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The control of the type I error during trials designed to establish drug efficacy is critical to avoid unnecessary and unethical studies. To analyse such studies, the standard (STD) non-linear mixed-effect models (NLMEM) have good power properties^{1,2}, but unsatisfactory type I error control because of model misspecifications and bias in drug effect estimates. We used real placebo data to explore a new NLMEM approach using mixture models, called individual model averaging (IMA)³, comparing its type I error rate sensitivity to model misspecification and its bias in drug effect estimates to the STD NLMEM approach.

Real placebo data

- **Likert pain score** (categorical data) from 230 patients with neuropathic pain receiving placebo^{4,5}
- **ADAS-Cog** (continuous data): severity test from the natural history of 800 patients with Alzheimer's disease⁶

Patients were randomized (1:1) to artificial placebo or drug treatment (TRT). The **type I error rate** is the frequency with which the full model (TRT as covariate, H_1) is significant ($\alpha=0.05$) relative to the base model (no TRT information, H_0) according to the likelihood ratio test (LRT).

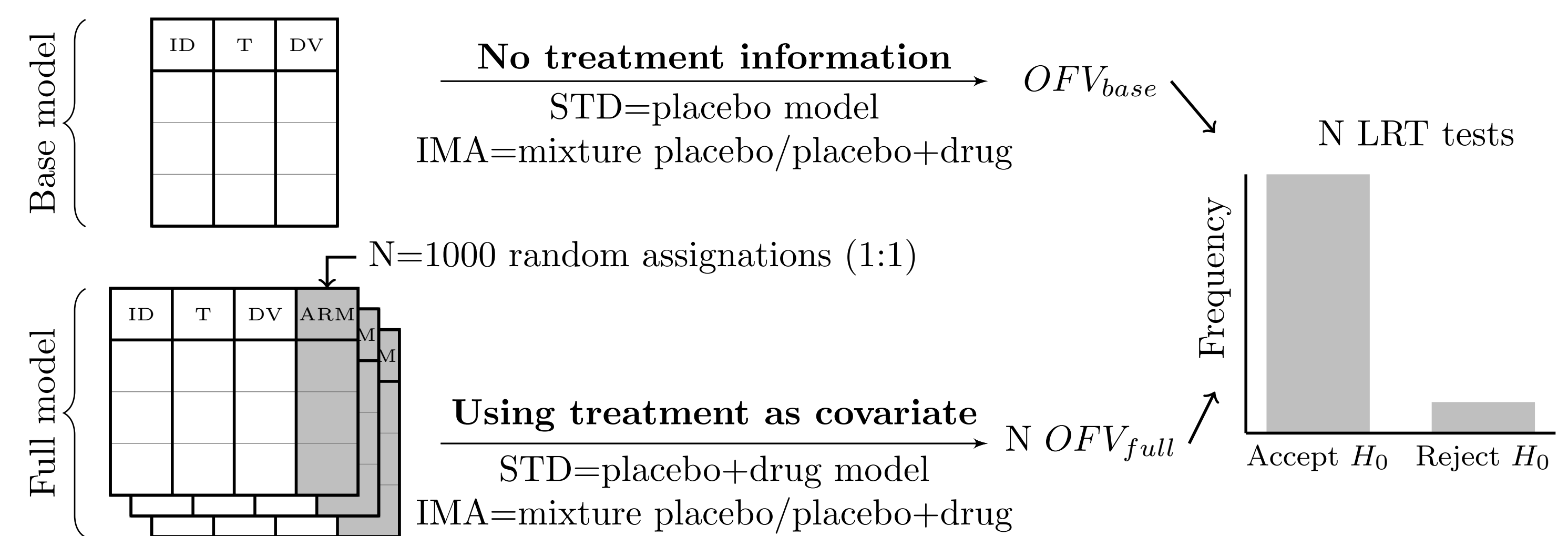


Figure 1: Workflow used to compute the type I error

Table 2: Computation of the median drug effect

	Base model	Full model
STD	$BASE + PLB$	$BASE + PLB + DRUG * \textcolor{teal}{TRT}$
IMA	Mixture 1: $BASE + PLB$ and mixture 2: $BASE + PLB + DRUG$	
	Mixture probability set to randomization: P(1) = 0.5 P(2) = 1 - P(1)	Mixture probability estimated: P(1) = $\textcolor{teal}{TRT} * \theta_{MIX} + (1 - \textcolor{teal}{TRT}) * (1 - \theta_{MIX})$ P(2) = 1 - P(1)

