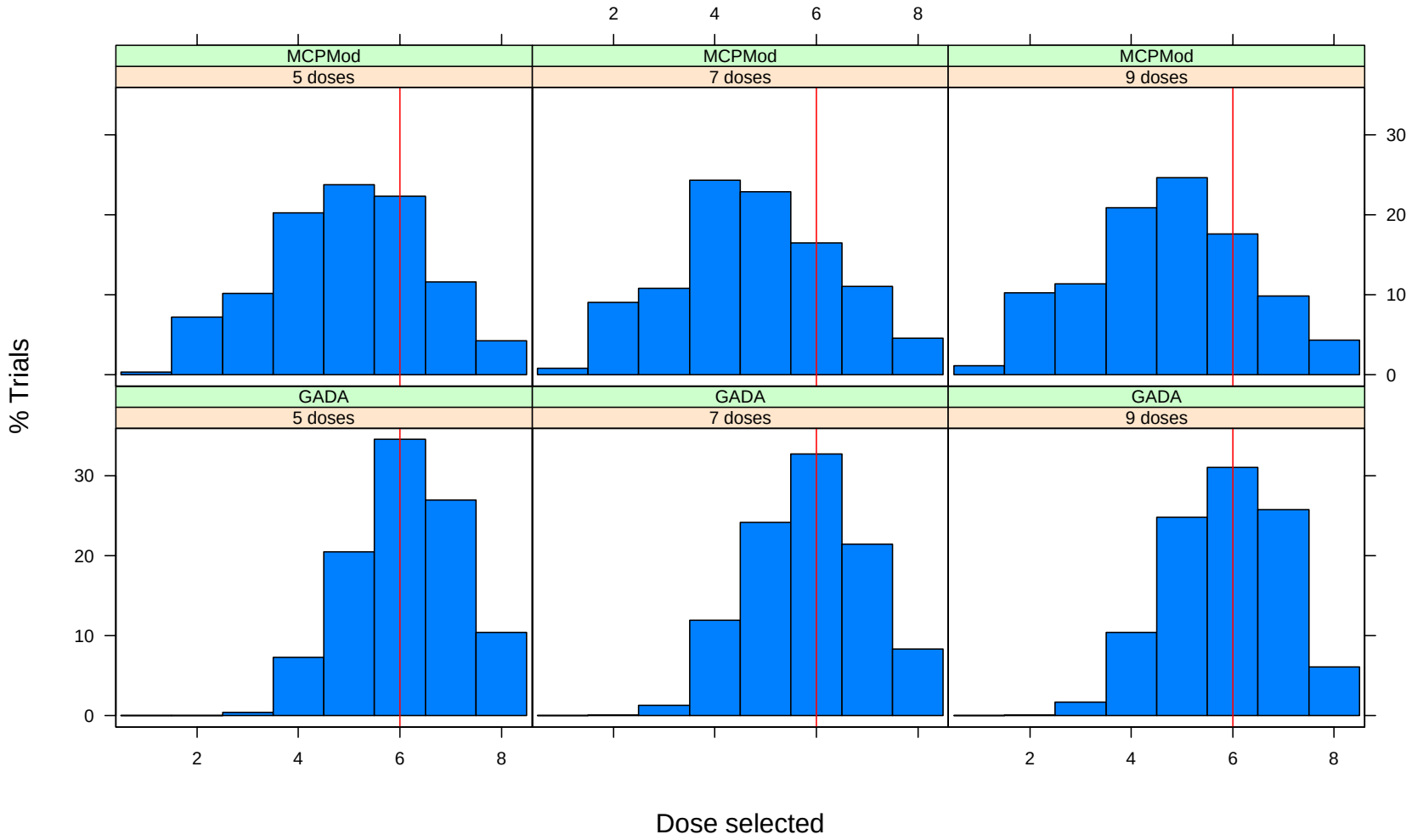
Logistic, N=150, with ET



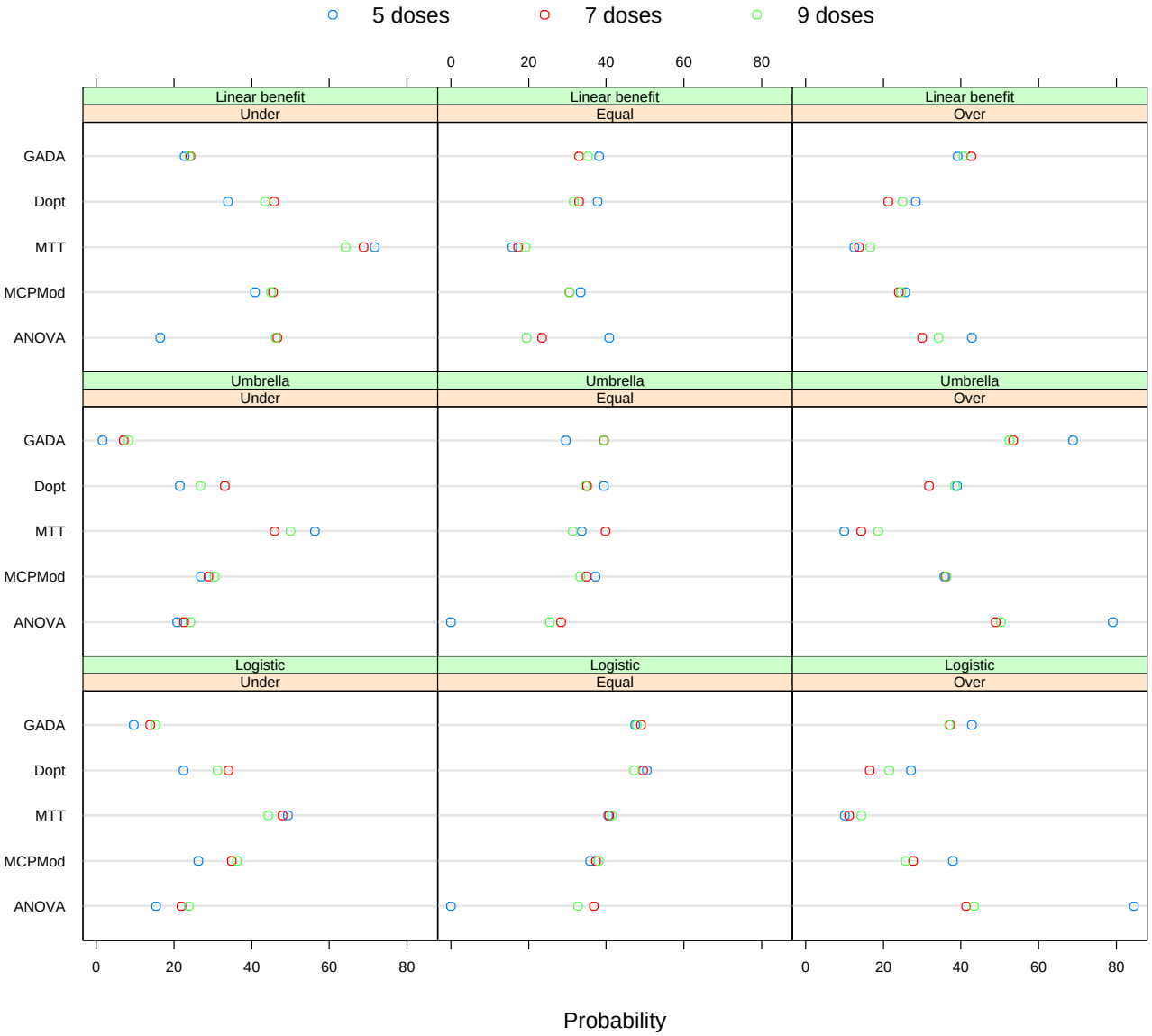
Umbrella, N=150, with ET



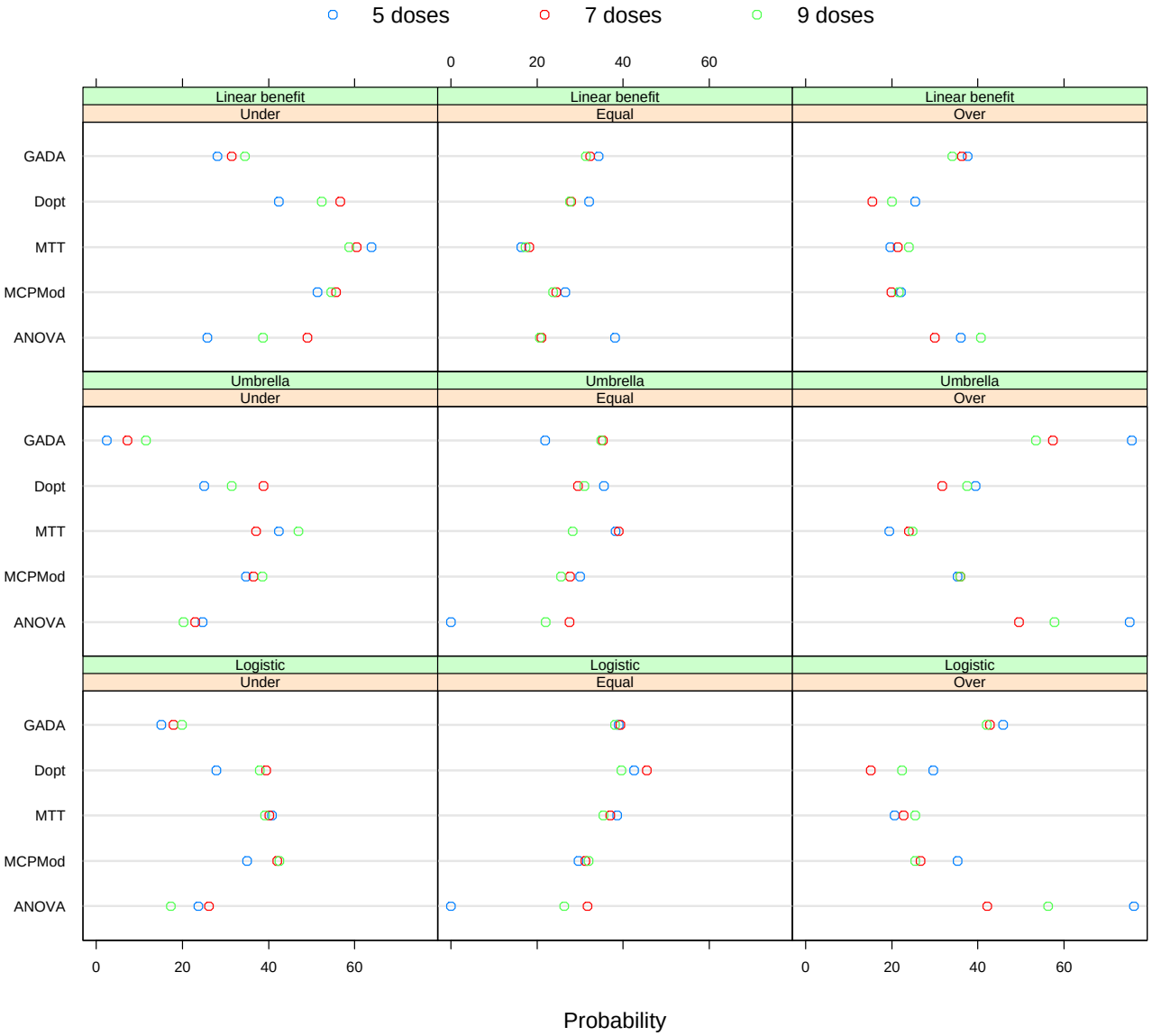
Linear benefit, N=150, with ET



Under/Over estimation probs., N = 250, no ET



