Proof **o**f **C**oncept and Dose Estimation in Phase II Clinical Trials

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Outline

- Introduction
  - Goals
  - Traditional Methods
    - Trend / Contrast Tests
    - Modeling
  - Advantages/ Disadvantages

- Unified Framework
  - Methodology
    - Candidate set
    - Permutation distribution of penalized LR-test
  - Dose Estimation
    - C.I. for target dose

- Example
  - Establish PoC for GI data (parallel, 5 dose clinical trial)
  - Estimate target dose

Introduction

- Existence, nature and extent of dose effect
- Four questions (Ruberg, 1995):
  1. Is there any evidence of a dose effect (PoC)?
  2. Which ... erent from control?
  3. What is the nature of the dose-response rela...
  4. Wha... er study/marketing?

Answer: Trend or single/multiple contrast tests

Answer: Statistical modeling, GLMs; dose estimation via inverse regression

Introduction

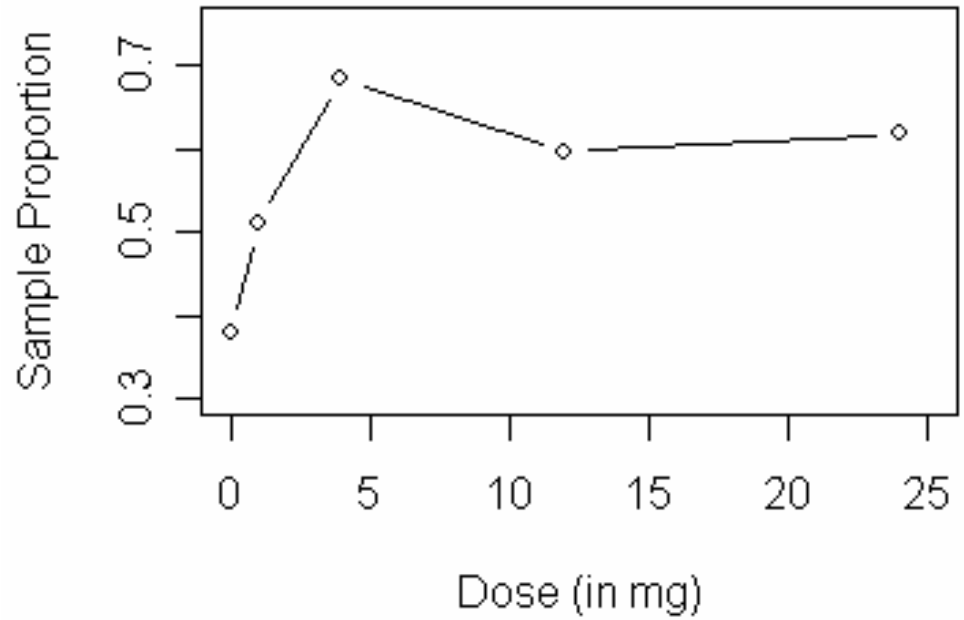
GI Example:

$d = (0, 1, 4, 12, 24)$ (in mg)

$n =$ btw. 90 and 105 per arm

$y =$ btw. 35 and 70

$p = (38, 51, 68, 60, 61)$ (in%)



Introduction

- Trend / Contrast Tests for binary responses:
  - General form of test statistic(s):

$$T^{(l)} = \sum_i c_i^{(l)} p_i \Big/ \sqrt{p_0(1-p_0)\sum_i (c_i^{(l)})^2 \Big/ n_i}$$

  - Cochran-Armitage: $c_i = n_i(d_i - \bar{d})$
  - Dunnett: $c^{(1)} = (-1, 1, 0, 0, 0); c^{(2)} = (-1, 0, 1, 0, 0)$
    $c^{(3)} = (-1, 0, 0, 1, 0); c^{(4)} = (-1, 0, 0, 0, 1)$
  - Williams, Hirotsu, Marcus, Helmert,…
  - **PoC**: $\max T^{(l)}$ > critical value