BASE: baseline model, PLB: placebo model, DRUG: drug effect model, θ_{MIX} : mixture probability, TRT: treatment allocation (0 for placebo and 1 for treatment).

Drug model	Drug effect parameterization	Median drug effect
Offset	$BASE + PLB + \theta_{drug}$	$(\theta_{MIX} * 2 - 1) * \theta_{drug}$
Linear with time <i>Likert pain score data</i>	$BASE + PLB + \theta_{drug} * t$	$(\theta_{MIX} * 2 - 1) * \theta_{drug} * t_{last}$
Linear with placebo <i>ADAS-cog data</i>	$BASE + PLB + \theta_{drug} * PLB$	$(\theta_{MIX} * 2 - 1) * \theta_{drug} * PLB$

BASE: baseline model, PLB: placebo model, θ_{drug} : drug effect parameter, θ_{MIX} : mixture probability (set to 1 for the standard approach), t_{last} : time at the end of the study.

Drug effect bias results

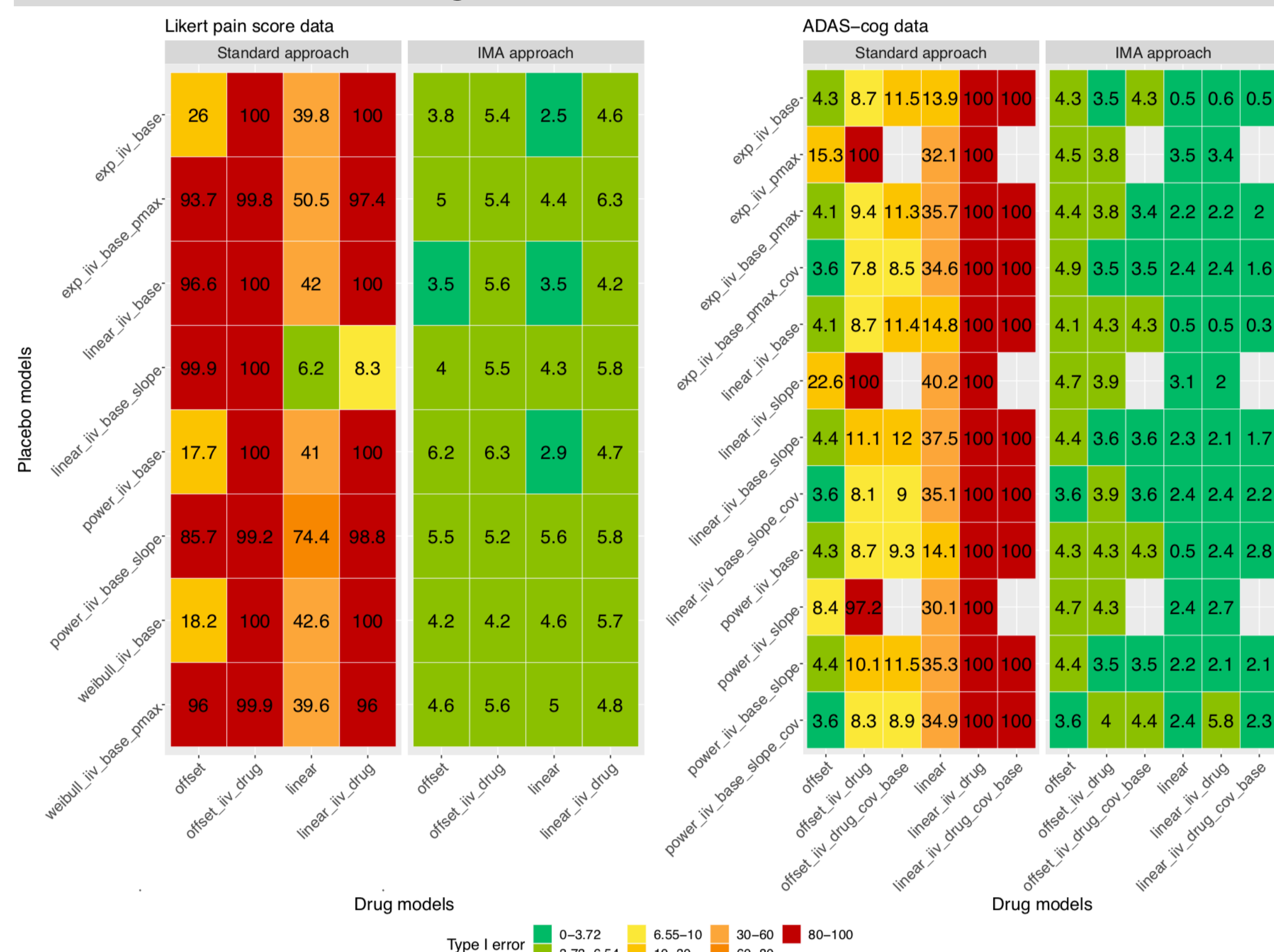


Figure 2: Type I error rate comparison between the two approaches with categorical data (left panel) and continuous data (right panel)

Standard approach

The type I error is very sensitive to model misspecifications: low only when the drug model offer little opportunity to improve the fit in the presence of placebo model misspecification.

IMA approach

The type I error is controlled for both categorical and continuous data ($\alpha = 0.05$), and often below α , especially with the ADAS-cog data.

