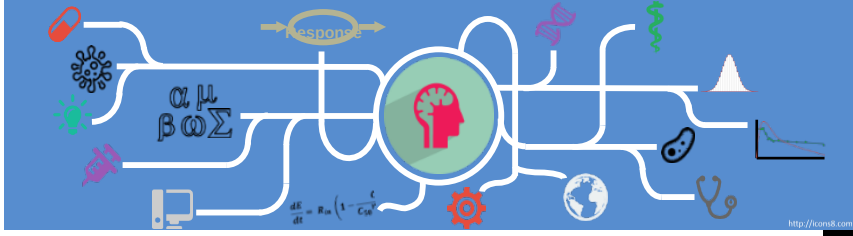


BRIDGING THE GAP BETWEEN PHARMACOMETRICIANS AND STATISTICIANS IN CLINICAL PHARMACOLOGY AND THERAPEUTICS

PR FRANCE MENTRÉ, PHD, MD

UNIVERSITY PARIS DIDEROT – INSERM – IAME

BIOSTATISTICAL MODELLING AND PHARMACOMETRICS

ASCPT - March 2017

Outline

1. **Pharmacometrics**
2. **Statisticians in pharmacometrics**
3. **Model evaluation: a core set of graphs**
4. **Design in pharmacometrics**
5. **Dose of favipiravir in Ebola infection**
6. **Bridging the gap between statisticians and pharmacometricians**

1. PHARMACOMETRICS

Started by Lew Sheiner

An impressive scientist who created a new discipline!