Introduction

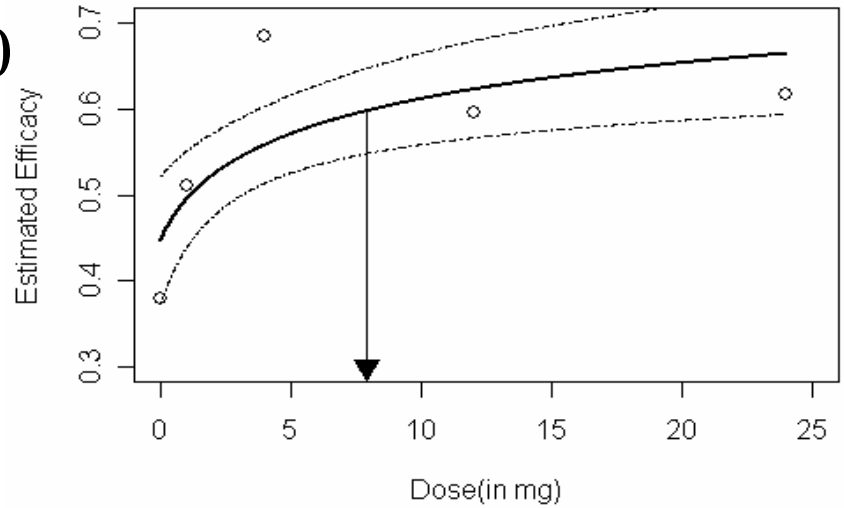
- Modeling approach for binary responses:
  - General form of model:

$$Y_i \sim Bin(n_i, \pi_i);\ g(\pi_i) = s(\text{dose, covariates})$$

  - E.g., logistic regression:

$$g(\pi_i) = \text{logit}(\pi_i)$$
$$s(\text{dose, covariates}) = \beta_0 + \beta_1 \log(\text{dose} + 1) + \ldots$$

  - PoC: $H_0 : \beta_1 = 0, H_A : \beta_1 > 0$
  - Get target dose estimate from fitted model