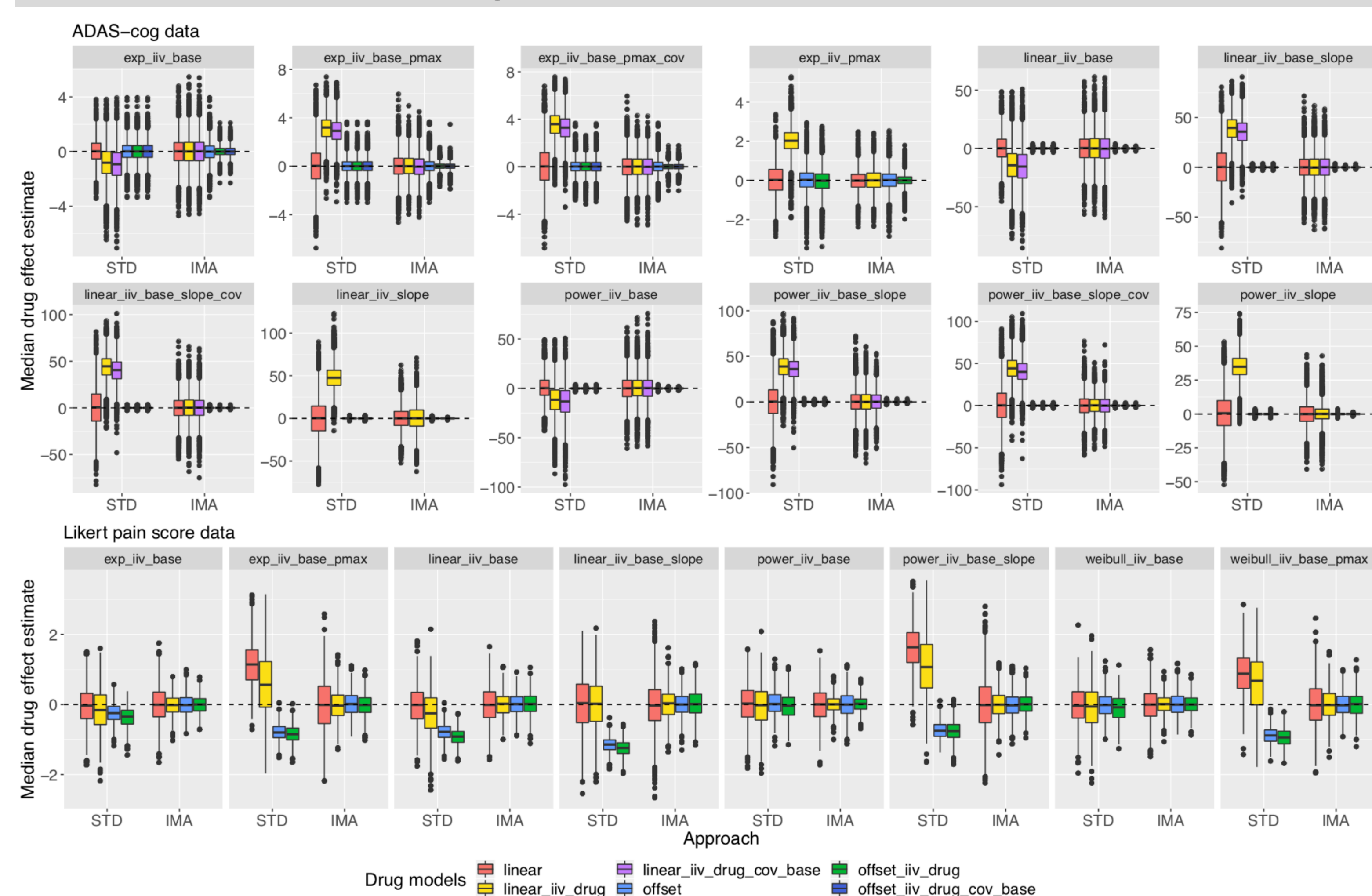


Figure 3: Bias in drug effect estimate faceted by placebo models for categorical data (bottom panel) and continuous data (top panel)

Standard approach

A pronounced bias in the median drug effect occurs for many drug/placebo model combinations. It is typically larger when the drug effect model contains inter-individual variability (iiv).

IMA approach

None of the placebo/drug combination tested had biased median drug estimate and the precision is slightly better than the STD approach.

- IMA has a better type I error control and is more robust towards misspecifications in the placebo model.
- IMA consistently provided unbiased estimates of drug effect, whereas the standard approach did not.
- IMA seems a promising method to address the drawbacks from the standard NLMEM approach to analyse efficacy trials