- **Web of Science**
  - 234 publications
  - 13,070 citations
  - H index = 59

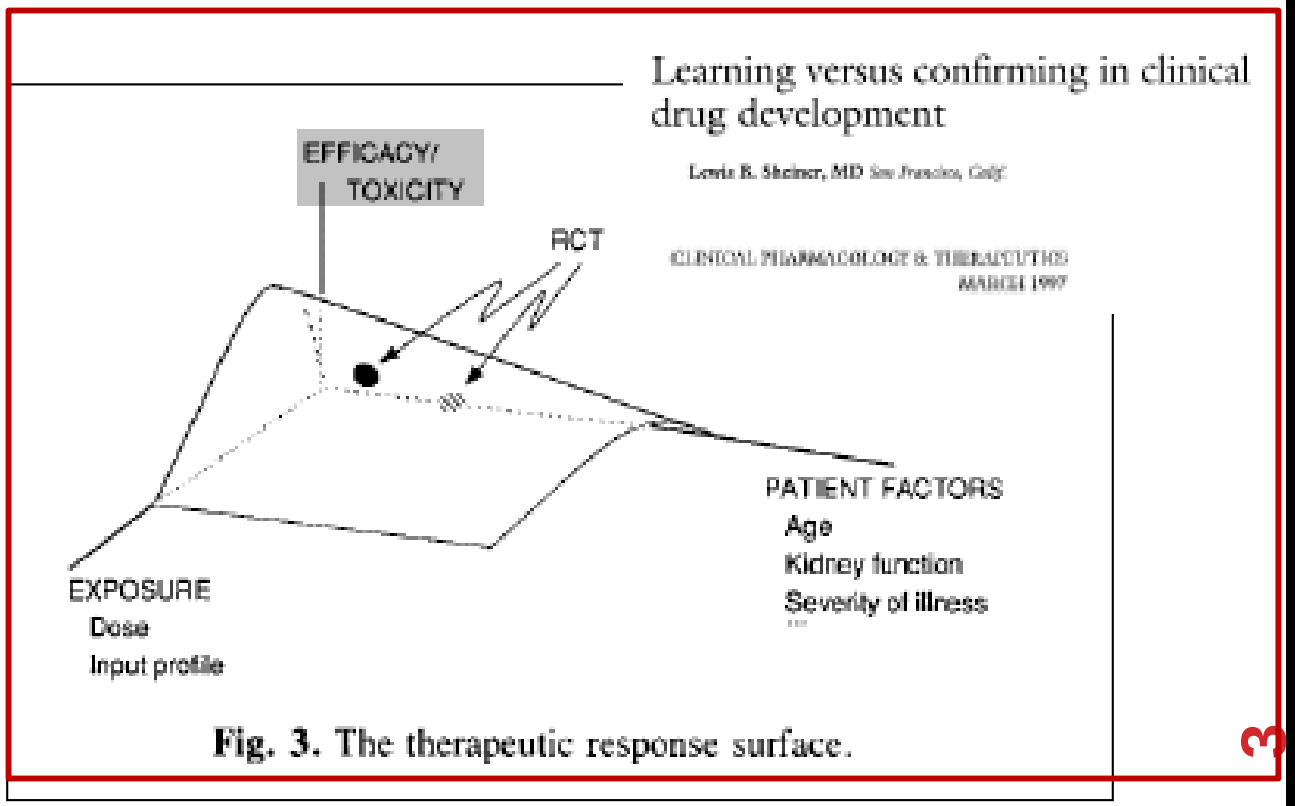


Fig. 3. The therapeutic response surface.

Impact of the Pharmaceutical Sciences on Health Care: A Reflection over the Past 50 Years

Journal of Pharmaceutical Sciences, Vol. 101, 4075–4099 (2012)

MALCOLM ROWLAND,[1,2] CHRISTIAN R. NOE,[3] DENNIS A. SMITH,[4,5] G. T. TUCKER,[6,7] DAAN J. A. CROMMELIN,[8] CARL C. PECK,[2] MARIO L. ROCCI Jr.,[9] LUC BESANÇON,[10] VINOD P. SHAH[10]

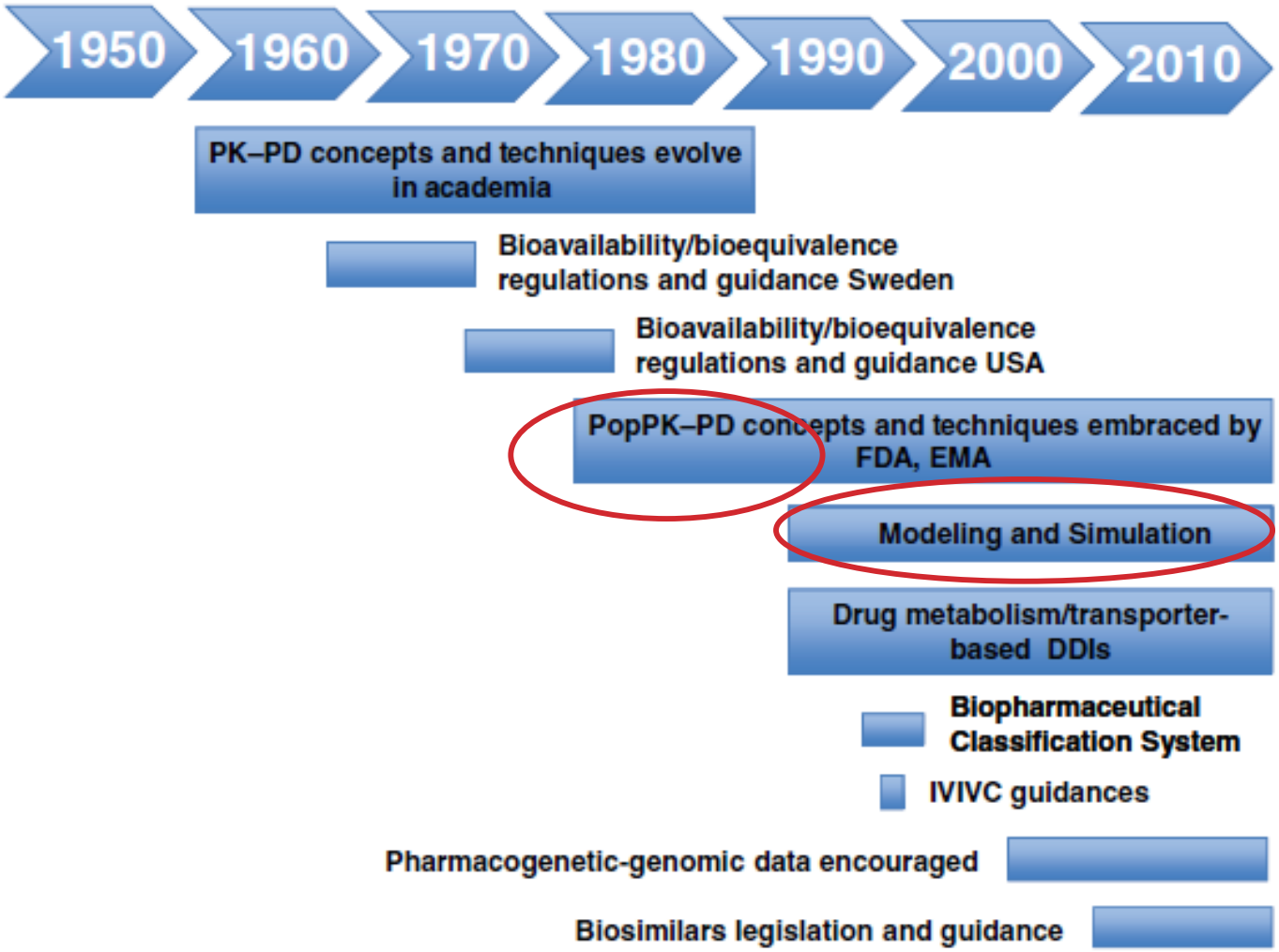
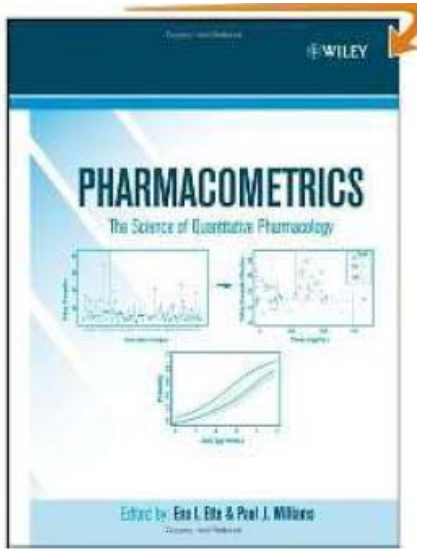