Unified Framework

- Goal: Combine advantages

Robustness +

Strong Error control +

Dose estimate with margin of error

Step 1: Specify candidate models

Step 2: Test PoC and select "best" ones, controlling FWER

Step 3: Get target dose estimate by model averaging over best models

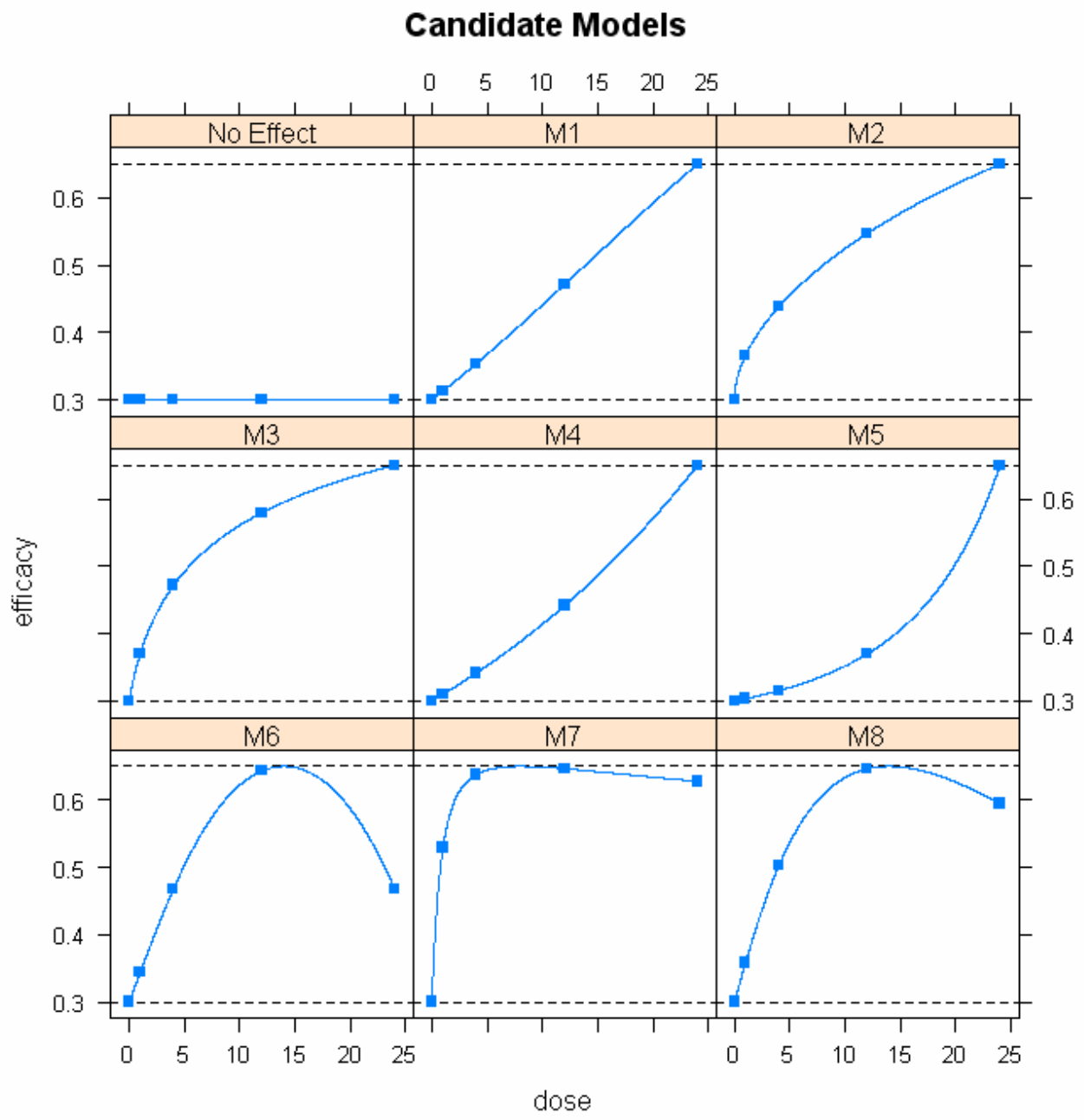
Unified Framework

❑ Step 1: *Specify candidate models*

- In consultation with clinical team
- Models can vary with respect to link function or nature of dose effect

Candidate dose-response models for the efficacy of a diarrhea compound

$\mathcal{M}$	Link	Predictor	# parms
M_1:	logit	$\beta_0 + \beta_1 d$	2
M_2:	logit	$\beta_0 + \beta_1 \sqrt{d}$	2
M_3:	logit	$\beta_0 + \beta_1 \log(d+1)$	2
M_4:	log	$\beta_0 + \beta_1 d$	2
M_5:	identity	$\beta_0 + \beta_1 \exp(\exp(d/\max(d)))$	2
M_6:	logit	$\beta_0 + \beta_1 d + \beta_2 d^2$	3
M_7:	logit	$\beta_0 + \beta_1 \log(d+1) + \beta_2/(d+1)$	3
M_8:	logit	$\beta_0 + \beta_1 d \exp(-d/\beta_2), \beta_2 > 0$	3


Candidate Models
No Effect
M1
M2
M3
M4
M5
M6
M7
M8
efficacy
dose
0
5
10
15
20
25
0.3
0.4
0.5
0.6

Unified Framework

❑ Step 2: *Test for PoC*

- For each model M_s, test for a (positive) dose effect via a signed penalized likelihood ratio test (difference in deviance):

$$G_s^2 = \pm\{-2[l_{\max}(M_0, y) - l_{\max}(M_s, y)]\} - \text{penalty}$$

- Common penalty term: 2(diff. in # of parms)