¹Karlsson KE, Vong C, Bergstrand M, Jonsson EN, Karlsson MO. Comparisons of Analysis Methods for Proof-of-Concept Trials. *CPT Pharmacomet Syst Pharmacol*. 2013 Jan;2(1):e23. ²Jonsson EN, Sheiner LB. More efficient clinical trials through use of scientific model-based statistical tests. *Clin Pharmacol Ther*. 2002 Dec;72(6):603–14. ³Plan EL, Elshoff J-P, Stockis A, Sargentini-Maier ML, Karlsson MO. Likert pain score modeling: a Markov integer model and an autoregressive continuous model. *Clin Pharmacol Ther*. 2012 May;91(5):820–8. ⁴Schindler E, Karlsson MO. A Minimal Continuous-Time Markov Pharmacometric Model. *AAPS J*. 2017;19(5):1424–35. ⁵Ito K, Corrigan B, Zhao Q, French J, Miller R, Soares H, Katz E, Nicholas T, Billing B, Anziano R, Fullerton T, Alzheimer's Disease Neuroimaging Initiative. Disease progression model for cognitive deterioration from Alzheimer's Disease Neuroimaging Initiative database. *Alzheimers Dement J Alzheimers Assoc*. 2011 Mar;7(2):151–60.

³More results (including power) with simulated data, in A. Tessier et al. Poster IV-75 (abstract 9233)