Figure 5. Timeline of introduction of some key developments and guidances in drug regulation.

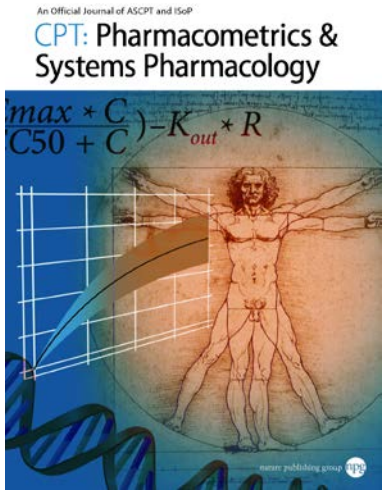
Pharmacometrics in the world

- **Conferences**
  - PAGE (1992-)
  - ACOP (2005-)
  - WCOP (2012-)

- **Book**
  - Pharmacometrics (2007)



- **Journal**
  - CPT: PSP (2012-)
- **Society**
  - ISOP (2012-)



From PopPK to MID3

- **Population pharmacokinetics (PopPK)**
- **Population pharmacokinetics /pharmacodynamics (Pop PKPD)**
- **Nonlinear mixed effect models (NONMEM, NLMEM)**
- **Modelling and Simulation (M&S)**
- **Pharmacometrics (PMX)**
- **Model Based Drug Development (MBDD)**
- **Model Informed Drug Development (MIDD)**
- **Model Informed Drug Discovery and Development (MID3)**

