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Mats Karlsson

Prof. Mats Karlsson, is Professor of Pharmacometrics at the Department of Pharmacy, Uppsala University, Uppsala, Sweden. He started the pharmacometrics research group at Uppsala University where more than 100 PhD students and postdocs have had pharmacometrics training. His research focus is methodological development and application of pharmacometrics to drug development and drug usage.

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Decisions based on longitudinal analysis

Mats Karlsson, PhD
Professor of Pharmacometrics

Department of Pharmacy
Uppsala University
Uppsala, Sweden

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Guidance for Industry

Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
April 2003
CP

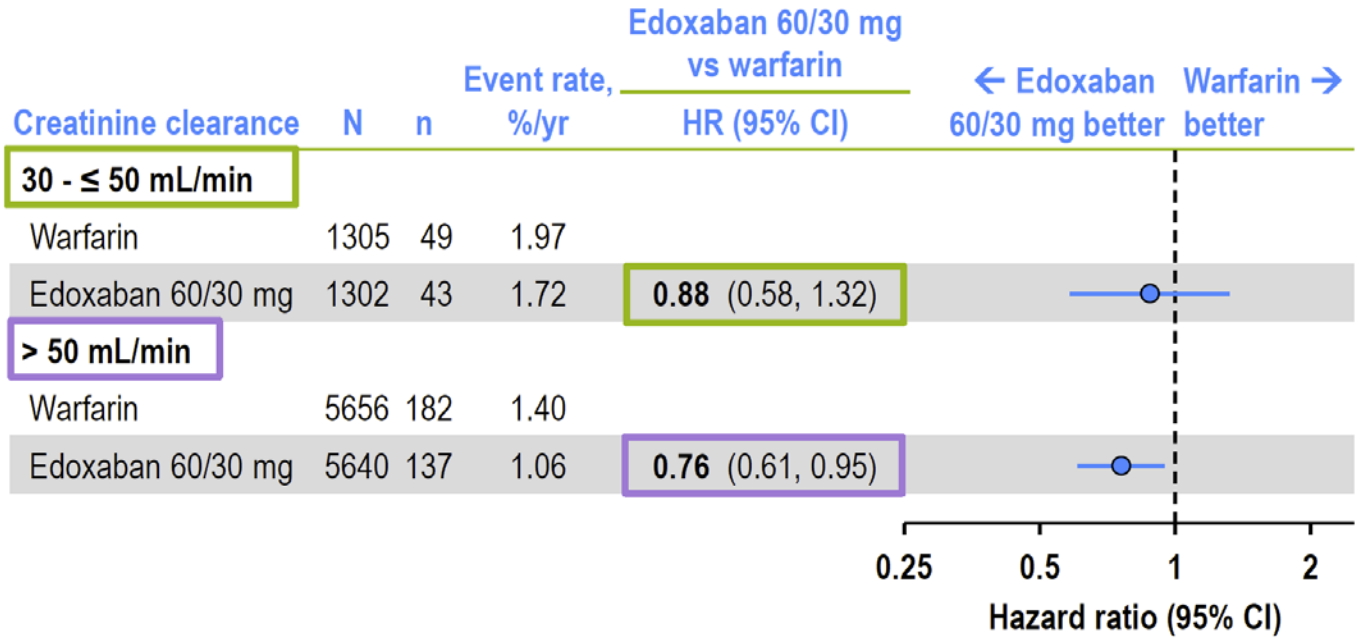
Exposure – response dose individualization assessment

CS-4

Stroke or SEE by Baseline CrCL

mITT On-Treatment

Protocol-defined subgroup analysis



https://wayback.archive-it.org/7993/20170404150219/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM421613.pdf

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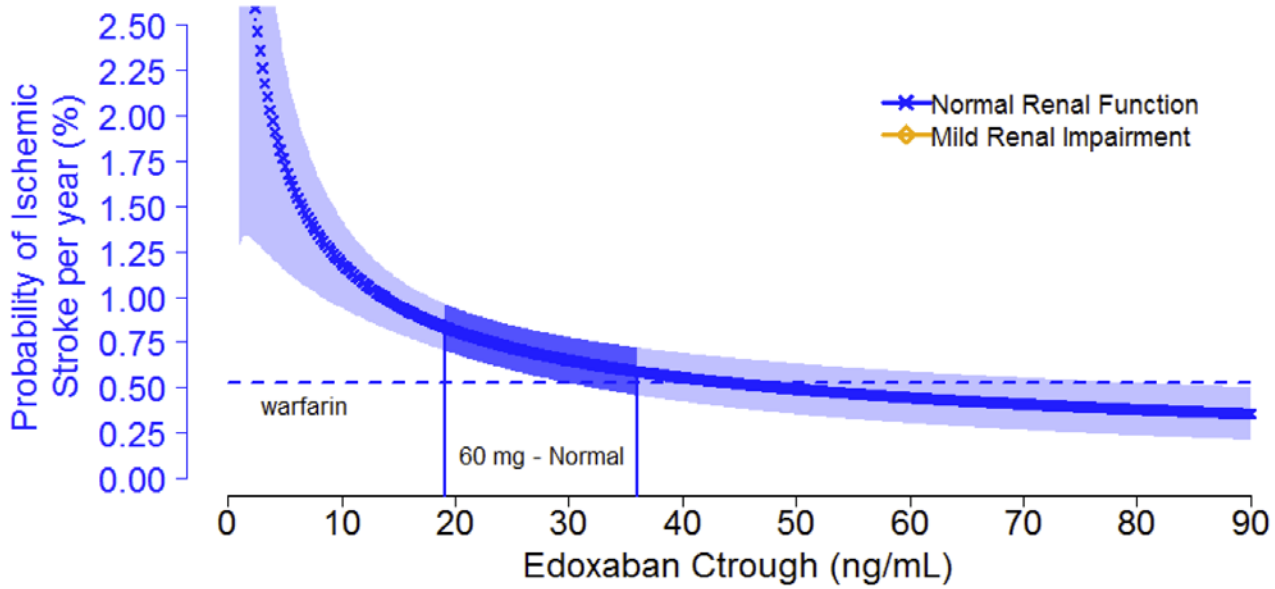
Exposure - response

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

The Probability of an Ischemic Stroke Increases with Decreasing Renal Function



Analysis shown for "typical" patient with normal renal function: 64 years old, CrCL of 100 mL/min, 24.8% with prior stroke, 29.2% with baseline aspirin use, body weight of 95.3 kg

https://wayback.archive-it.org/7993/20170404150219/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM421612.pdf

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Guidance for Industry

Population Pharmacokinetics

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

February 1999
CP 1

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Pop PK in exposure matching

Clarification on Precision Criteria to Derive Sample Size When Designing Pediatric Pharmacokinetic Studies

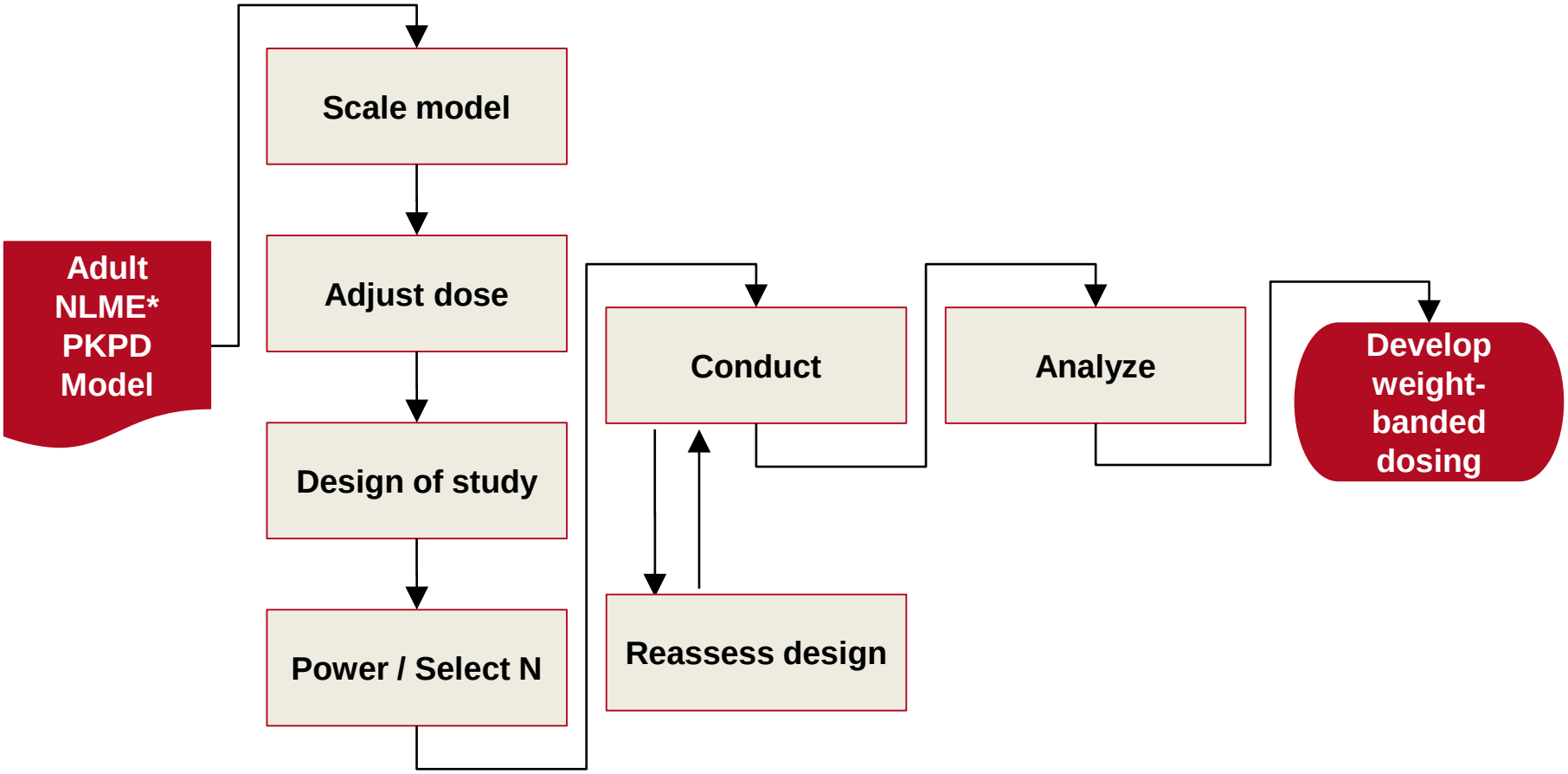
Yaning Wang, PhD, Pravin R. Jadhav, PhD, Mallika Lala, PhD, and Jogarao V. Gobburu, PhD

Keywords: *pediatric drug development; pharmacokinetics; regulatory requirement; precision*

Journal of Clinical Pharmacology, 2012;52:1601-1606

Workflow

for pediatric studies



*NLME = NonLinear Mixed Effects

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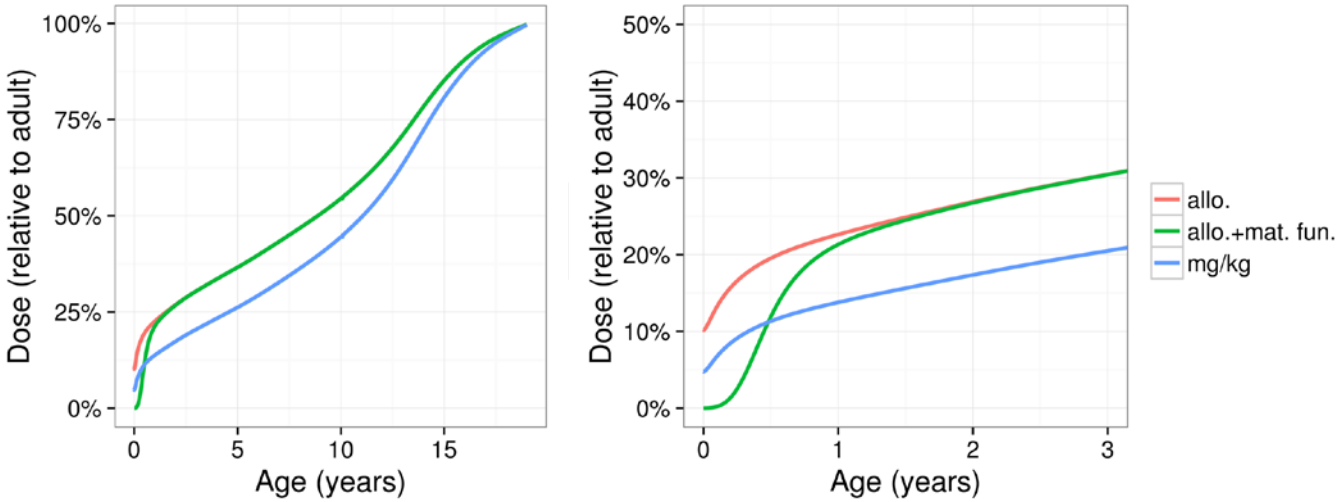
Scale

PKPD model from adults to children

Example: Comparison of scaling approaches for vancomycin (main elimination by glomerular filtration)[1,2]



[1] *Parameter value from*:
Anderson et al. “Vancomycin pharmacokinetics in preterm neonates and the prediction of adult clearance.” Br J Clin Pharmacol 2007; 63 (1): 75-84

[2] *Growth data from*:
WHO Multicentre Growth Reference Study Group. "WHO Child Growth Standards based on length/height, weight and age". Acta Paediatr, Suppl. 2006, 450, 76-85.
de Onis M et al. "Development of a WHO growth reference for school-aged children and adolescents" Bull WHO, 2007;85:660-7.

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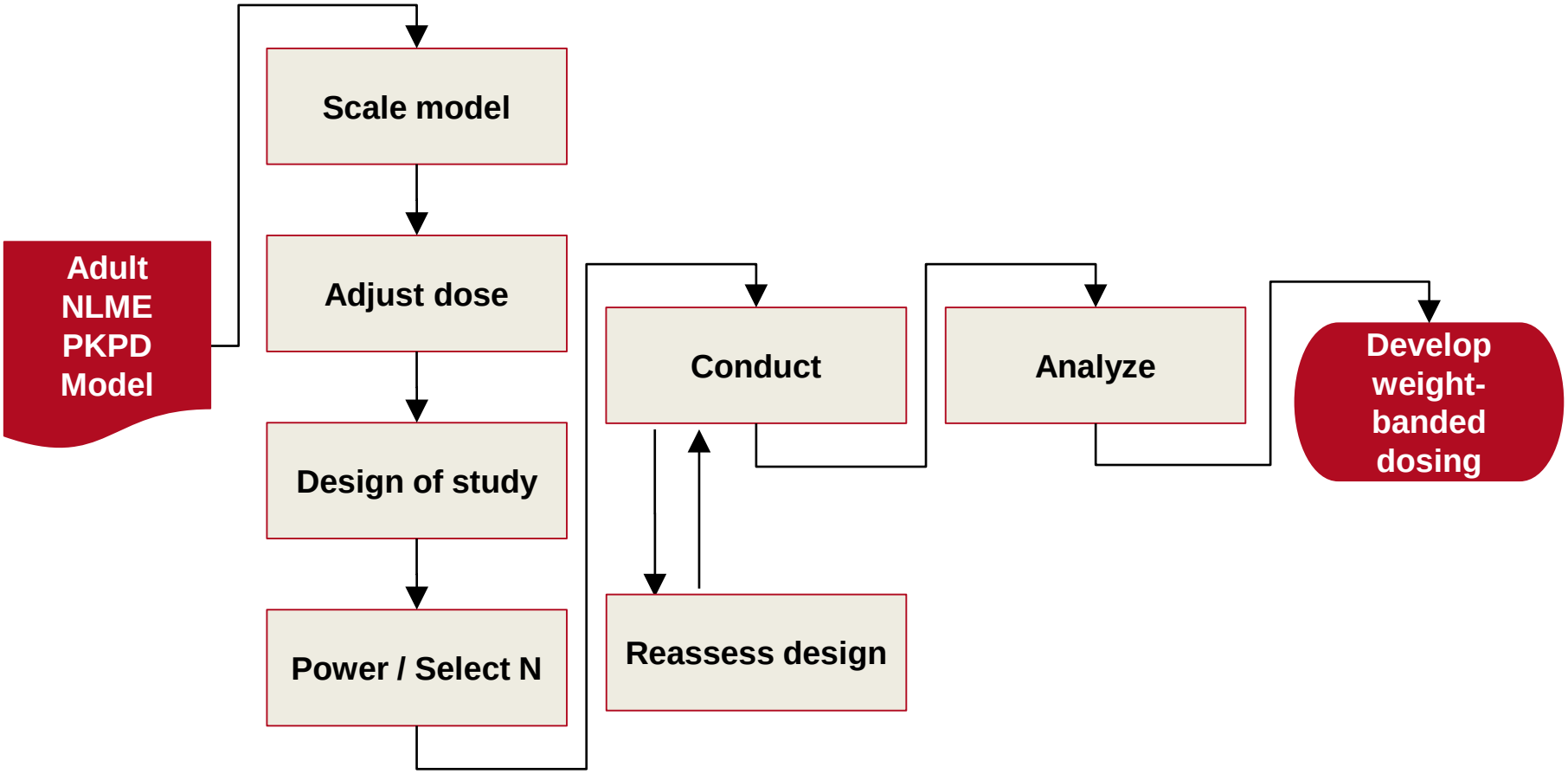
Workflow

for pediatric studies



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Power

study for required parameter precision

- Sample size needs to be chosen to fulfill precision criteria:
  ".. target a 95% CI within 60% and 140% of the geometric mean estimates of clearance and volume of distribution … in each pediatric sub-group with at least 80% power." [1]