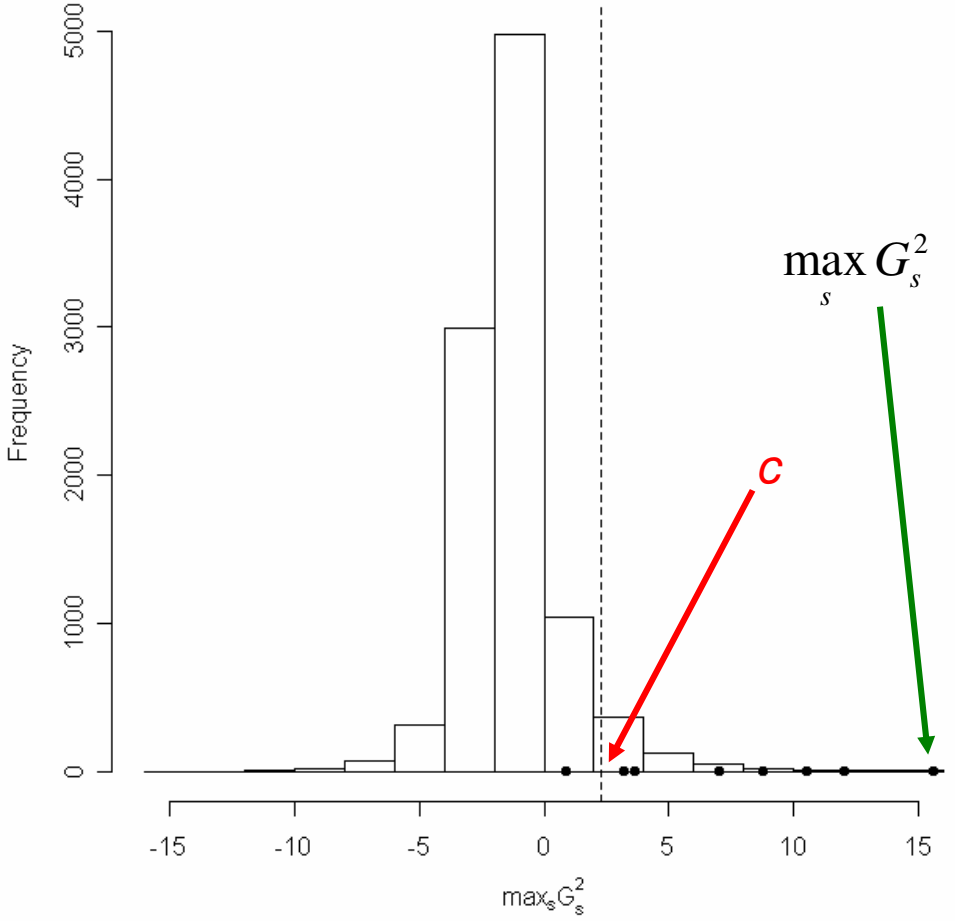
$$G_s^2 = \pm(AIC_0 - AIC_s)$$

- Interested in models that "best" pick up observed dose-response signal, i.e., that deviate the most from no-effect model M_0
- Establish PoC if $\max_s G_s^2 > c$ (some critical value)

Unified Framework

❑ Step 2: *Determining c that controls FWER*

- Under H_0: no dose effect, doses are interchangeable
- To determine *c*, look at permutation distribution of $\max_s G_s^2$
- This controls familywise error rate of declaring spurious signals as real



Unified Framework

- **Step 2:** ***Test for PoC, IBS Example***

$\mathcal{M}$	G^2	raw p-value	adj. p-value
M_1:	3.68	0.0089	0.0248
M_2:	8.76	0.0007	0.0028
M_3:	10.53	0.0003	0.0014
M_4:	3.25	0.0112	0.0310
M_5:	0.90	0.0458	0.1020
M_6:	7.01	0.0028	0.0057
M_7:	15.63	0.0001	0.0001
M_8:	12.07	0.0003	0.0008