Model Based Drug Development

nature publishing group

STATE OF THE ART

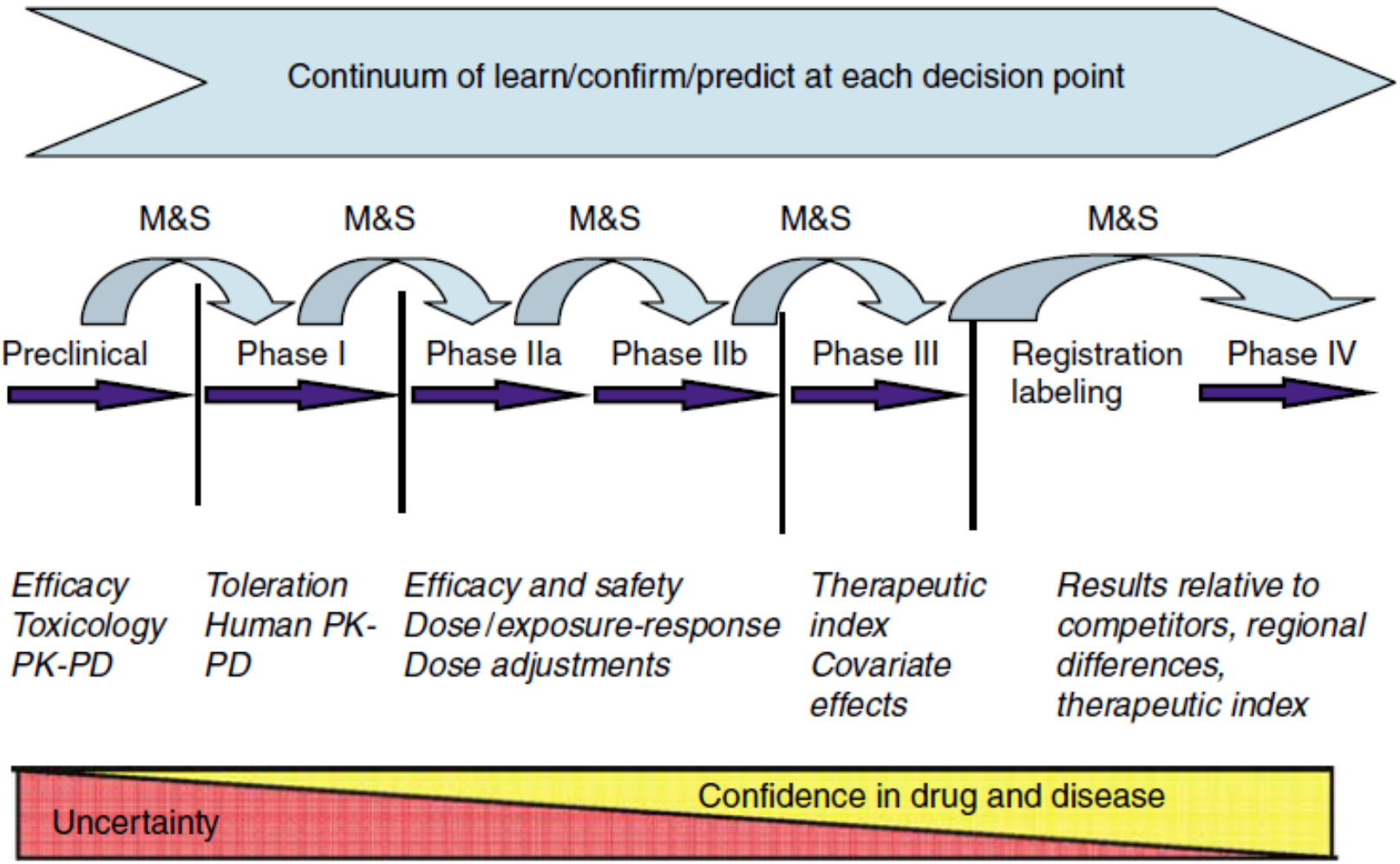
Model-based Drug Development

RL Lalonde[1], KG Kowalski[2], MM Hutmacher[1], W Ewy[2], DJ Nichols[1], PA Milligan[1], BW Corrigan[1], PA Lockwood[1], SA Marshall[1], LJ Benincosa[1], TG Tensfeldt[1], K Parivar[1], M Amantea[1], P Glue[1], H Koide[1] and R Miller[1]

The low productivity and escalating costs of drug development have been well documented over the past several years. Less than 10% of new compounds that enter clinical trials ultimately make it to the market, and many more fail in the preclinical stages of development. These challenges in the "critical path" of drug development are discussed in a 2004 publication by the US Food and Drug Administration. The document emphasizes new tools and various opportunities to improve drug development. One of the opportunities recommended is the application of "model-based drug development (MBDD)." This paper discusses what constitutes the key elements of MBDD and how these elements should fit together to inform drug development strategy and decision-making.