Methodology:

1. Determine expected parameter standard errors (SE) for sample size N using CTS
2. Scale parameter SE and determine approximate sample size for intended precision
3. Verify approximate sample size calculation using CTS (asymp. nature of scaling, non-normality of estimates)

[1] Yaning Wang et al. "Clarification on precision criteria to derive sample size when designing pediatric pharmacokinetic studies." J Clin Pharmacol 2012;52:1601-1606

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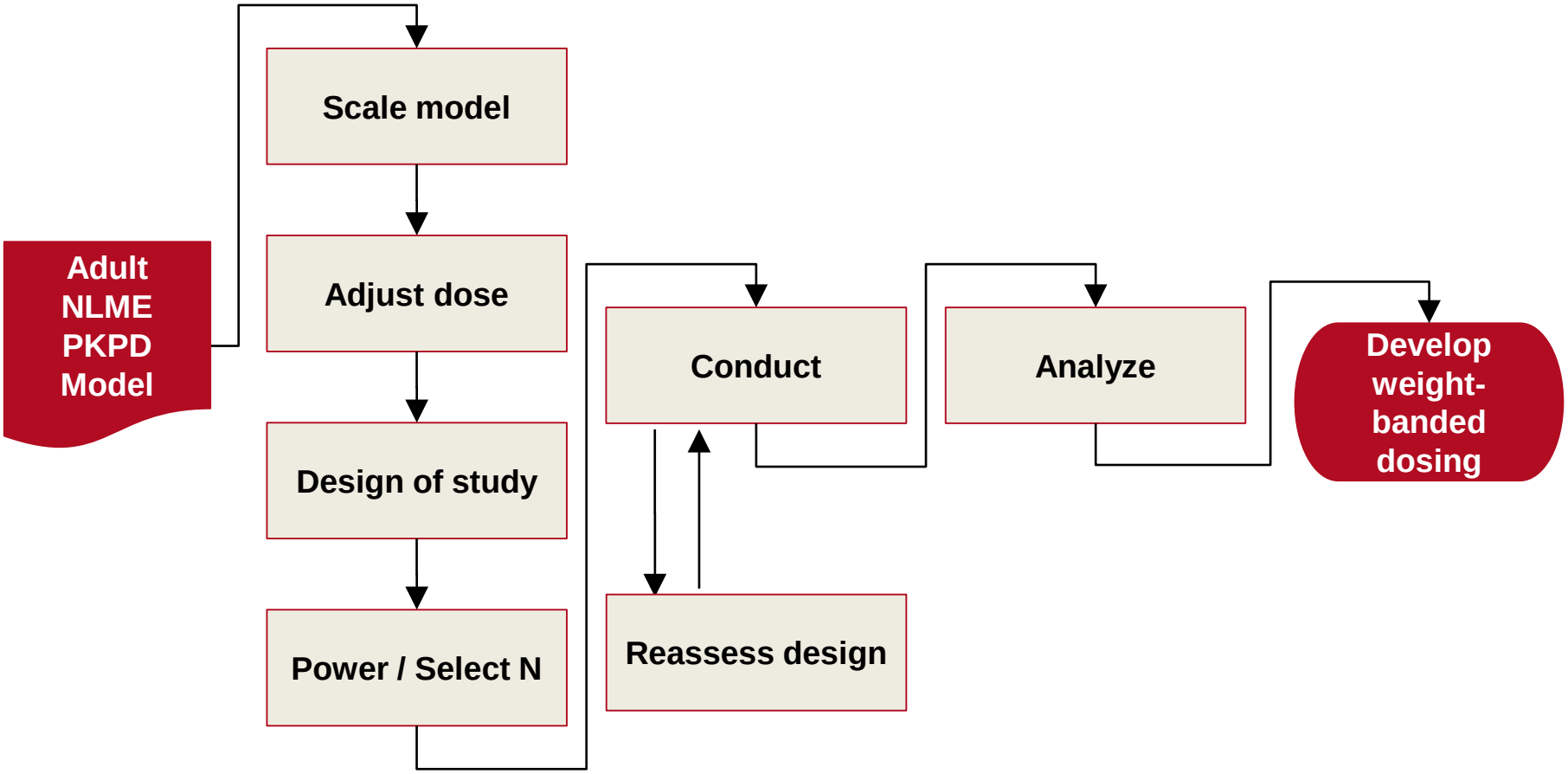
Workflow

for pediatric studies



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Motivating example for use of longitudinal modelling as primary analysis

- Proof-of-Concept study in gastroesophageal reflux
  - –Back-up compound
  - –Protocol for planned PoC already developed
  - –Prior internal experience of PoC-study with same endpoint
    - •Data
    - •Longitudinal NLME model
  - –Could NLME offer any advantage to planned design/analysis?

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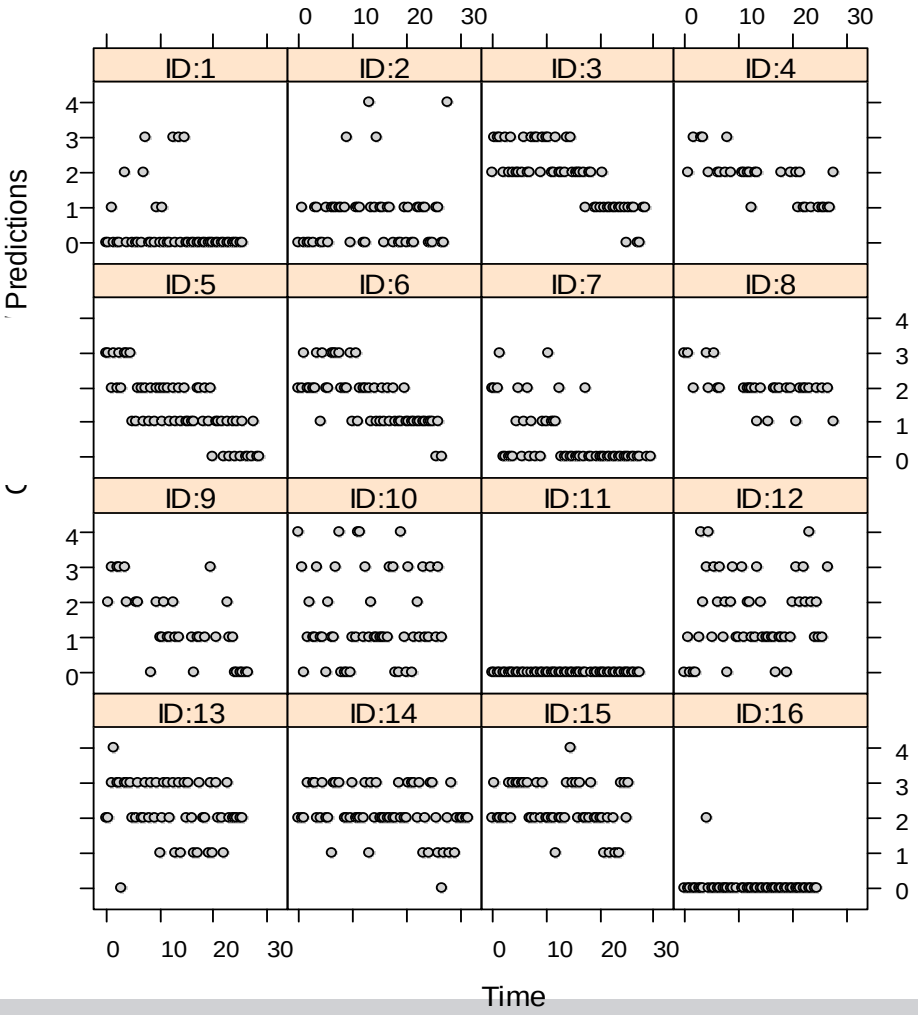
Data from previous trial

Clinical symptom data in reflux disease



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Two options in testing for a drug effect

- Based on a responder definition
  - Maximally 1 symptom during last week
  - Test for differences in responder rates (RR)

- Based on a non-linear mixed effects model for longitudinal ordered categorical data (OC model)
  - Test for a non-zero drug effect

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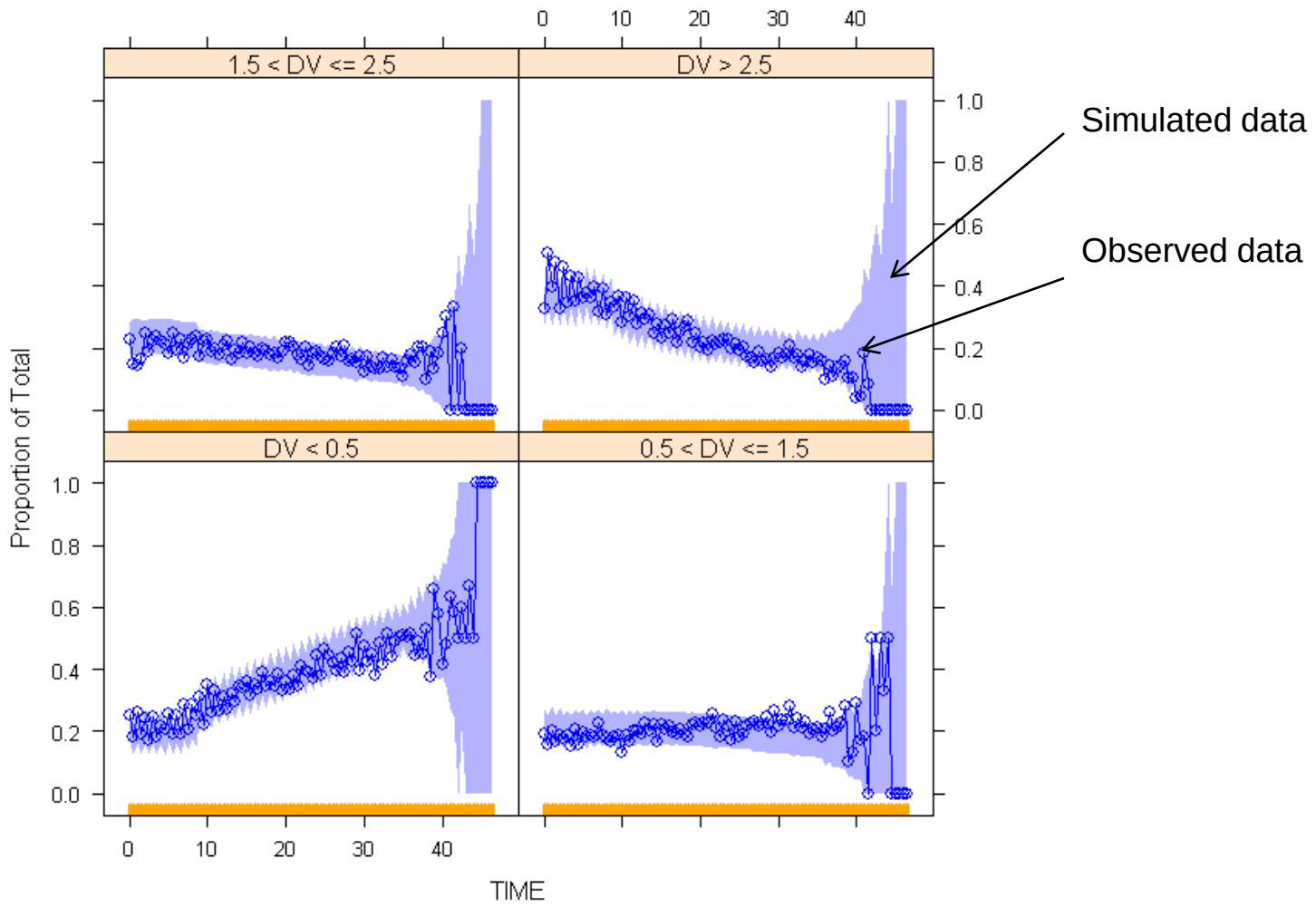
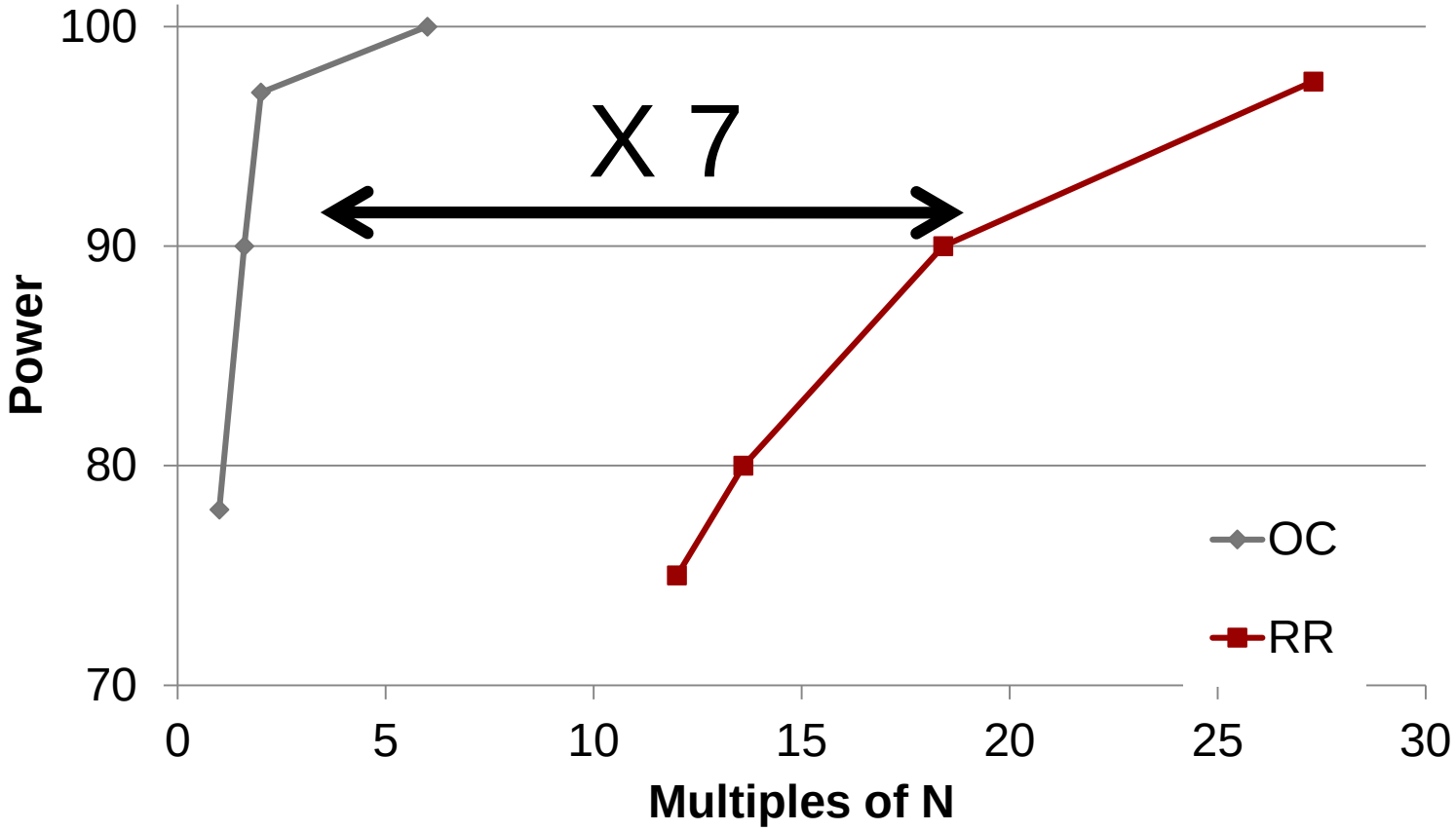
Extensive diagnostics to assure sufficient quality of model on prior data

e.g. visual predictive check (VPC)