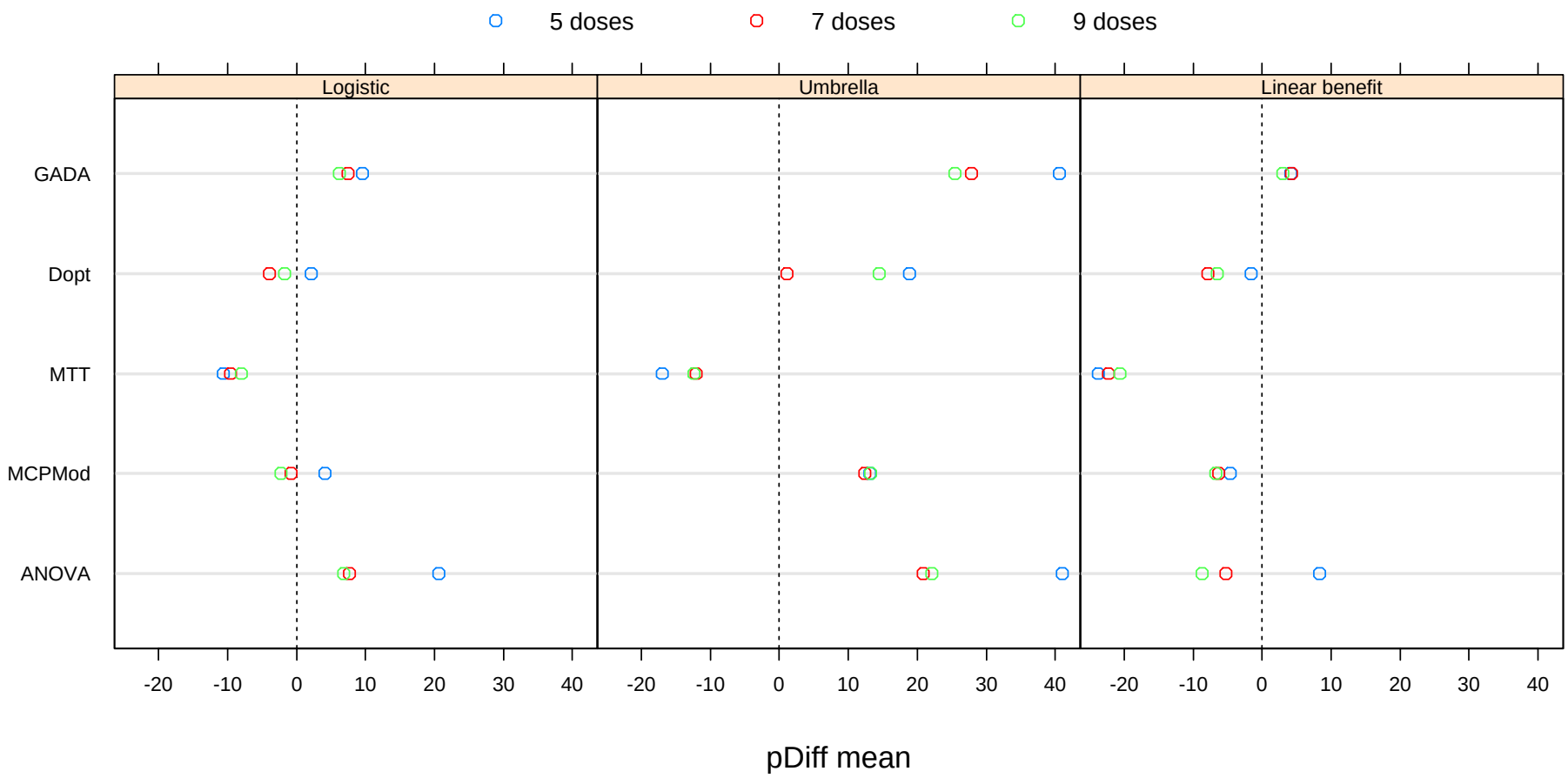
Under/Over estimation probs., N = 150, no ET



pDiff summaries, N=250, no ET

		ANOVA		D-Opt		GADA		MCP-Mod		MTT	
Mod.	Dose	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Log.	5	20.6	23.2	2.1	17.6	9.5	17.8	4.1	22.4	-10.6	18.7
	7	7.7	25.7	-4.0	19.2	7.4	18.6	-0.8	21.8	-9.5	18.0
	9	6.8	26.7	-1.7	19.6	6.2	17.1	-2.2	21.8	-8.0	19.1
Umb.	5	41.0	52.2	18.9	51.7	14.5	51.3	13.1	44.8	-17.0	30.1
	7	20.9	44.2	1.1	44.3	40.6	41.0	12.3	44.4	-12.1	32.0
	9	22.2	52.0	14.5	51.3	27.8	40.4	13.2	46.9	-12.3	38.7
Lin.	5	8.3	25.3	-1.6	18.5	4.1	17.0	-4.6	20.2	-23.8	26.6
	7	-5.3	30.6	-7.8	21.4	4.2	17.5	-6.3	20.9	-22.3	26.7
	9	-8.7	31.2	-6.5	21.3	3.0	17.7	-6.7	21.8	-20.7	28.5