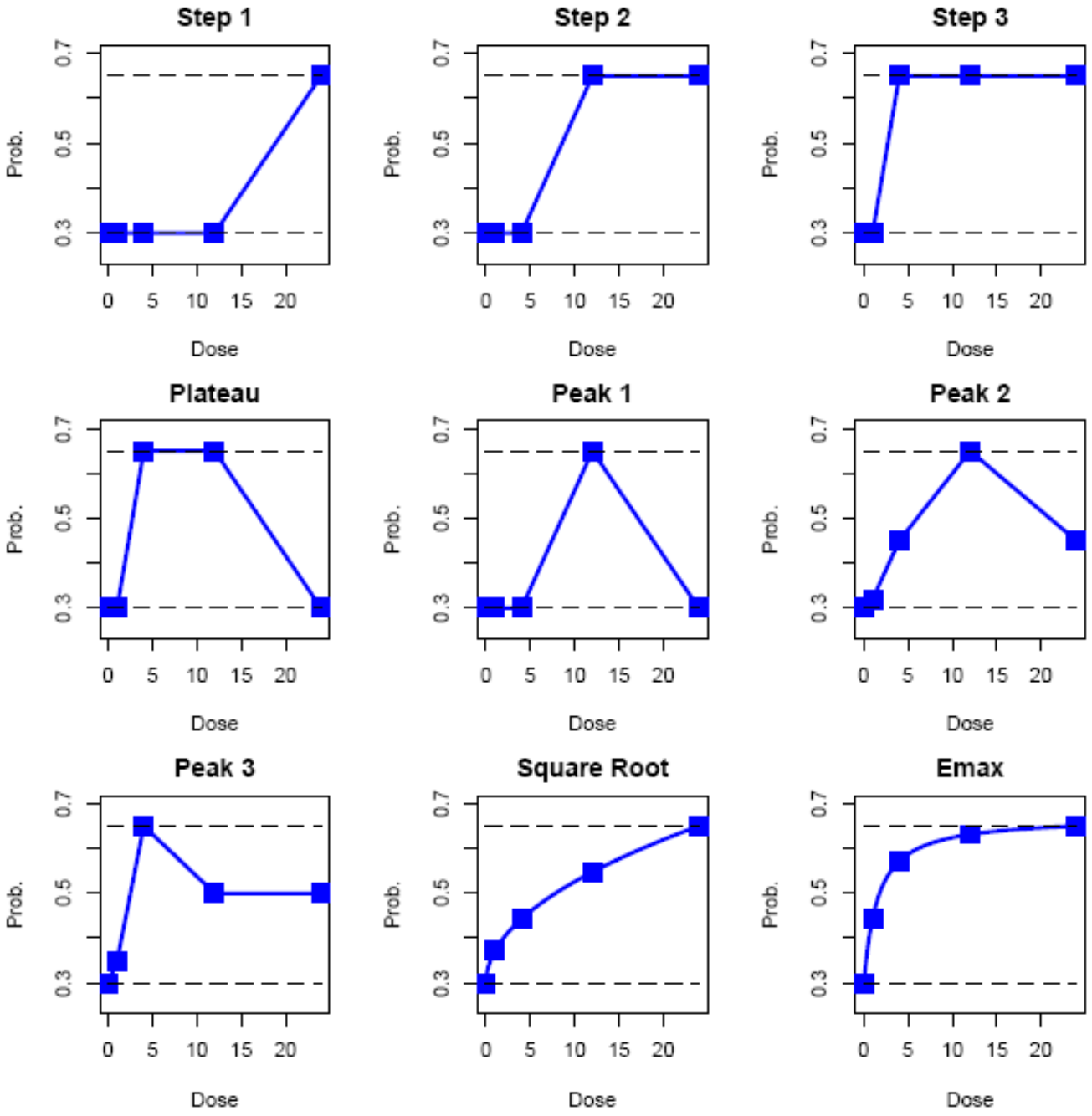
Critical value $c = 2.29$

Unified Framework

Power Comparison:

Percent of establishing Proof of Concept

n	Method	Dose-response profile									Avg. Power
		M_0	M_1	M_2	M_3	M_4	M_5	M_6	M_7	M_8	
25	AIC (no adj.)	8.7	90	90	91	91	91	75	86	86	
	max G^2	4.9	88	88	89	87	87	73	84	85	85
	CA	4.9	92	91	88	91	90	44	52	76	78
	Dunnett	4.9	68	68	75	69	66	68	86	76	72
	Williams	4.2	78	78	83	78	77	64	90	83	79
	Hirotsu	4.7	86	86	87	87	86	67	84	85	84
	Helmert	4.8	87	87	87	87	88	56	85	83	83
	Marcus	5.1	87	86	87	87	88	67	85	86	84