Analysis alternatives for the PoC study

Power to detect a clinically relevant effect



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Citation: CPT: Pharmacometrics & Systems Pharmacology (2013) 2, e23; doi:10.1038/psp.2012.24

www.nature.com/psp

ORIGINAL ARTICLE

Comparisons of Analysis Methods for Proof-of-Concept Trials

KE Karlsson[1], C Vong[1], M Bergstrand[1], EN Jonsson[1,2] and MO Karlsson[1]

Drug development struggles with high costs and time consuming processes. Hence, a need for new strategies has been accentuated by many stakeholders in drug development. This study proposes the use of pharmacometric models to rationalize drug development. Two simulated examples, within the therapeutic areas of acute stroke and type 2 diabetes, are utilized to compare a pharmacometric model–based analysis to a *t*-test with respect to study power of proof-of-concept (POC) trials. In all investigated examples and scenarios, the conventional statistical analysis resulted in several fold larger study sizes to achieve 80% power. For a scenario with a parallel design of one placebo group and one active dose arm, the difference between the conventional and pharmacometric approach was 4.3- and 8.4-fold, for the stroke and diabetes example, respectively. Although the model-based power depend on the model assumptions, in these scenarios, the pharmacometric model–based approach was demonstrated to permit drastic streamlining of POC trials.
CPT: Pharmacometrics & Systems Pharmacology (2013) **2,** e23; doi:10.1038/psp.2012.24; advance online publication 16 January 2013

Pharmacometric vs. traditional approach to establish PoC

Stroke

- Traditional:
  - –NIH stroke scale change from baseline at end of treatment (~90 days), LOCF for drop-out
  - –Two sided t-test ($p<0.05$) placebo vs. top dose level
- Model based:

The AAPS Journal (© 2010)
DOI: 10.1208/s12248-010-9230-0

Research Article

Modeling Disease Progression in Acute Stroke Using Clinical Assessment Scales

Kristin E. Karlsson,[1,5] Justin J. Wilkins,[1] Fredrik Jonsson,[2] Per-Henrik Zingmark,[3] Mats O. Karlsson,[1] and E. Niclas Jonsson[1,4]

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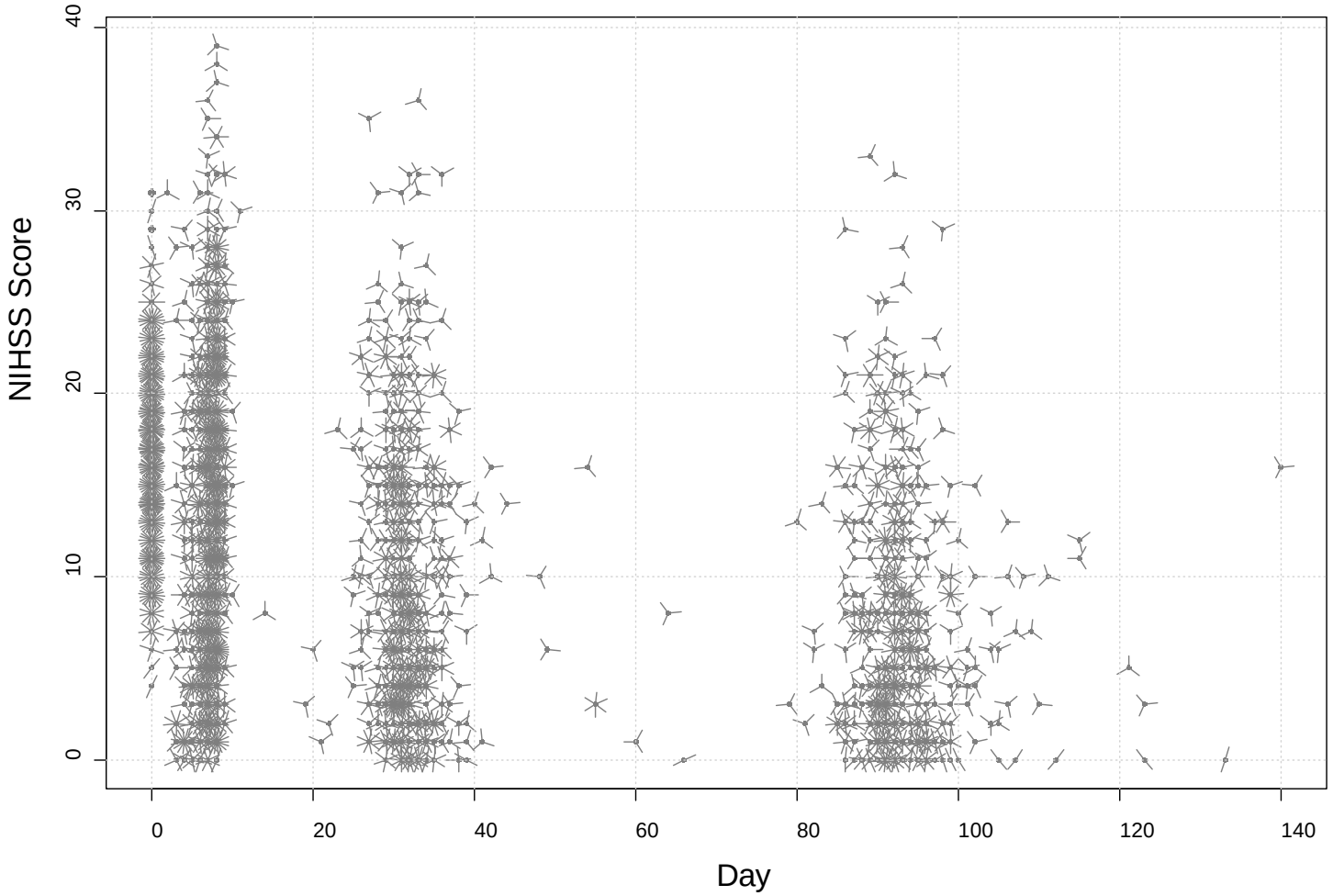
Benefits of using all available data; NIHSS observations

Observations made at day 0, 7, 30 and 90



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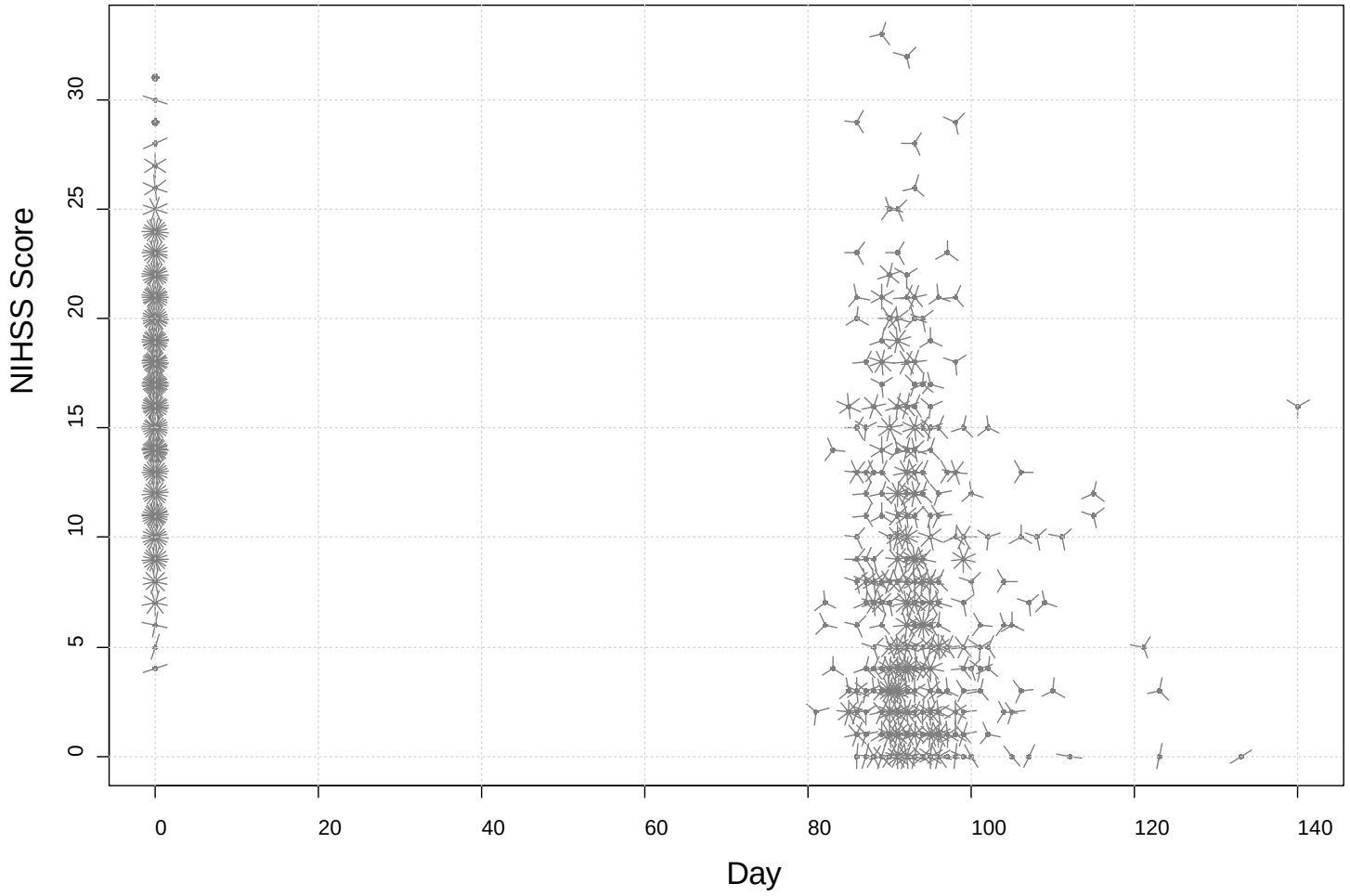
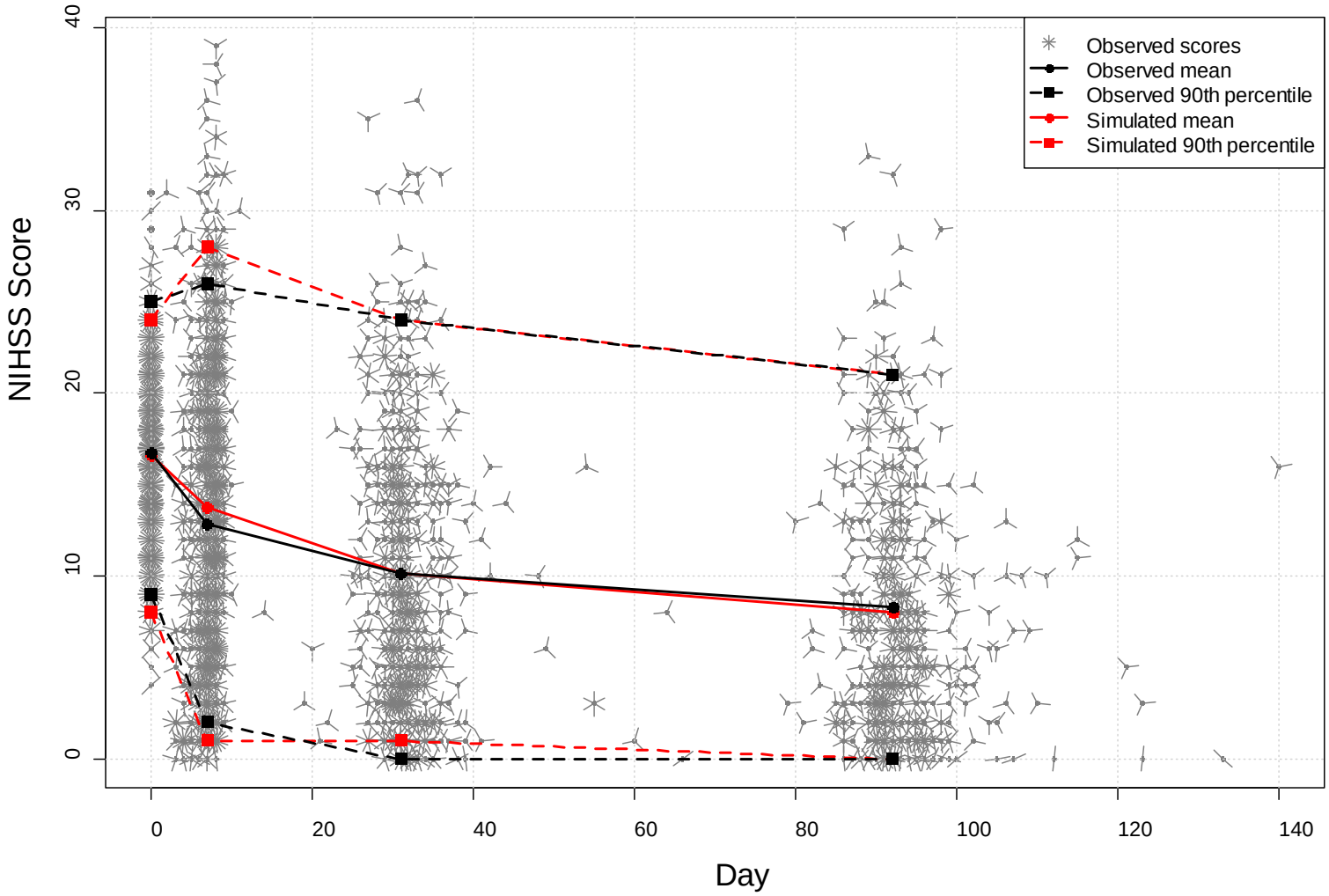
Data used in a traditional analysis; NIHSS observations