pDiff means, N = 250, no ET



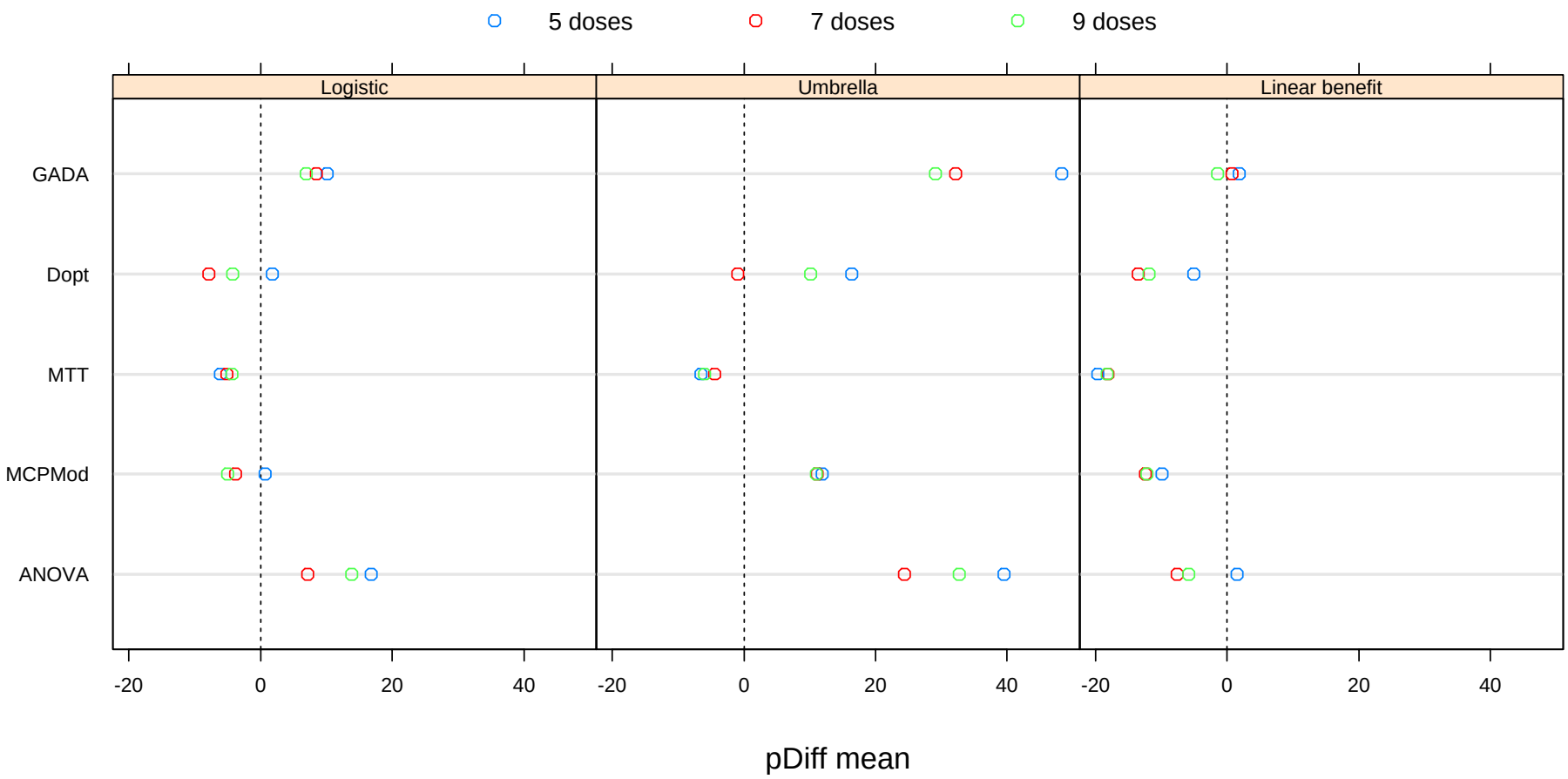
pDiff summaries, N=250, with ET

		GADA		MCP-Mod	
Model	Dose	Mean	SD	Mean	SD
Logistic	5	9.1	18.4	-0.3	27.7
	7	7.4	19.1	-6.2	25.1
	9	6.3	18.4	-6.9	26.1
Umbrella	5	38.4	40.7	13.5	51.0
	7	25.0	38.6	9.6	47.3
	9	23.3	39.3	10.9	51.5
Linear I	5	2.8	17.0	-9.9	24.6
	7	3.3	18.3	-13.1	23.9
	9	1.9	17.9	-13.6	25.3

pDiff summaries, N=150, no ET

		ANOVA		D-Opt		GADA		MCP-Mod		MTT	
Mod.	Dose	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Log.	5	16.8	27.1	1.8	20.5	10.1	21.4	0.7	26.0	-6.1	23.3
	7	7.1	29.1	-7.9	24.1	8.5	20.9	-3.8	25.2	-5.1	22.3
	9	13.9	28.9	-4.3	22.6	7.0	20.3	-5.1	25.7	-4.3	24.2
Umb.	5	39.5	55.5	16.4	51.0	48.3	44.5	11.9	49.6	-6.6	40.7
	7	24.4	48.8	-1.0	47.6	32.1	42.3	11.1	49.4	-4.4	39.7
	9	32.7	57.2	10.1	51.0	29.1	44.1	11.0	51.4	-5.9	45.8
Lin.	5	1.5	29.6	-5.1	20.8	1.8	19.1	-10.0	23.2	-19.7	29.7
	7	-7.6	32.5	-13.5	23.8	0.8	18.9	-12.4	23.7	-18.2	29.8
	9	-5.8	32.5	-11.9	24.0	-1.5	19.6	-12.2	24.8	-18.2	32.0