Step 1
Step 2
Step 3
Plateau
Peak 1
Peak 2
Peak 3
Square Root
Emax
Prob.
Dose
0.3
0.5
0.7
0
5
10
15
20

Unified Framework

- **Step 2: Power Comparison under model misspecification**

		Dose-response profile							
n	Method	Step 1	Step 2	Step 3	Plateau	Peak 1	Peak 2	Sqrt	Emax
25	$\max G^2$	88	97	93	81	36	70	82	81
	CA	88	98	86	3	1	39	83	72
	Dunnett	60	76	82	76	61	63	66	77
	Williams	71	85	89	51	18	55	78	85
	Hirotsu	88	97	96	65	16	63	80	82
	Helmert	91	93	91	36	10	51	82	82
	Marcus	87	98	96	64	16	62	82	84

Unified Framework

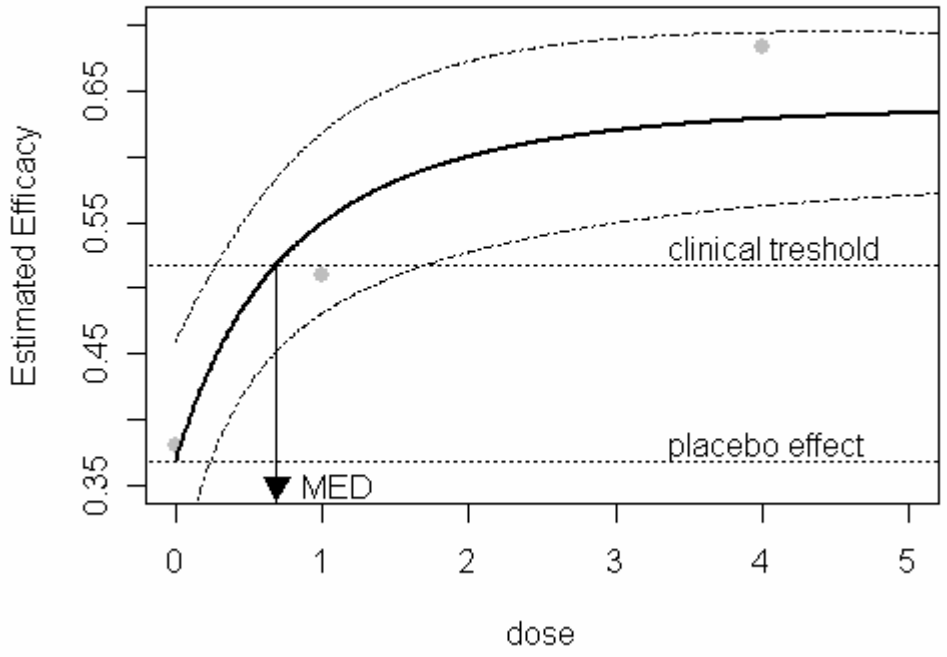
❑ Step 3: Target Dose Estimation

- Settle on model(s) that pass the PoC filter
- Estimate target dose via inverse regression
- Here: Estimation of Minimum Effective Dose (MED)

$$\widehat{\text{MED}} = \text{argmin}_{d \in (d_1, d_k]} \{\hat{\pi}(d) > \hat{\pi}(d_1) + \Delta, \hat{\pi}_L(d) > \hat{\pi}(d_1)\}$$

- MED: Smallest dose that is clinically relevant and statistically significant
- GI-data:

  MED=0.7mg [0.4; 3.9]



Unified Framework

- **Step 3: Target Dose Estimation under model uncertainty**
  - Combine MED's from significant models (weighted average) with existing MED's.