Data used in pharmacometric analysis; NIHSS observations



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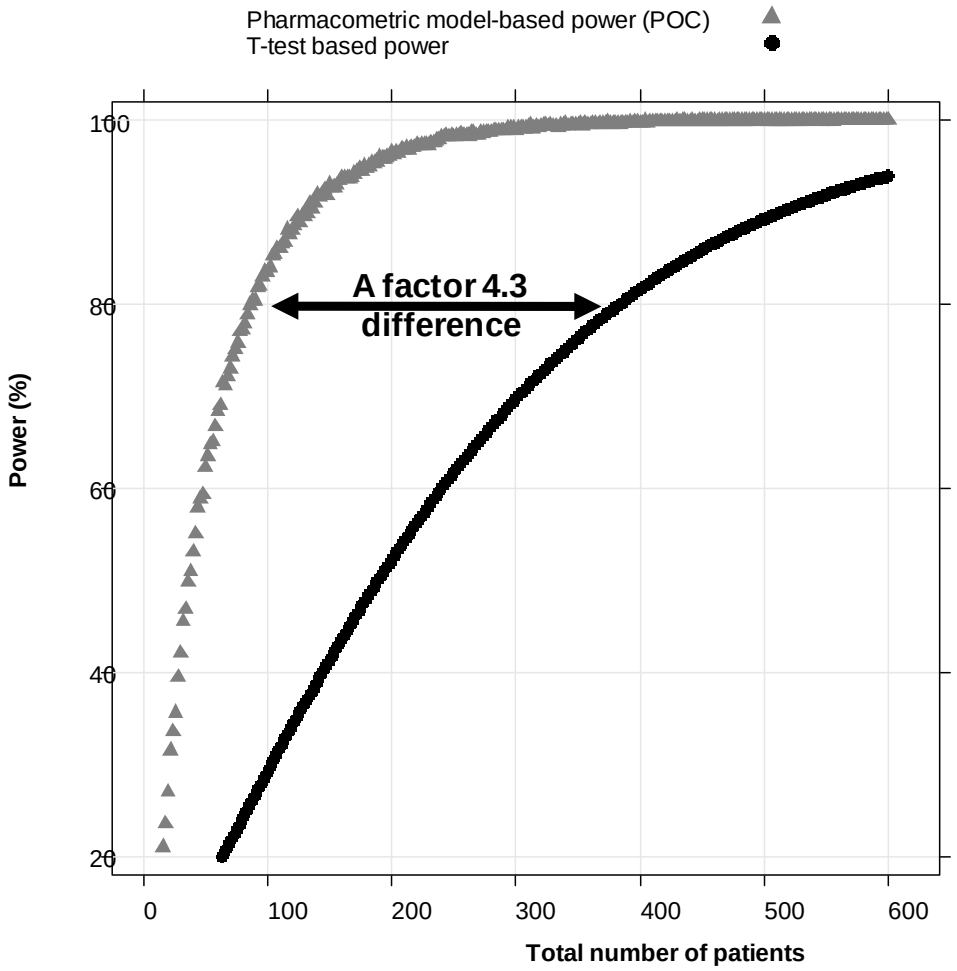
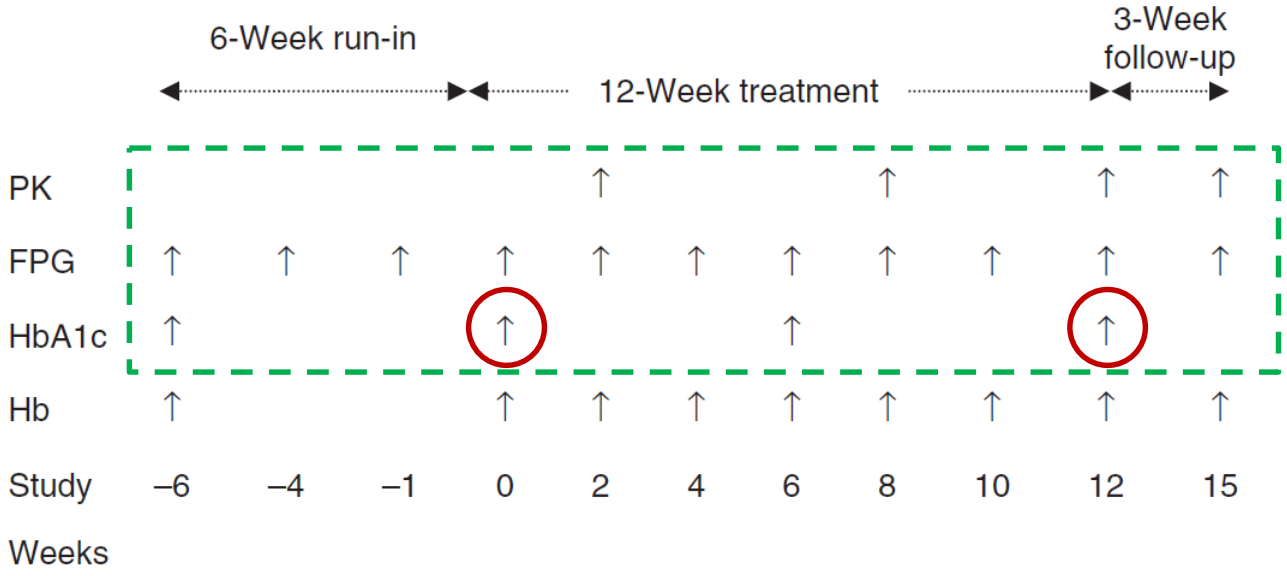
PoC in Stroke



Pharmacometric power gain:

- Use longitudinal data
- Sensible handling of drop-out information

Design of a PoC study for an anti-diabetic study



Information utilized with the traditional approach

Information utilized with the pharmacometric approach

Pharmacometric vs. traditional approach to establish PoC

Diabetes

- Model used in model-based analysis:

nature publishing group ARTICLES

Models for Plasma Glucose, HbA1c, and Hemoglobin Interrelationships in Patients with Type 2 Diabetes Following Tesaglitazar Treatment

B Hamrén[1,2], E Björk[3], M Sunzel[4] and MO Karlsson[2]

[1]Department of Medical Science, Clinical Pharmacology, AstraZeneca R&D Mölndal, Mölndal, Sweden; [2]Department of Biopharmaceutical Sciences, Division of Pharmacokinetics and Drug Therapy, Uppsala University, Uppsala, Sweden; [3]Clinical Cardiovascular, AstraZeneca R&D Wilmington, Wilmington, Delaware, USA; [4]Department of Medical Science, Clinical Pharmacology, AstraZeneca R&D Wilmington, Wilmington, Delaware, USA.
Correspondence: B Hamrén (bengt.hamren@astrazeneca.com)

Received 31 October 2007; accepted 2 January 2008; advance online publication 19 March 2008. doi:10.1038/clpt.2008.2

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FPG – HbA1c model

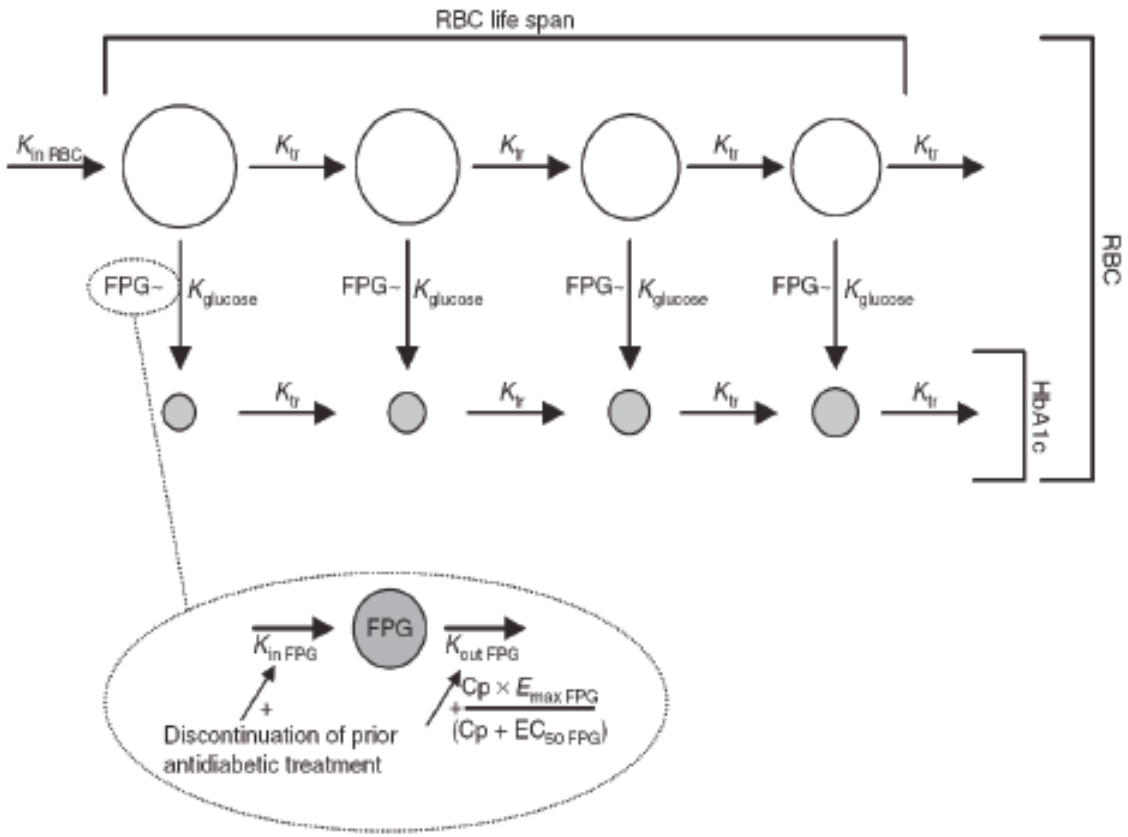
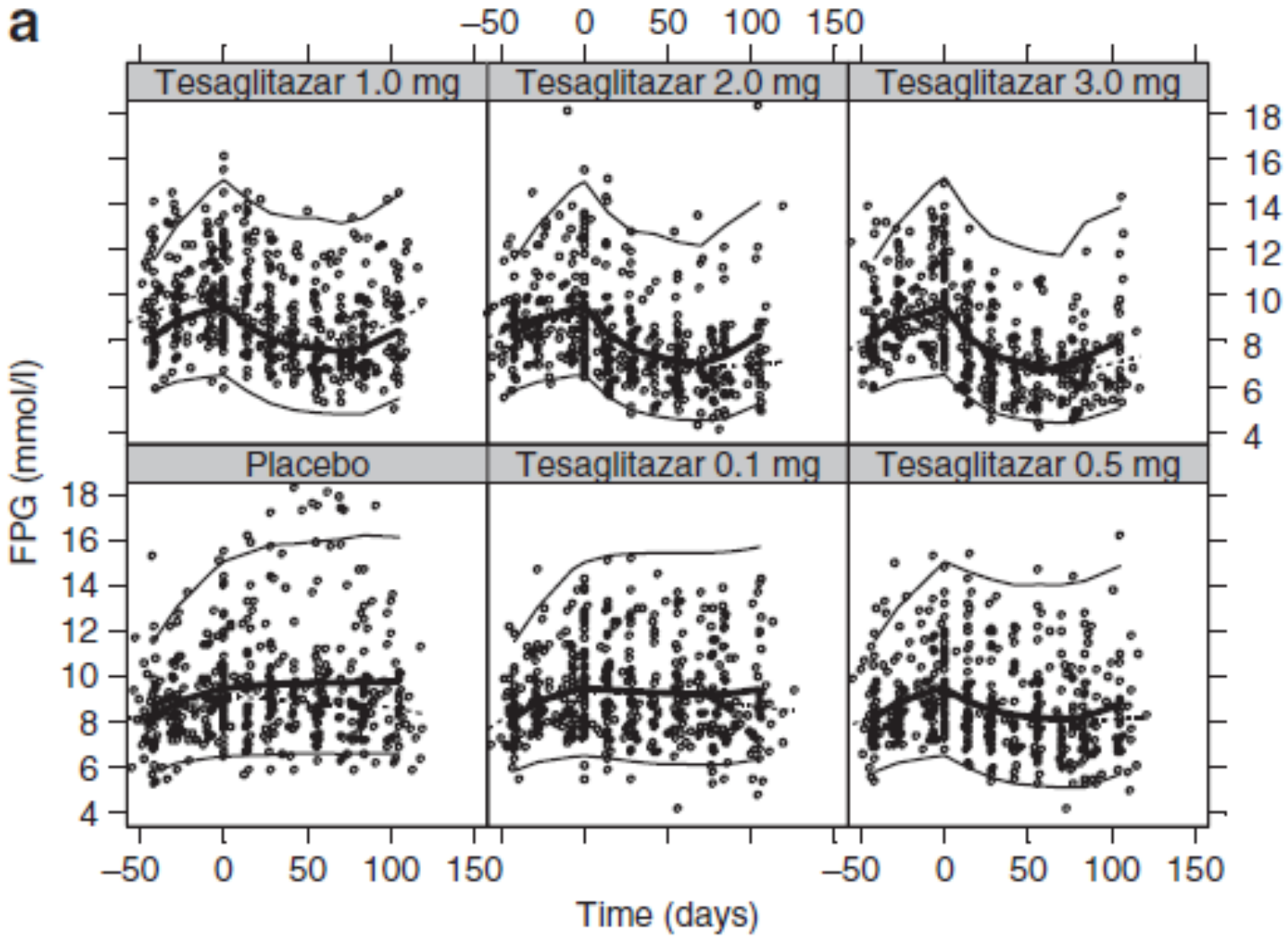


Figure 2. Schematic representation of the mechanism-based model for the FPG–HbA1c relationship,

VPC for FPG-HbA1c model FPG



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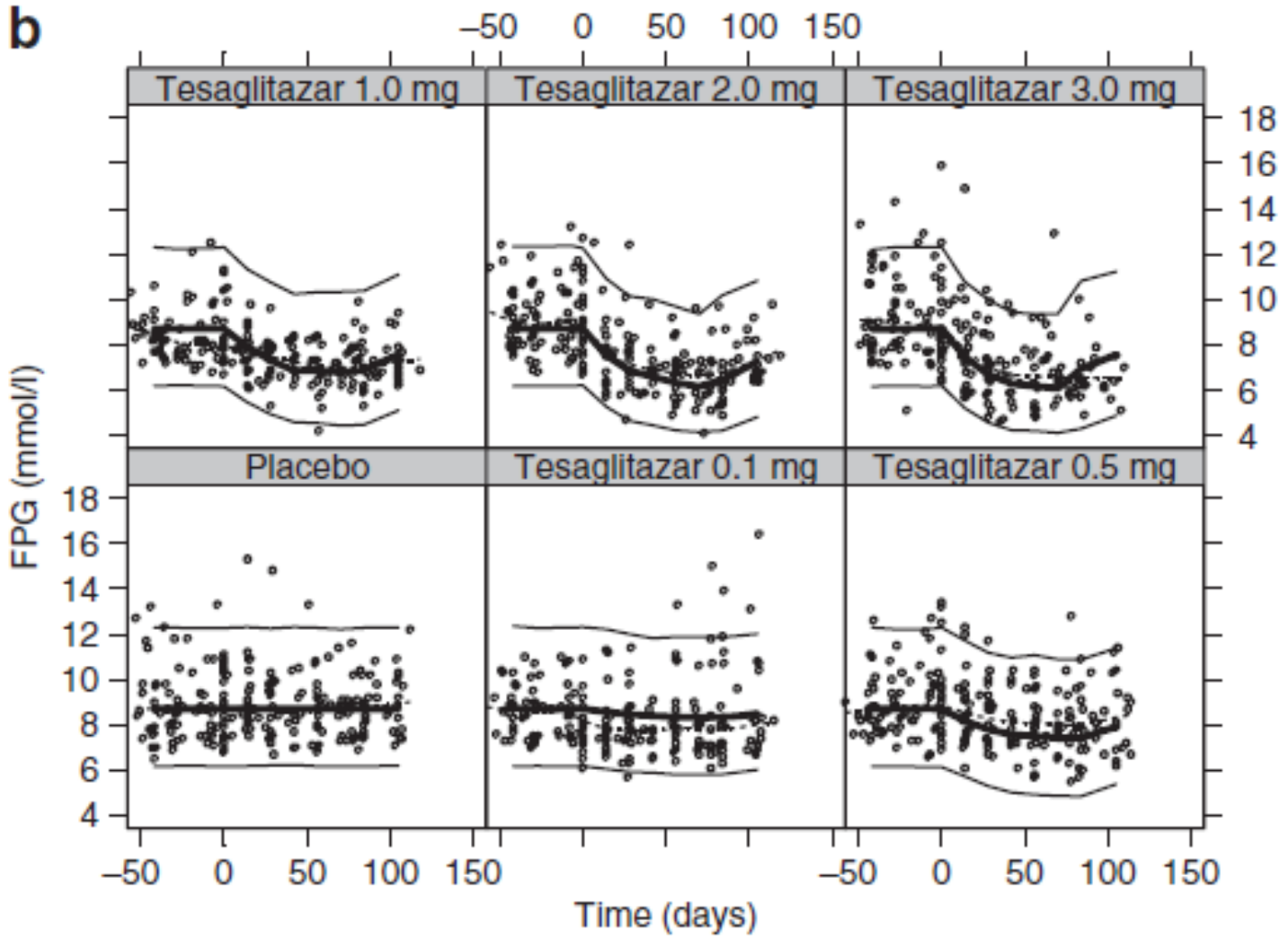
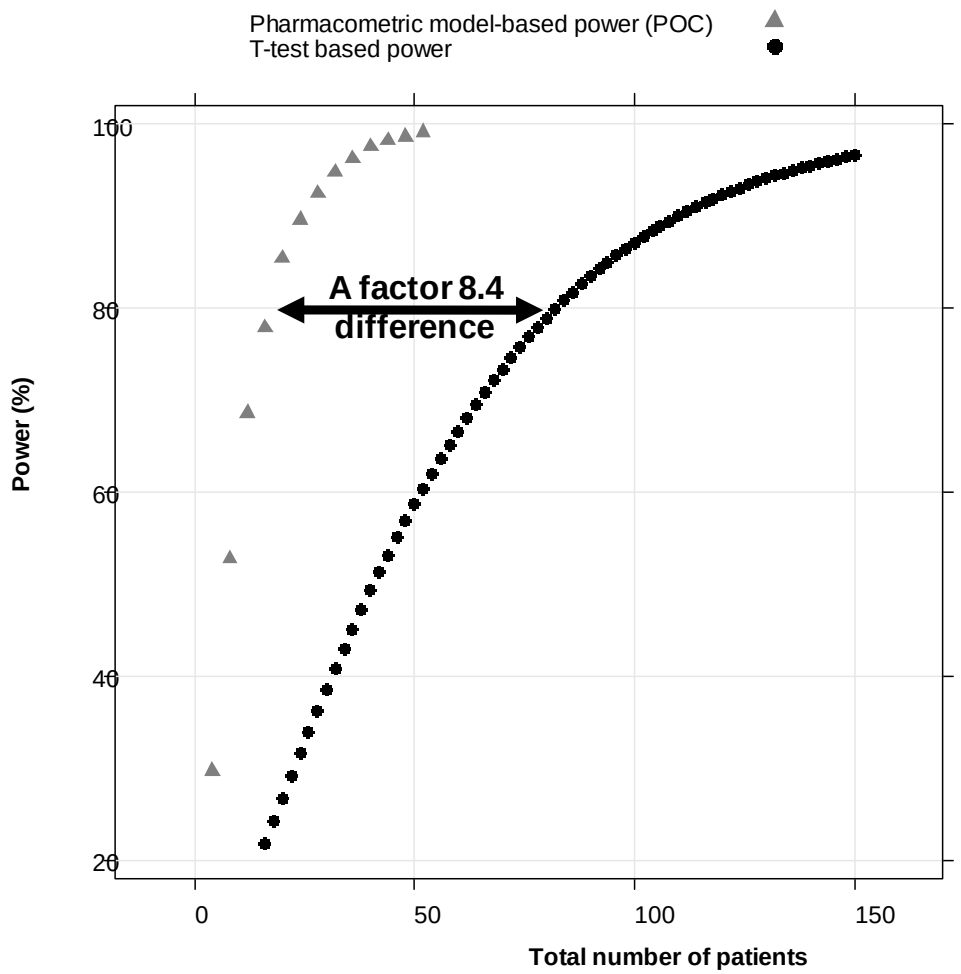
VPC for FPG-HbA1c model HbA1c