pDiff means, N = 150, no ET



pDiff summaries, N=250, with ET

		GADA		MCP-Mod	
Model	Dose	Mean	SD	Mean	SD
Logistic	5	8.3	20.5	-7.0	28.7
	7	6.9	21.6	-12.5	27.9
	9	6.4	20.8	-12.9	28.5
Umbrella	5	47.5	45.3	7.5	50.8
	7	29.5	41.2	2.1	49.1
	9	27.1	42.8	4.4	52.0
Linear I	5	1.9	18.3	-17.6	25.8
	7	-2.4	19.6	-20.7	26.8
	9	-2.2	19.2	-21.4	27.1

Dose Response Estimation

Average PE summaries, N=250, no ET

		ANOVA		D-Opt		GADA		MCP-Mod		MTT	
Mod.	Dose	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Log.	5	22.8	7.7	15.8	7.7	12.1	5.8	21.6	8.2	30.3	14.7
	7	21.8	7.4	26.6	12.4	18.1	7.6	21.1	8.2	28.1	13.5
	9	22.3	8.0	24.6	11.8	17.2	7.0	21.8	8.8	30.0	15.1
Umb.	5	15.3	7.2	14.9	7.2	12.1	5.7	14.7	7.5	25.9	11.3
	7	16.1	7.3	16.3	6.2	11.8	5.3	14.8	7.3	26.4	11.5
	9	16.1	7.3	20.8	8.0	13.8	5.8	15.1	7.3	24.3	10.5
Lin.	5	17.2	10.6	26.5	14.7	17.5	8.6	17.8	11.0	34.9	15.9
	7	17.9	10.8	30.4	12.7	17.8	8.6	17.8	10.5	34.2	14.7
	9	17.7	10.8	28.1	12.5	17.6	8.5	18.1	10.8	38.6	17.5

Average PE summaries, N=250, with ET

		GADA		MCP-Mod	
Model	Dose	Mean	SD	Mean	SD
Logistic	5	12.5	6.0	26.8	12.2
	7	18.8	8.2	26.0	11.6
	9	17.6	7.6	26.5	12.2
Umbrella	5	12.7	5.8	19.9	10.3
	7	12.1	5.5	19.2	9.9
	9	13.8	5.9	19.9	10.1
Linear I	5	17.7	8.7	23.7	15.0
	7	18.5	8.9	23.0	14.1
	9	18.4	8.7	23.6	14.5

Average PE summaries, N=150, no ET

		ANOVA		D-Opt		GADA		MCP-Mod		MTT	
Mod.	Dose	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Log.	5	26.0	11.3	20.1	10.1	14.8	7.0	25.3	11.0	38.6	18.5
	7	26.1	10.8	34.0	16.3	21.3	9.2	25.4	10.7	35.7	16.8
	9	25.5	11.7	31.9	14.9	20.9	8.8	25.5	11.3	39.2	18.7
Umb.	5	19.9	9.0	19.1	9.9	14.9	6.9	18.9	9.5	31.9	13.9
	7	20.1	8.8	21.4	8.8	13.5	6.3	19.3	9.4	32.4	13.7
	9	20.6	8.8	27.2	10.5	16.0	6.9	19.3	9.2	30.6	12.9
Lin.	5	21.6	14.0	33.8	19.0	20.1	10.3	22.6	13.7	43.9	19.3
	7	23.2	13.8	38.9	16.8	20.4	10.2	23.1	13.6	42.5	17.4
	9	22.1	13.2	35.9	15.7	20.7	10.1	22.7	13.4	48.5	20.5

Average PE summaries, N=150, with ET

		GADA		MCP-Mod	
Model	Dose	Mean	SD	Mean	SD
Logistic	5	14.7	6.8	30.3	15.9
	7	21.7	9.7	30.1	15.2
	9	20.9	9.4	30.7	16.0
Umbrella	5	14.6	6.8	23.9	12.9
	7	13.6	6.3	24.3	12.8
	9	15.9	7.2	24.2	12.5
Linear I	5	19.4	9.6	28.7	17.9
	7	20.6	10.9	28.9	17.5
	9	20.0	9.5	28.9	17.7