$$\widetilde{\mathrm{MED}} = \sum_{s:G_s^2 \geq c,\ \widehat{\mathrm{MED}}_s \leq d_k} w_s \widehat{\mathrm{MED}}_s \Big/ \sum_{s:G_s^2 \geq c,\ \widehat{\mathrm{MED}}_s \leq d_k} w_s$$

  - (Penalized) likelihood ratio btw. models M_s and $M_{s'}$:

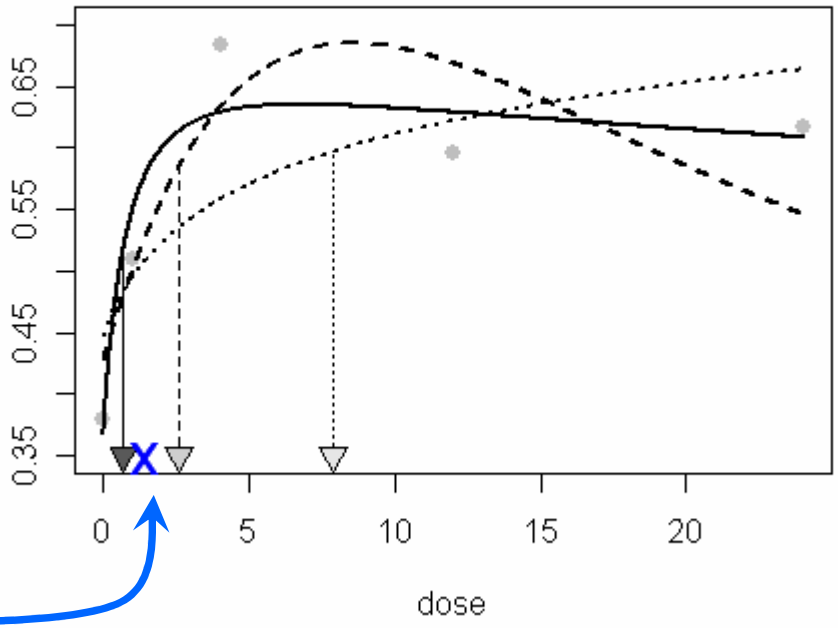
$$\exp\{1/2(G_s^2 - G_{s'}^2)\}$$

  - Weights: $w_s = \exp\{1/2\, G_s^2\}$

Unified Framework

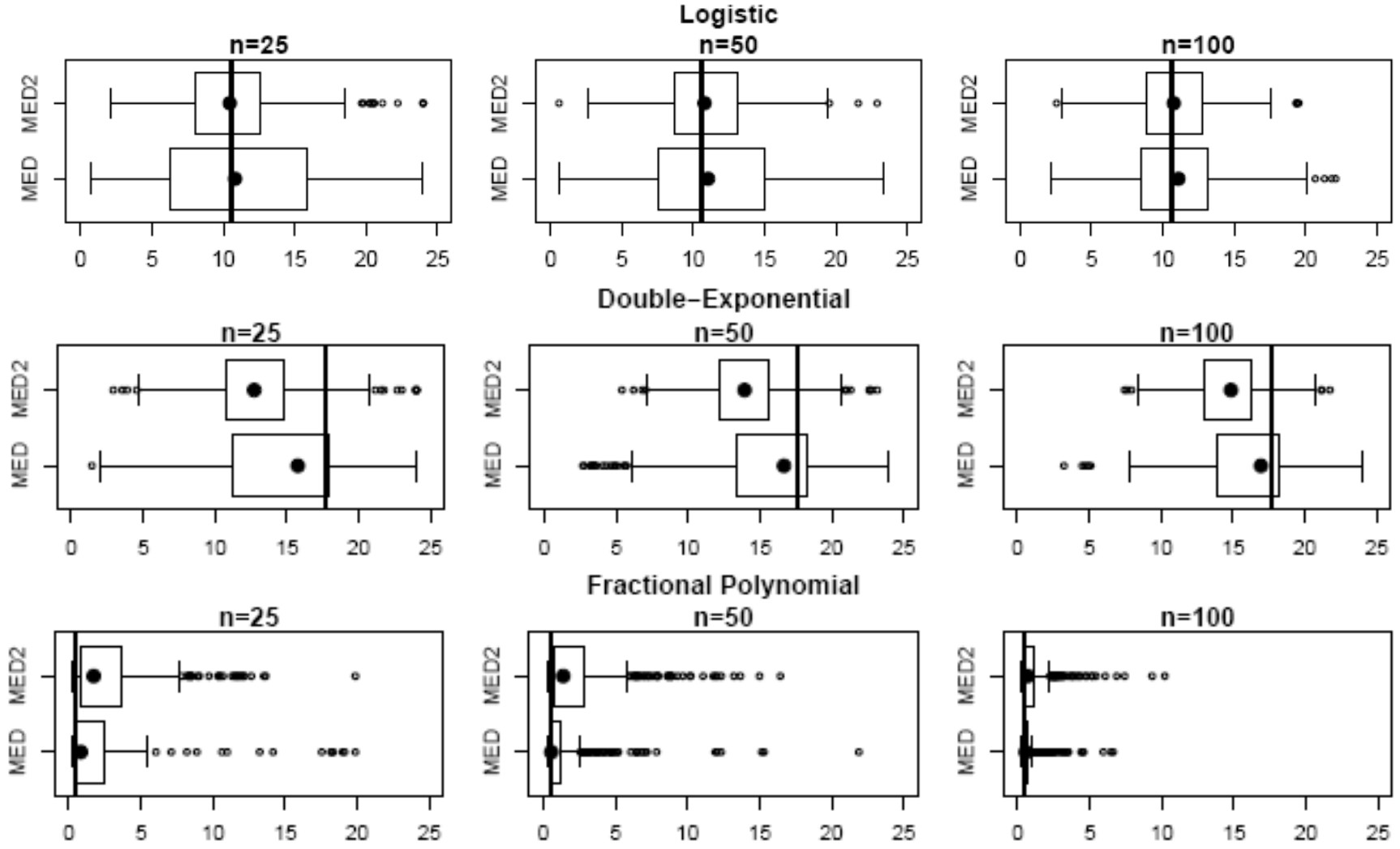
- **Step 3: Target Dose Estimation under model uncertainty**

$\mathcal{M}$	Model	G^2	$\widehat{\text{MED}}$ (mg)	$w_s / \sum w_s$ (%)
M_1:	Logistic	3.68	N.A.	0
M_2:	Log-Log	3.85	N.A.	0
M_3:	Logistic in log-dose	10.53	7.9	6
M_4:	Log-linear	3.25	N.A.	0
M_5:	Double-exponential	0.90	N.A.	0
M_6:	Quadratic	6.71	7.3	1
M_7:	Fractional Poly	15.63	0.7	81
M_8:	Compartment	11.79	2.5	12
	Critical value $c = 2.40$		$\widetilde{\text{MED}} = 1.4$ [0.4; 12.0]	



Unified Framework

❑ Step 3: Target Dose Estimation: Performance



Summary

- Unified Framework for PoC and dose estimation
  - Combines elements from multiple contrast tests and modeling

Framework

- Step 1: Specify candidate model set
- Step 2: Obtain permutation distribution of maximum signed penalized deviance statistic $\max_s G_s^2$ and critical value
- Step 3: Obtain target dose estimate from significant model(s) via model averaging

Conclusion

- PoC Analysis
  - Incorporates model uncertainty in PoC decision
  - Controls Type I error in strong sense
  - As powerful or more powerful in establishing PoC as competing contrast tests, uniformly under a variety of shapes
- Target Dose Estimation
  - Incorporates model uncertainty
  - Provides confidence bounds for target dose estimate
  - Covariates, unbalanced sample size, unequally spaced doses

Extensions

- Framework applicable to PoC and dose estimation in more complicated categorical data sets such as:
  - Bivariate binary responses
    - Two primary endpoints
    - Efficacy and safety endpoint considered jointly
  - Repeated categorical data
    - Contrast tests not well developed
    - With GEE implementation: Consider generalized score statistic (Boos, 1992) instead of LR-statistic