PoC in Diabetes



Pharmacometric power gain:

- Use longitudinal data
- FPG and HbA1c simultaneously

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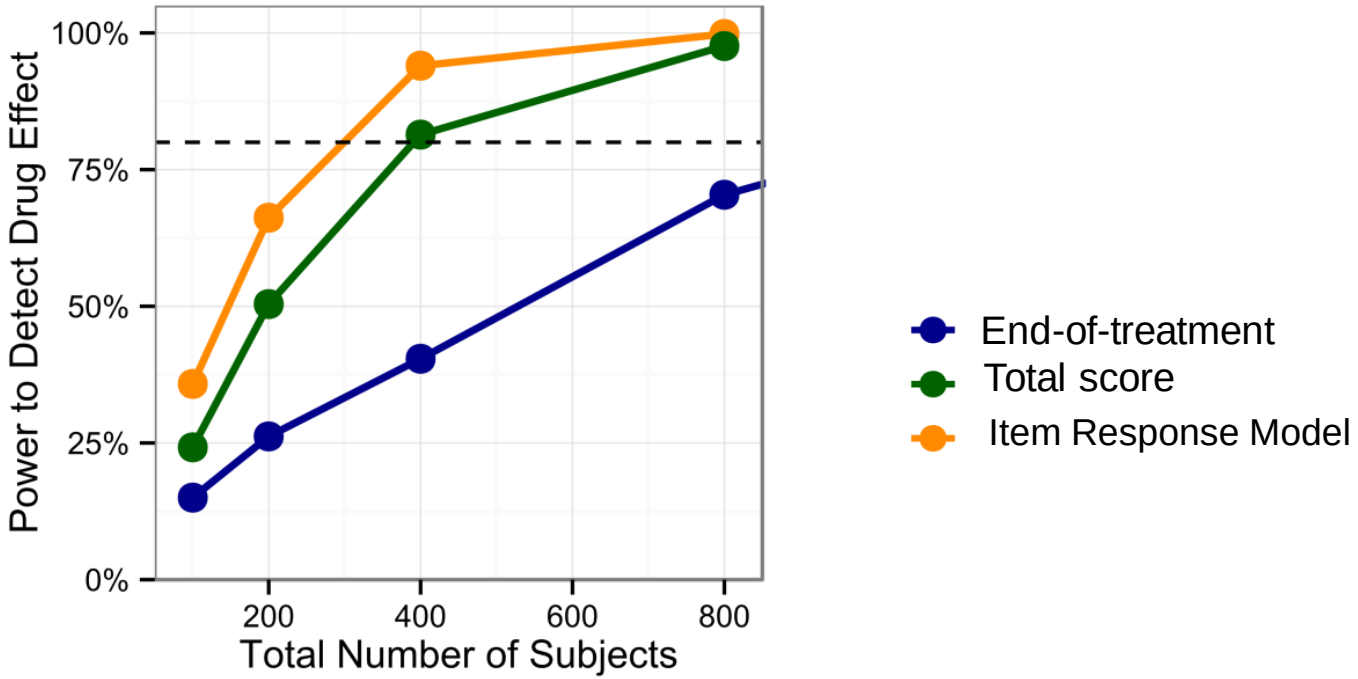
Models for ADAS-Cog in Alzheimer's disease

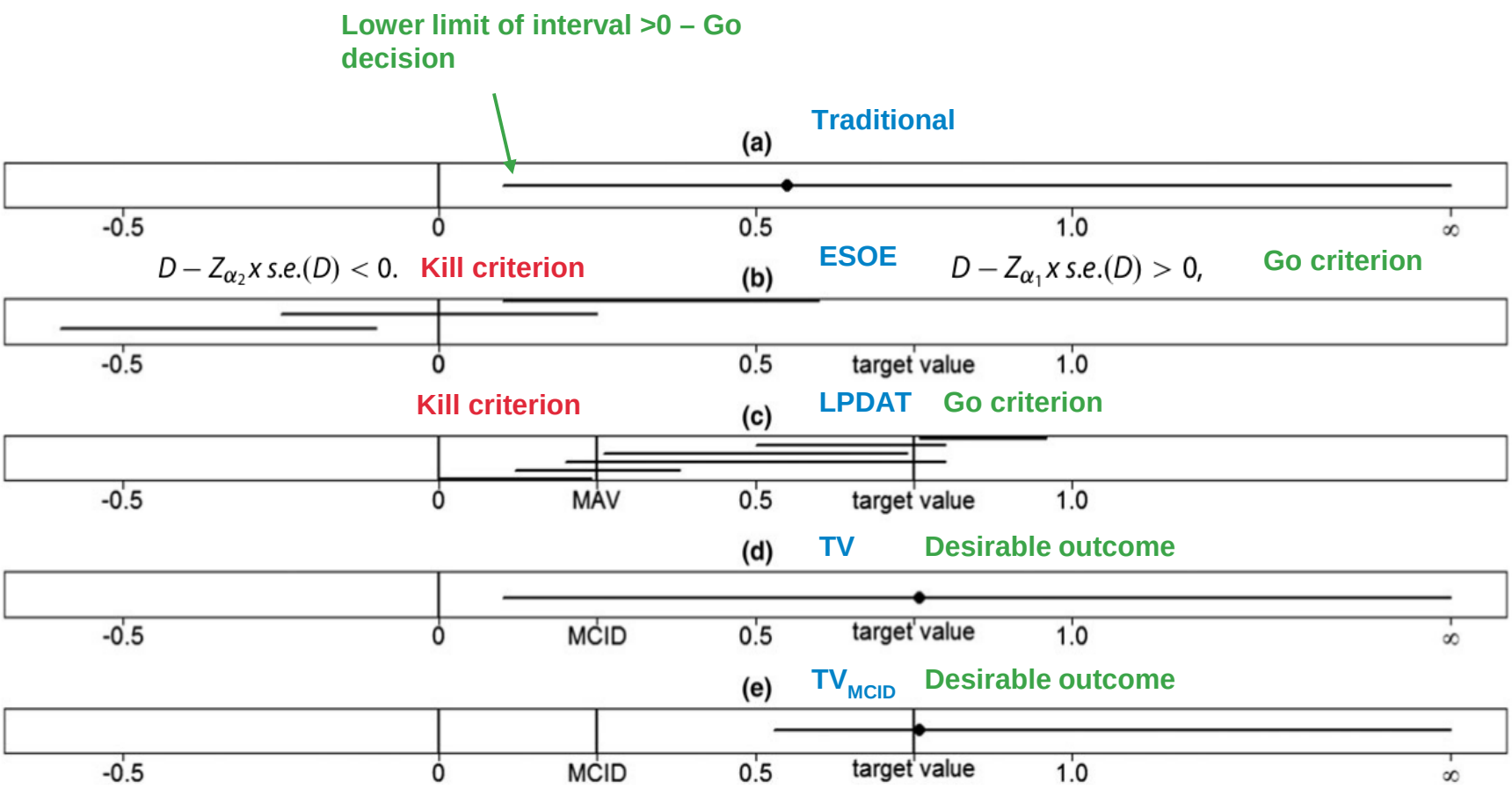
Simulated data – power to detect a hypothetical drug effect



Reference:
Ueckert et al. Pharm Res 31 (2014)

A comparison of five approaches to decision-making for a first clinical trial of efficacy

Simon Kirby[a*] and Christy Chuang-Stein[b]



Kirby and Chuang-Stein Pharmaceutic. Statist (2017)

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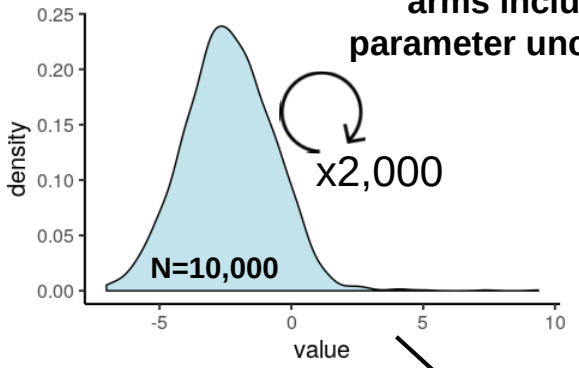
How precise is the estimated drug effect?

Confidence intervals

Pharmacometrics (model-based approach)

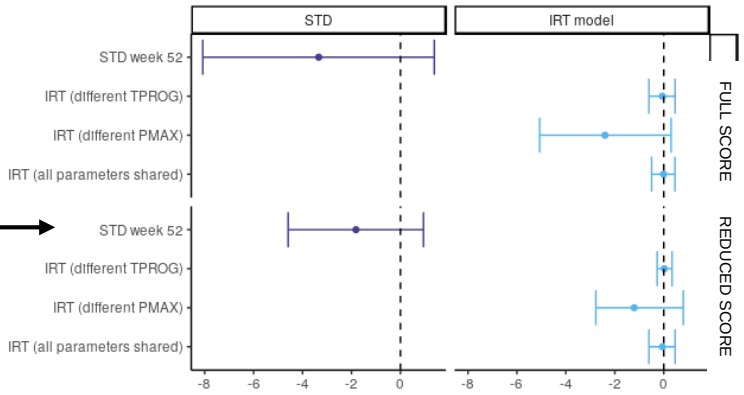
Simulate difference in total scores between arms including parameter uncertainty



Standard approach

$$\overline{X_1} - \overline{X_2} \pm Z * \sqrt{\left(\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}\right)}$$

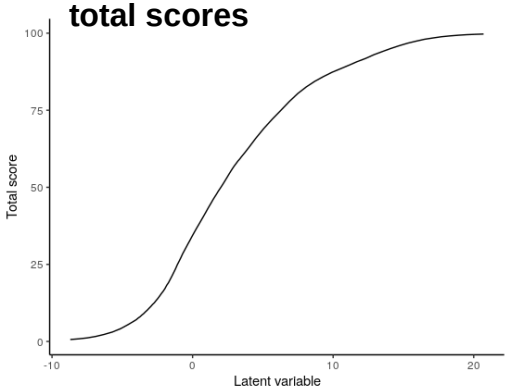
$\overline{X_1}$: mean total score ∈ treatment arm
$\overline{X_2}$: mean total score ∈ placebo arm
Z : z − score
s_1 : sample standard deviation of total score ∈ treatment arm
s_2 : sample standard deviation of total score ∈ placebo arm
n_1 : number of patients ∈ treatment arm
n_2 : number of patients ∈ placebo arm



Llanos-Paez et al. ACoP 2020

Simulating total score using IRT model

Relationship between **latent variable** and **total scores**

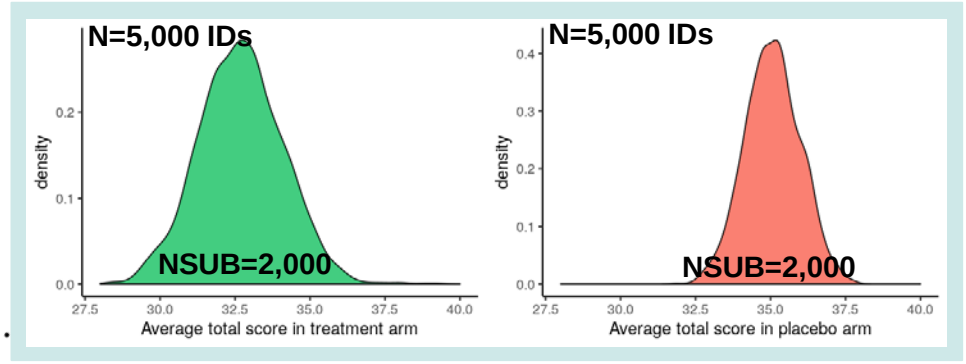


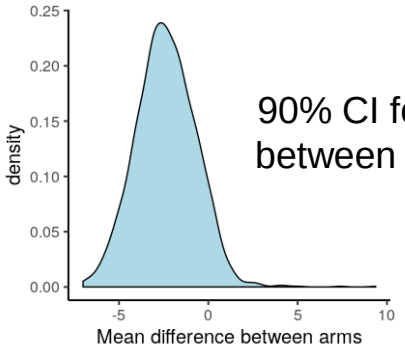
Simulate total scores for each arm X2,000

Simulations include uncertainty for each parameter value ($PRIOR)

NWPRI:

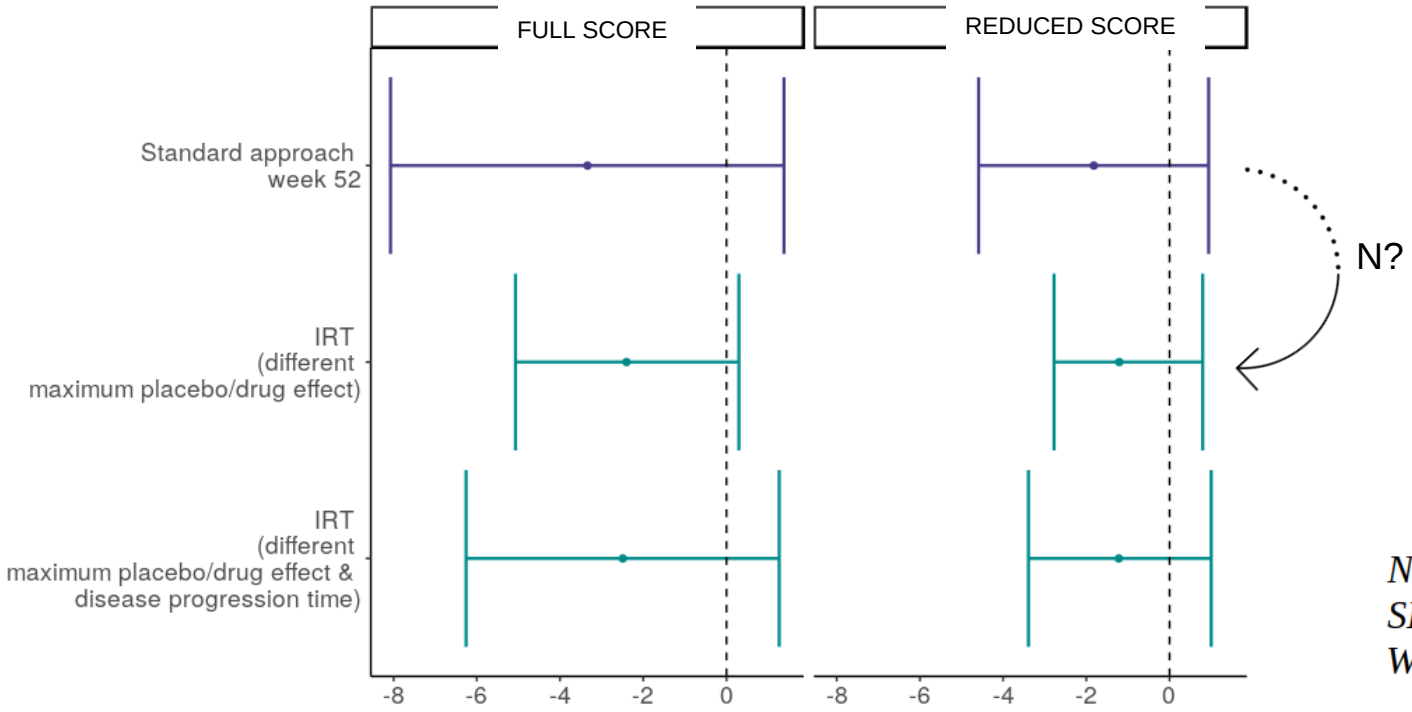
- MVN distribution for THETAs
- Inverse Wishart distribution for OMEGAs





90% CI for the mean difference between averages is calculated

Results for a placebo-controlled PoC trial in COPD using the EXACT score



90% CI

How many subjects are required to achieve the precision obtained with the longitudinal IRT model?

$$N = \frac{4 * Z_{\alpha}^2 * SE^2}{W^2}$$

$N = relative\ sample\ size$
$SE = standard\ error$
$W = width\ CI$

Results for a placebo-controlled PoC trial in COPD using the EXACT score

90% CI

Approach	Mean (90%CI) difference in total score between arms FULL SCORE	Mean (90%CI) difference in total score between arms REDUCED SCORE	CI width FULL SCORE	CI width REDUCED SCORE	Relative sample size FULL SCORE	Relative sample size REDUCED SCORE
Standard – week 52	-3.34 (-8.08, 1.38)	-1.82 (-4.59, 0.94)	9.46	5.53	1	1
IRT – different P_{MAX}	-2.40 (-5.07, 0.29)	-1.21 (-2.77, 0.80)	5.36	3.57	**3.1***	**2.4***
IRT – different P_{MAX} & T_{PROG}	-2.49 (-6.26, 1.27)	-1.22 (-3.39, 1.00)	7.53	4.39	**1.6**	**1.6**

* This means that using the **standard approach** the sample size should be **3.1/2.4 times larger** to achieve the precision obtained with IRT model

Llanos-Paez et al. ACoP 2020

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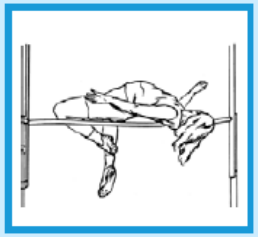
Framework for M&S in regulatory review according to impact on regulatory decision

High impact

Scientific Advice, Supporting Documentation, Regulatory Scrutiny } +++

Medium impact

Scientific Advice, Supporting Documentation, Regulatory Scrutiny } ++



Low impact

Scientific Advice, Supporting Documentation, Regulatory Scrutiny } +

Impact on regulatory decision

Manolis et al. CPT:PSP 2013:2 e31

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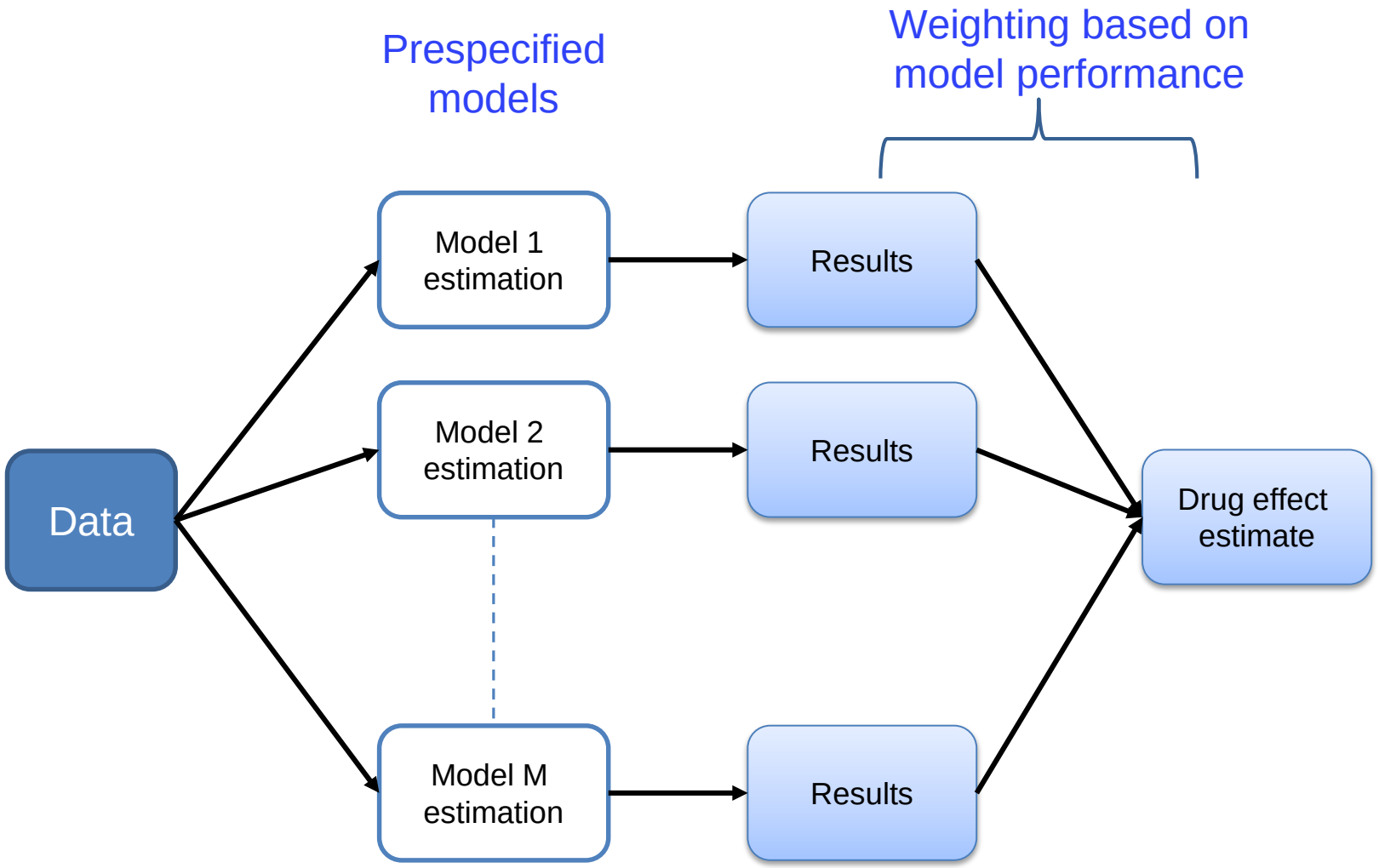
Aspects to consider in model-based drug effect estimation

- 1. Selection bias
  - The model building process, where typically the best of many tested models is selected, may result in drug effect bias
- 2. Model misspecification
  - Models for longitudinal data are always misspecified to some degree. Consequences may include:
    - Inflated Type 1 error rate from misspecified placebo model
    - Loss of power from misspecified drug model
    - Bias in drug effect estimates from misspecified drug or placebo model

Model averaging



Model averaging in pharmacometrics

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CrossMark

ORIGINAL PAPER

Model selection and averaging of nonlinear mixed-effect models for robust phase III dose selection

Yasunori Aoki[1,2]

Research Article

Comparison of Model Averaging and Model Selection in Dose Finding Trials Analyzed by Nonlinear Mixed Effect Models

Simon Buatois,[1,2,3,5] Sebastian Ueckert,[4] Nicolas Frey,[1] Sylvie Retout,[1,2] and France Mentré[3]

WILEY

Citation: CPT Pharmacometrics Syst. Pharmacol. (2017) 6, 418–429; doi:10.1002/psp4.12196

WHITE PAPER

Advanced Methods for Dose and Regimen Finding During Drug Development: Summary of the EMA/EFPIA Workshop on Dose Finding (London 4–5 December 2014)

FT Musuamba[1,2,3]*, E Manolis[1,4], N Holford[5], SYA Cheung[6], LE Friberg[7], K Ogungbenro[8], M Posch[9], JWT Yates[6], S Berry[10], N Thomas[11], S Corriol-Rohou[6], B Bornkamp[12], F Bretz[9,12], AC Hooker[7], PH Van der Graaf[13,14], JF Standing[1,15], J Hay[1,16], S Cole[1,16], V Gigante[1,17], K Karlsson[1,18], T Dumortier[12], N Benda[1,19], F Serone[1,17], S Das[6], A Brochot[20], F Ehmann[4], R Hemmings[16] and I Skottheim Rusten[1,21]

Inadequate dose selection for confirmatory trials is currently still one of the most challenging issues in drug development, as illustrated by high rates of late-stage attritions in clinical development and postmarketing commitments required by regulatory institutions. In an effort to shift the current paradigm in dose and regimen selection and highlight the availability and usefulness of well-established and regulatory-acceptable methods, the European Medicines Agency (EMA) in collaboration with the European Federation of Pharmaceutical Industries Association (EFPIA) hosted a multistakeholder workshop on dose finding (London 4–5 December 2014). Some methodologies that could constitute a toolkit for drug developers and regulators were presented. These methods are described in the present report: they include five advanced methods for data analysis ls, quantitative systems pharmacology models, MCP-Mod, and model ization (Fisher information matrix (FIM)-based methods, clinical trial ons were also discussed during the workshop; however, mostly for alue and limitations of these methods as well as challenges for their implementation. Some applications in different therapeutic areas are also summarized, in line with the discussions at the workshop. There was agreement at the workshop on the fact that selection of dose for phase III is an estimation problem and should not be addressed via hypothesis testing. Dose selection for phase III trials should be informed by well-designed dose-finding studies; however, the specific choice of method(s) will depend on several aspects and it is not possible to recommend a generalized decision tree. There are many valuable methods available, the methods are not mutually exclusive, and they should be used in conjunction to ensure a scientifically rigorous understanding of the dosing rationale.
CPT Pharmacometrics Syst. Pharmacol. (2017) **6**, 418–429; doi:10.1002/psp4.12196; published online 0 Month 2017.

There was agreement at the workshop on the fact that selection of dose for phase III is an estimation problem and should not be addressed via hypothesis testing.

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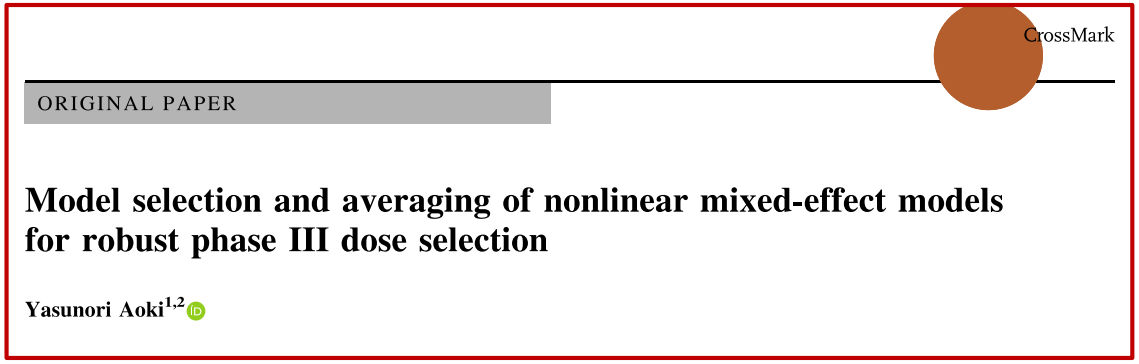
Model averaging for determining dose-response from longitudinal data



CrossMark

ORIGINAL PAPER

Model selection and averaging of nonlinear mixed-effect models for robust phase III dose selection

Yasunori Aoki[1,2]

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Placebo Model

Placebo Model + Linear

Placebo Model + Log-linear

Placebo Model + Emax

Placebo Model + Sigmoidal

Bootstrap

$$(\theta_1, \theta_2, ..., \omega_1, \omega_2, ..., \sigma_1, \sigma_2)$$
$$(\theta_1, \theta_2, ..., \omega_1, \omega_2, ..., \sigma_1, \sigma_2)$$
$$(\theta_1, \theta_2, ..., \omega_1, \omega_2, ..., \sigma_1, \sigma_2)$$
$$\vdots$$

$$(\theta_1, \theta_2, ..., \omega_1, \omega_2, ..., \sigma_1, \sigma_2)$$
$$(\theta_1, \theta_2, ..., \omega_1, \omega_2, ..., \sigma_1, \sigma_2)$$
$$(\theta_1, \theta_2, ..., \omega_1, \omega_2, ..., \sigma_1, \sigma_2)$$
$$\vdots$$

$$(\theta_1, \theta_2, ..., \omega_1, \omega_2, ..., \sigma_1, \sigma_2)$$
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$$(\theta_1, \theta_2, ..., \omega_1, \omega_2, ..., \sigma_1, \sigma_2)$$
$$\vdots$$

$$(\theta_1, \theta_2, ..., \omega_1, \omega_2, ..., \sigma_1, \sigma_2)$$
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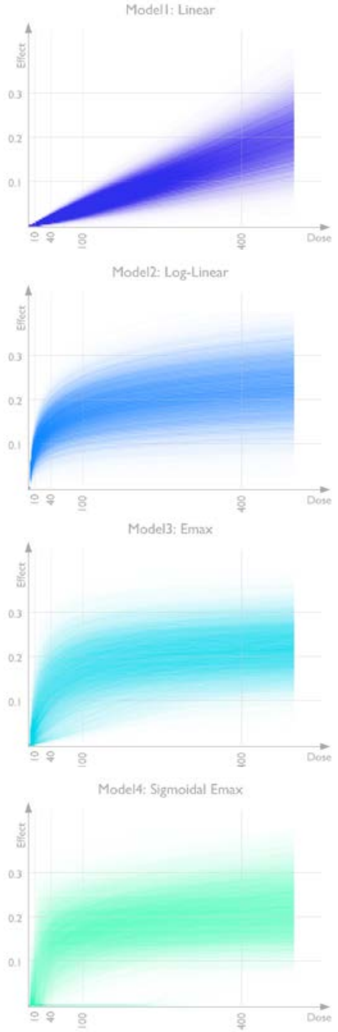
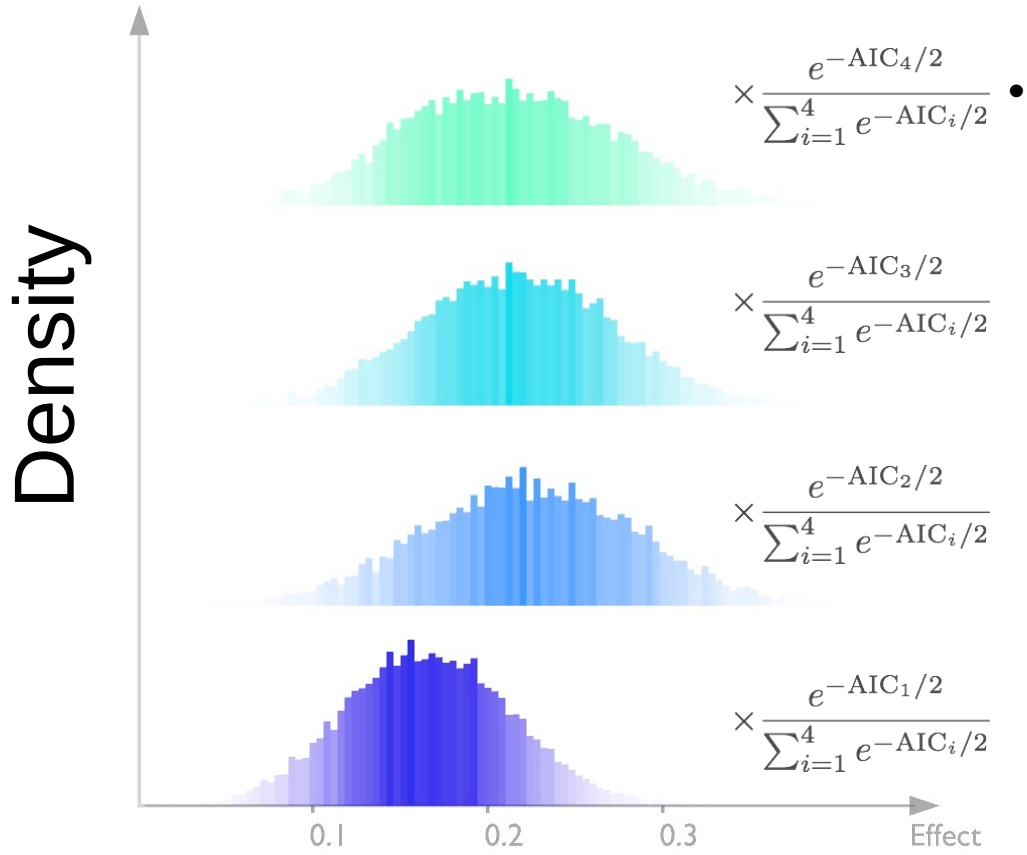
$$\vdots$$



\+
PhIIb clinical trial data

Model weighting by goodness-of-fit



- Weighting scheme proposed by Buckland et al. 1997

Effect

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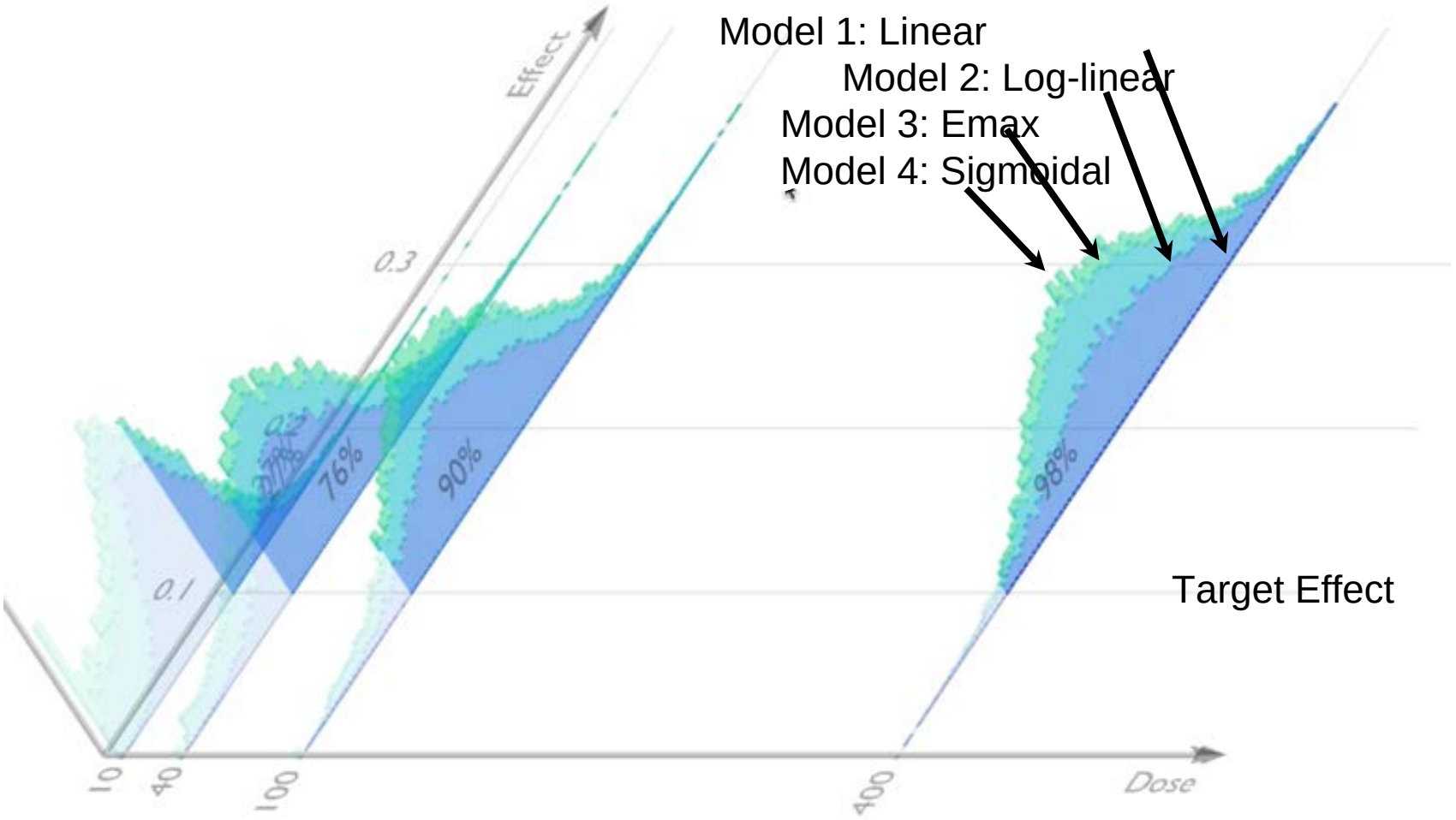
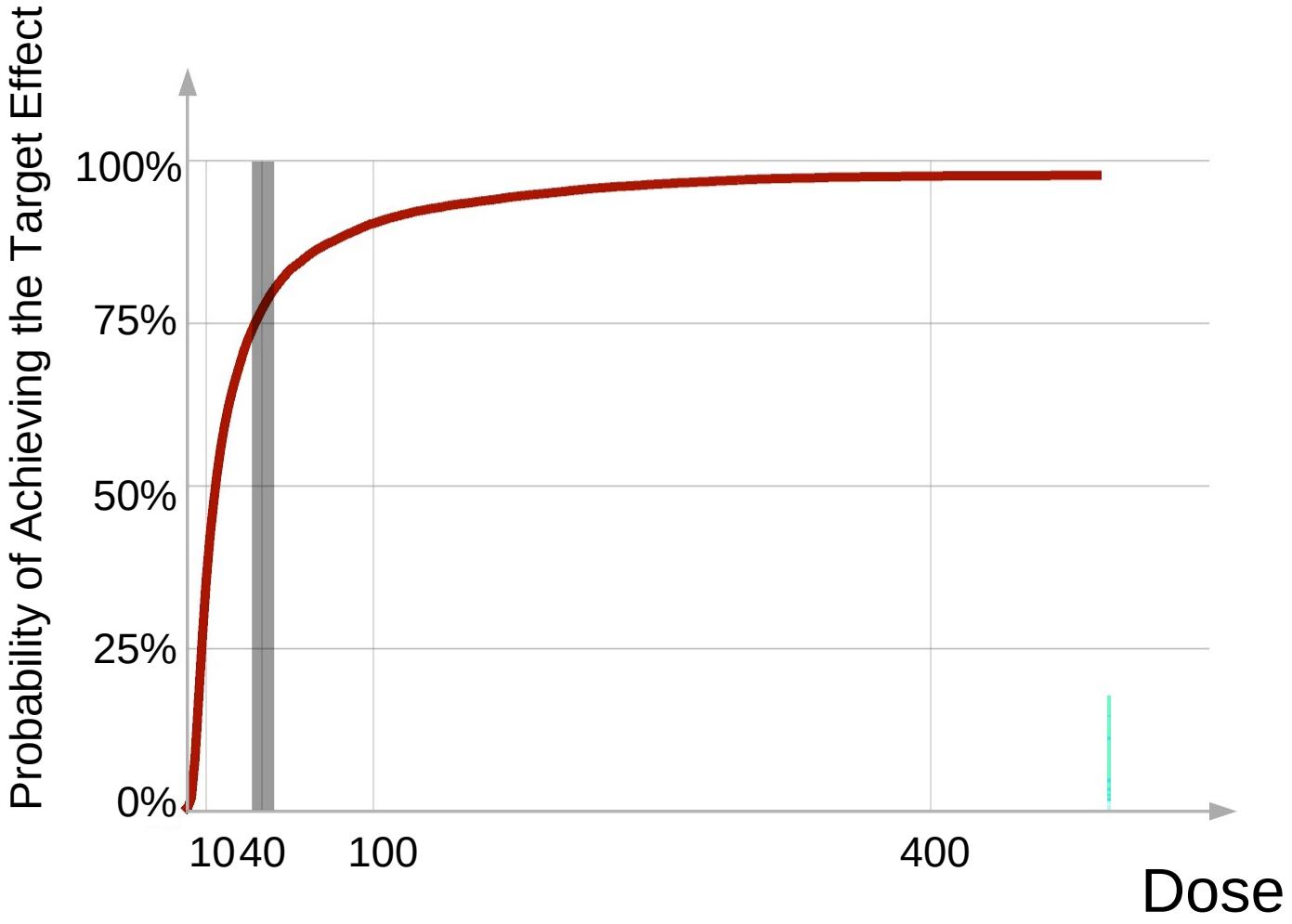
This model averaging methodology combines both the parameter estimation uncertainty and model structure uncertainty to quantify overall uncertainty



Probability of Success based on Quantified Overall Uncertainty



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Simulation Studies based on AZD 1981

	Frequencies of making the correct dose selection		
	Study Protocol (ANOVA + Averaged Effect)	Averaged Model Based	
Case 1 correct dose = 10mg	582	788	35% improvement
Case 2 correct dose = 40mg	361	592	64% improvement
Case 3 correct dose = 100mg	312	432	38% improvement
Case 4 correct dose = 400mg	402	519	29% improvement

Aoki et al. J Pharmacokinet Pharmacodyn 2017

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Received: 16 April 2019 | Revised: 14 December 2020 | Accepted: 1 February 2021

DOI: 10.1002/sim.8913

RESEARCH ARTICLE

Statistics in Medicine WILEY

cLRT-Mod: An efficient methodology for pharmacometric model-based analysis of longitudinal phase II dose finding studies under model uncertainty

Simon Buatois[1,2] | Sebastian Ueckert[3] | Nicolas Frey[2] | Sylvie Retout[2] | France Mentré[1]

Statistics in Medicine

Research Article

Received 30 April 2013, Accepted 1 November 2013 Published online 3 December 2013 in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/sim.6052

Model-based dose finding under model uncertainty using general parametric models

José Pinheiro,[a] Björn Bornkamp,[b*†] Ekkehard Glimm[b] and Frank Bretz[b]

MCP-MOD[1]	*PMX*
▪ Starting from a predefined set of dose-response candidate models:	
1. **MCP-step:** Assessment of dose-response signal using contrast test on the best model (MS)	1. Model building using multiple LRT on nonlinear mixed effect models (MS)
2. **MOD-step:** Estimate the dose-response curve using either model selection (MS) or model averaging (MA)	2. Estimate the dose-response curve using the selected model
Advantages vs PMX	**Advantages vs MCP-MOD**
• Models pre-specified • Takes model uncertainty into account • Control the type I error	• Longitudinal analysis of the data

Slide courtesy of Simon Buatois

MCP-MOD[1]

- Starting from a predefined set of dc response candidate models:

1. **MCP-step:** Assessment of dose-response signal using contrast test on the best model (MS)

2. **MOD-step:** Estimate the dose-response curve using either model selection (MS) or model averaging (MA)

Best of both worlds ?

PMX

1. Model building using multiple LRT on nonlinear mixed effect models (MS)

2. Estimate the dose-response curve using the selected model

Advantages vs PMX

- Models pre-specified
- Takes model uncertainty into account
- Control the type I error

Advantages vs MCP-MOD

- Longitudinal analysis of the data

Slide courtesy of Simon Buatois

MCP-MOD[1]

cLRT-MOD

Predefined set of dose-response candidate models:

1. **MCP-step:** Assessment of dose-response signal using contrast test on the best model (MS)

1. **cLRT-step:** Assessment of dose-response signal using a corrected-Likelihood Ratio Test[2]

2. **MOD-step:** Estimate the dose-response curve using either model selection (MS) or model averaging (MA)

[1] Bretz F . *et al*, Biometrics, 2005

[2] Dette H. et al, Biometrics, 2015

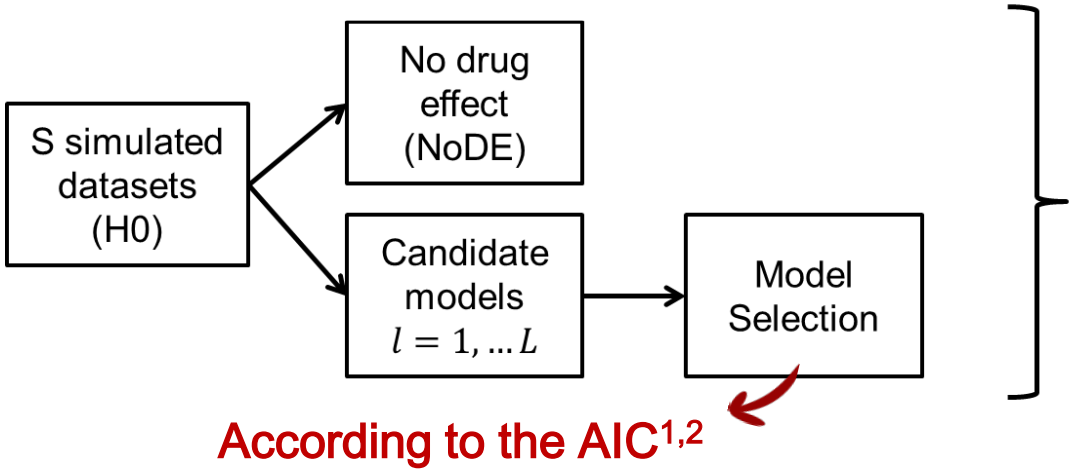
Slide courtesy of Simon Buatois

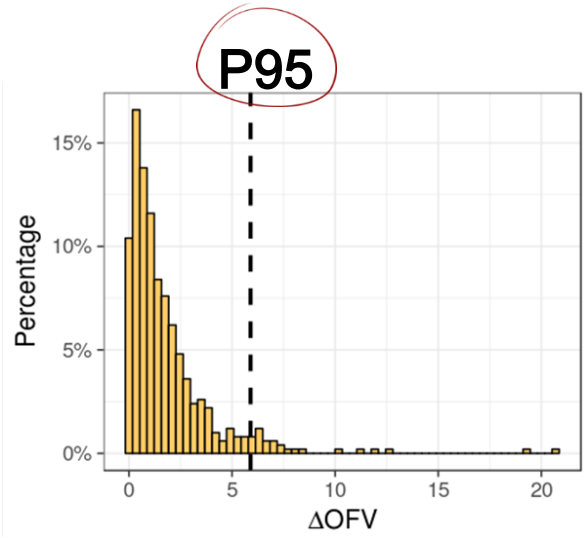
I. Corrected-LRT step:

- Observed dataset:

$$2LL\left(y, \hat{\Psi}_{NoDE}\right) - 2LL\left(y, \hat{\Psi}_{MS}\right) = \Delta OFV_{obs}$$

- cLRT statistic:





[1] Aoki Y. et al, JPKPD, 2017
[2] Buatois S. et al, AAPS, 2018

Slide courtesy of Simon Buatois

Assessments of a treatment effect with **I**ndividual **M**odel **A**veraging (IMA)

	Base model (H0)	**Full model (H1)**
STD	$f(BASE, PLB)$	$f(BASE, PLB, DRUG * TRT)$
IMA	Mixture 1: $f(BASE, PLB)$ Mixture 2: $f(BASE, PLB, DRUG)$	
	Mixture probability fixed to randomization: P(1) = 0.5 P(2) = 1 - P(1)	Mixture probability estimated: P(1) = **TRT***(1-θ_{MIX}) + (1-**TRT**)*θ_{MIX} P(2) = 1 - P(1)

Chasseloup et al PAGE 28 (2019) Abstr 9149 [www.page-meeting.org/?abstract=9149]

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Clinical data sets – placebo or natural history data

Likert pain score (categorical data) from 230 patients with neuropathic pain[3,4] followed-up for 4 months

Seizure (count data) from 500 epileptic patients[5] followed-up for 3 months

ADAS-Cog (continuous data): natural history of 800 patients with Alzheimer's disease[6] followed-up for 36 months

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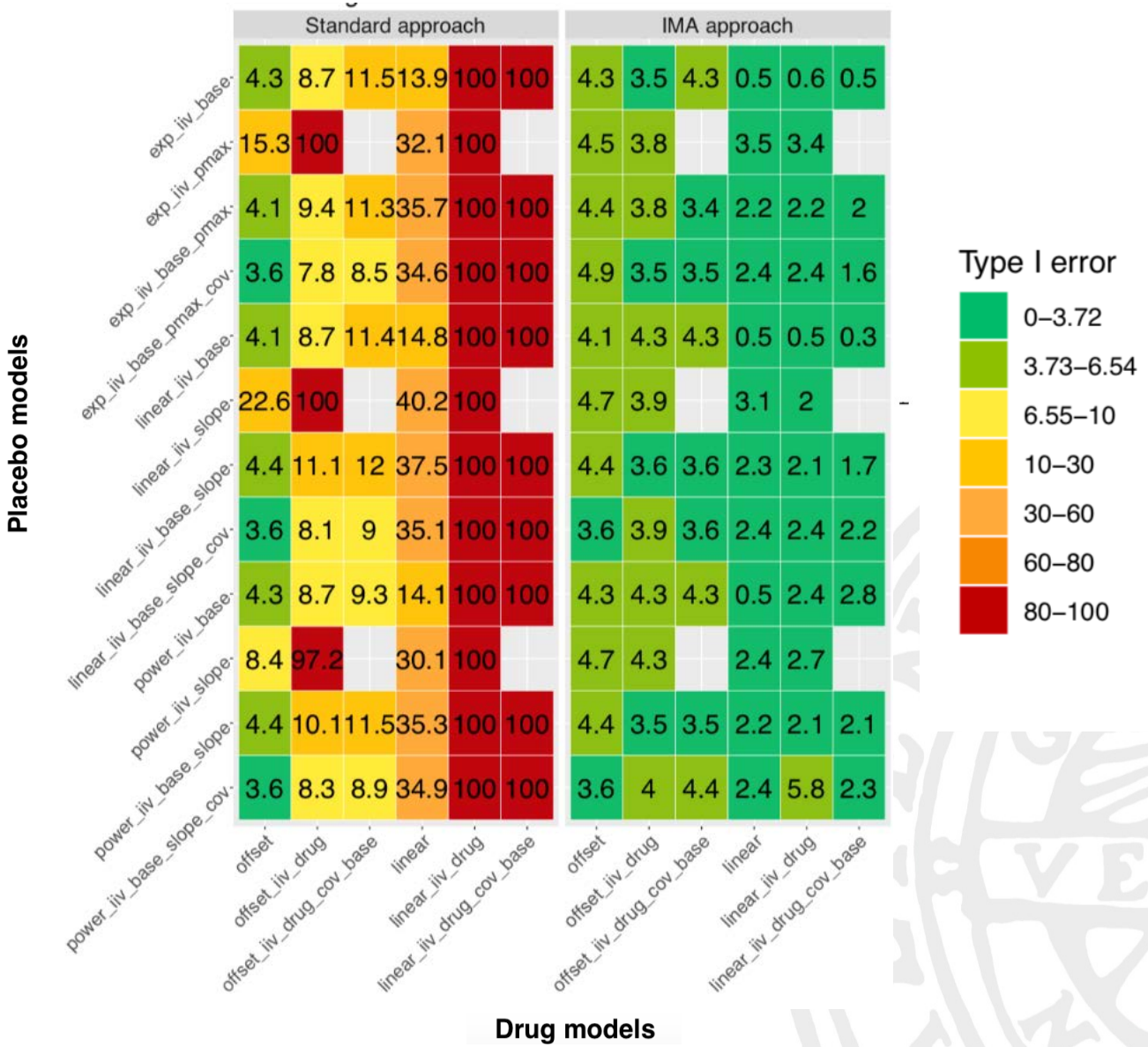
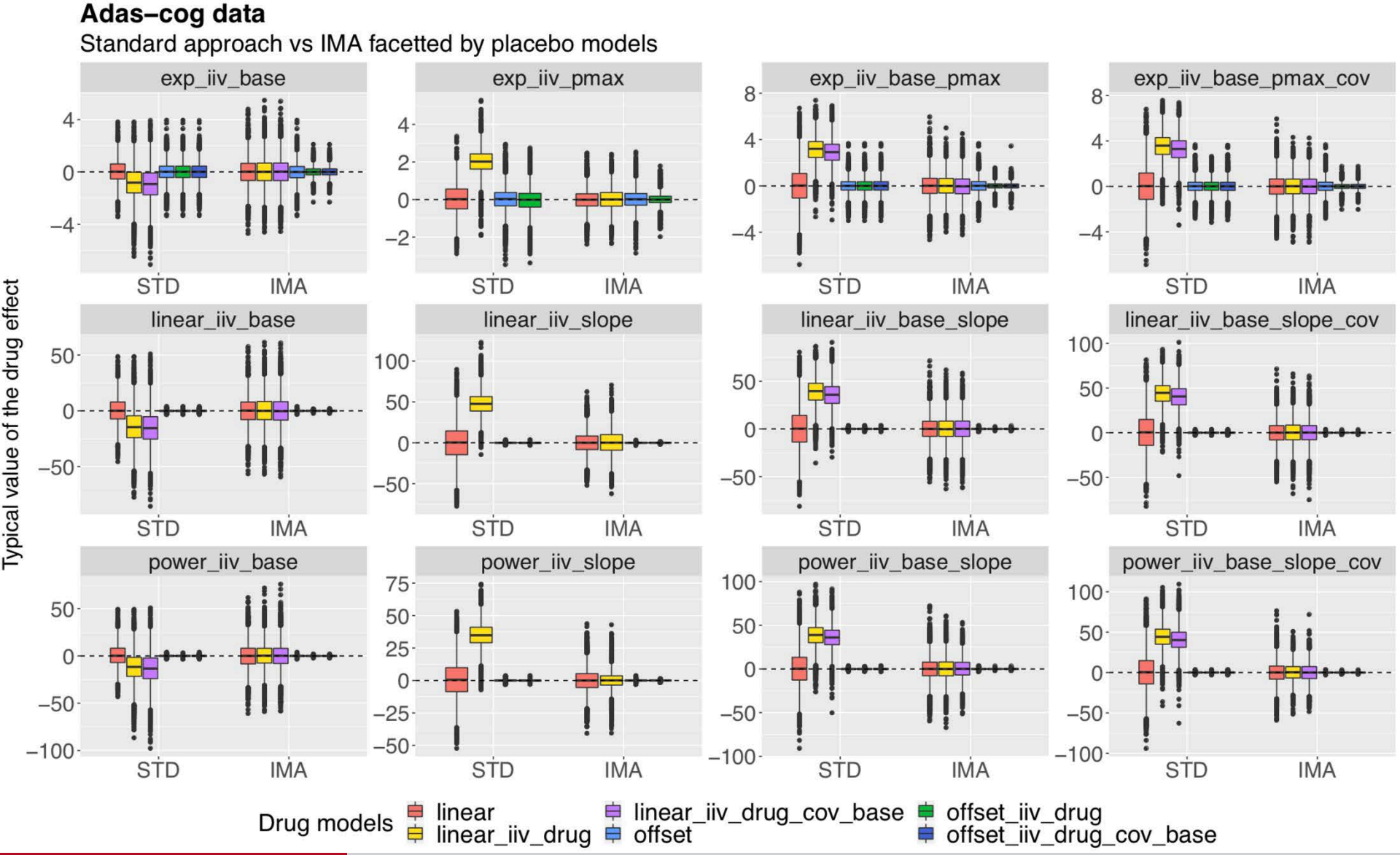
Procedure to assess type 1 error

- **For each data set (Pain, Seizures and ADAS-Cog), placebo patients were randomized 1:1 to TRT=0 (“placebo”) or TRT=1 (“active”)**
- **This creates a data set similar to a two-arm trial, where the “active” treatment has zero effect**
- **The randomization was repeated to generate 1000 data sets for each disease**

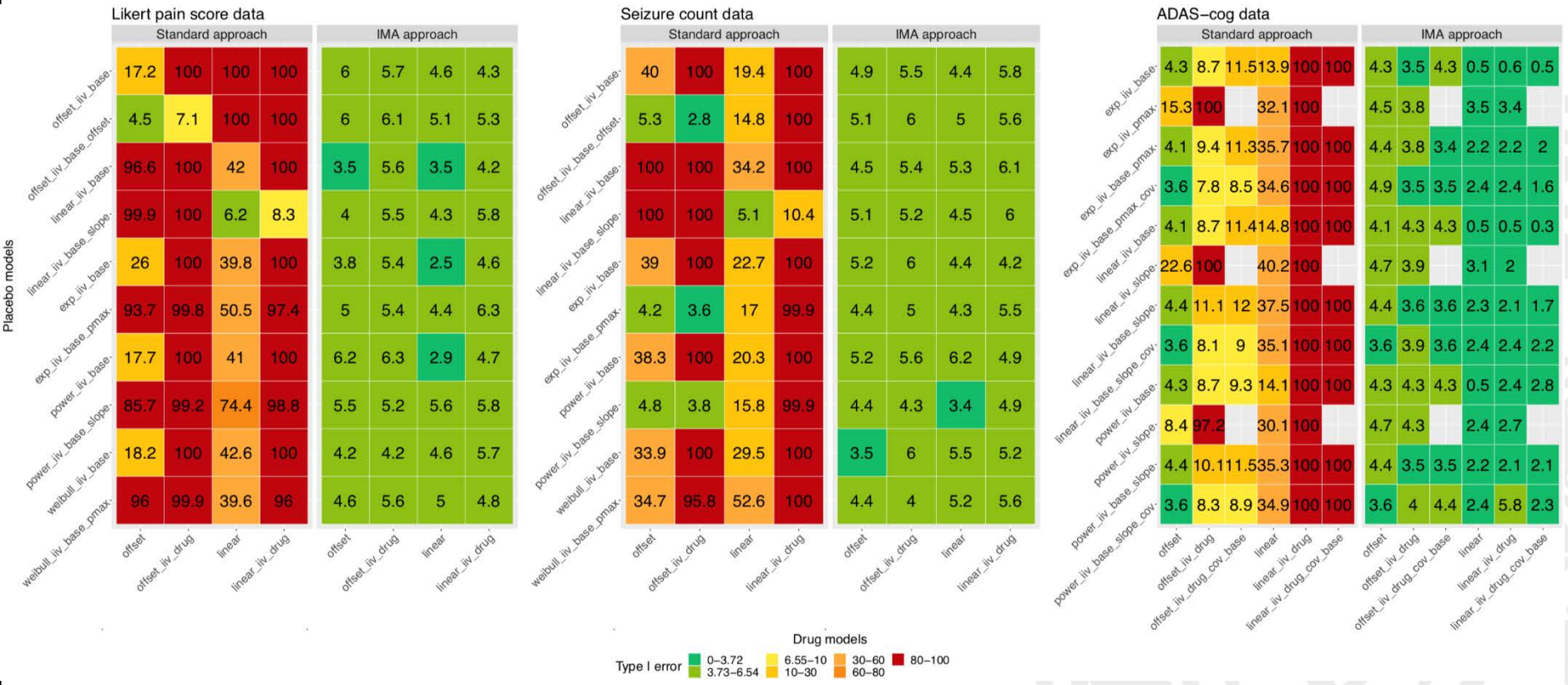
ADAS-Cog data – STD and IMA



ADAS-Cog – drug effect estimates



Type 1 error rates – STD and IMA
Pain, Seizures & ADAS-Cog



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Summary IMA vs STD approach

- Type 1 error rates:
  - typically inflated for standard approach
  - controlled for individual model averaging (IMA)

- Drug effect estimates
  - typically biased for standard approach
  - unbiased for individual model averaging (IMA)

Rare diseases: Example of single-subject customized antisense oligonucleotide treatment

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Patient-Customized Oligonucleotide Therapy for a Rare Genetic Disease

1 year

- Genetic diagnosis
- AON design
- Tests in fibroblasts
- Tox studies in rats
- First treatment

Kim et al, 2019, NEJM

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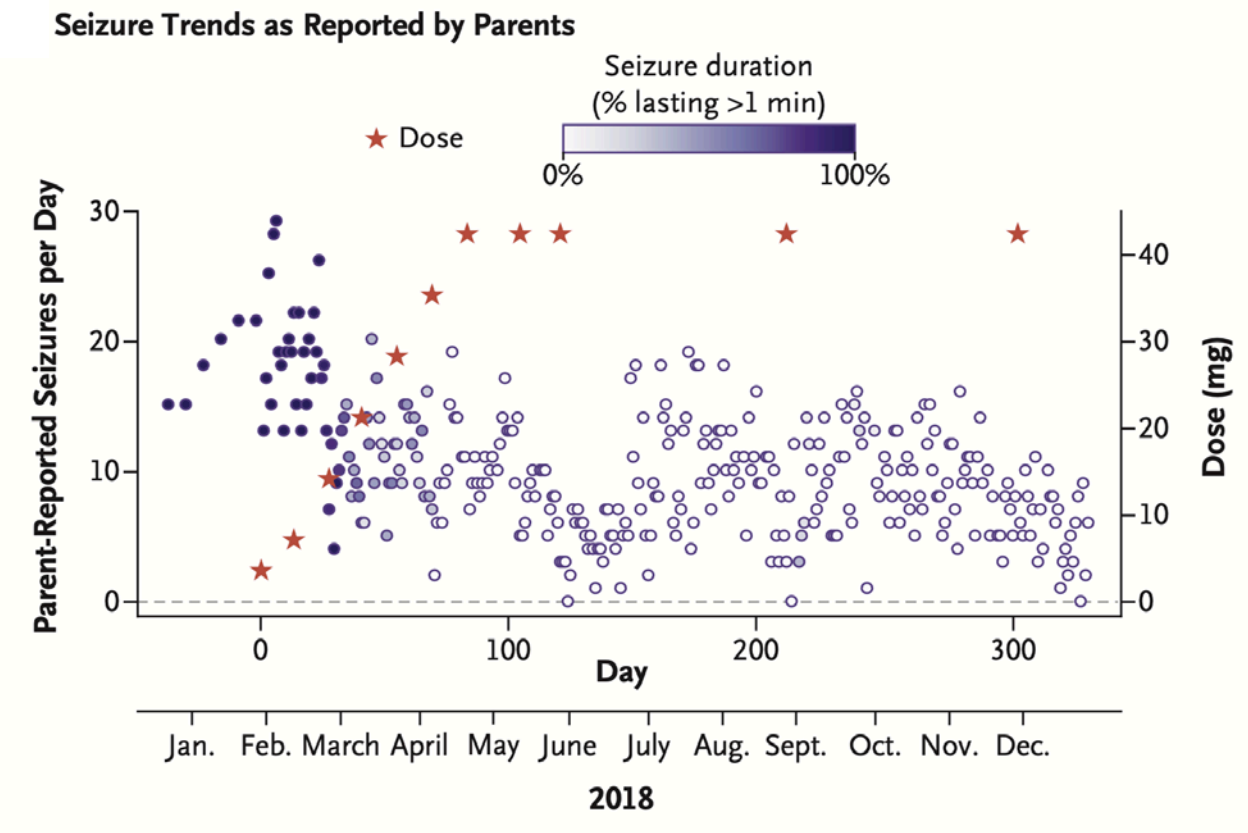
Milasen treatment: first year



Kim et al, 2019, NEJM

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Response from FDA

Drug Regulation in the Era of Individualized Therapies

Janet Woodcock, M.D., and Peter Marks, M.D., Ph.D.

Kim et al., in a report now published in the *Journal*,[1] describe the discovery, development, and administration of an antisense oligonucleotide (ASO) therapy specifically designed for a single patient with CLN7 neuronal ceroid lipofuscinosis (a form of Batten's disease), a fatal genetic neurodegenerative disorder.[2] In this patient, a known pathogenic point mutation was found to be present in one copy of the gene *MFSD8* (also known as *CLN7*), and a previously undescribed insertion of a retrotransposon was present in the other copy. Retrotransposons are stretches of DNA that are sometimes described as mobile elements; thousands are present in the human genome, and some are capable of moving to a new location — such as the middle of a gene — through a "copy and paste" mechanism. The authors showed that the retrotransposon insertion in this patient led to missplicing of the *MFSD8* messenger RNA (mRNA) and probably to premature translational termination. The authors devised candidate ASOs that were intended to "correct" the missplicing of the mRNA and selected a candidate ASO that, in cultured patient fibroblasts, resulted in an increase in the ratio of normal to mutant mRNA. Evaluation of lysosomal function in vitro showed improvements in the presence of the ASO. After an abbreviated toxicologic evaluation and after obtaining authorization from the Food and Drug Administration (FDA) and expedited institutional review board approval, could ultimately be treated affect the decision-making process?

In addition, how will efficacy be evaluated? At the very least, during the time needed to discover and develop an intervention, quantifiable, objective measures of the patient's disease status should be identified and tracked, since, in an N-of-one experiment, evaluation of disease trends before and after treatment will usually be the primary method of assessing effectiveness. In this regard, there is precedent for the application of new efficacy measures to the study of small numbers of patients.[5]

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Concluding remarks

- Longitudinal data analysis using pharmacometric (NLME) models are already an important tool in drug development
- Such analyses use available data very efficiently and are for that reason attractive
- To date, their use in primary analyses has been limited, but this may change as
  - the insight in their advantages is increasing
  - the methodology for their use is maturing
  - situations where good alternatives are lacking is increasing