VOLUME 82 NUMBER 1 | JULY 2007 | www.nature.com/cpt

Drug development and model building
Learning and confirming



Model Informed Drug Discovery and Development

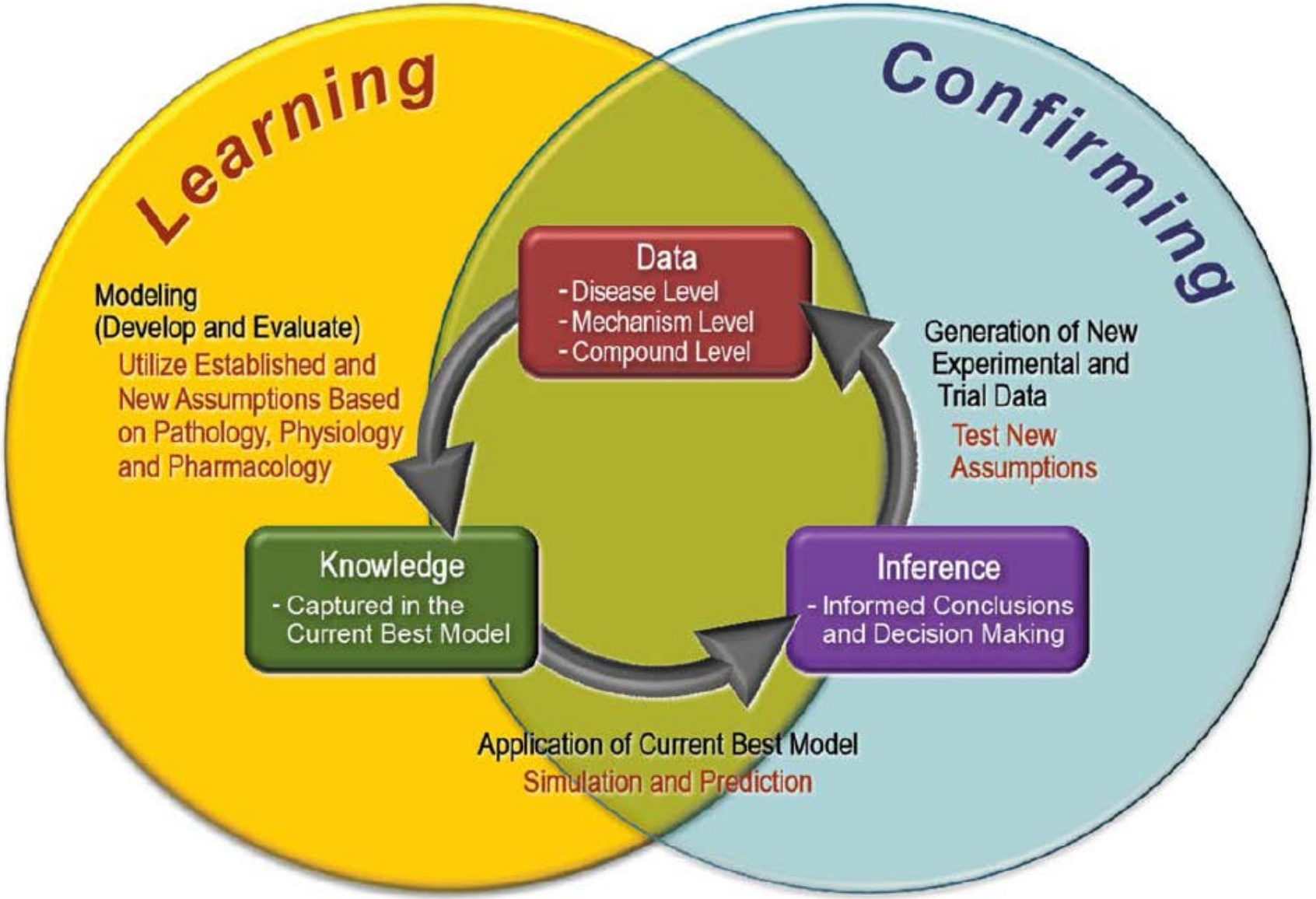
Citation: CPT Pharmacometrics Syst. Pharmacol. (2016) 5, 93–122; doi:10.1002/psp4.12049

WHITE PAPER

Good Practices in Model-Informed Drug Discovery and Development: Practice, Application, and Documentation

EFPIA MID3 Workgroup: SF Marshall[1]*, R Burghaus[2], V Cosson[3], SYA Cheung[4], M Chenel[5], O DellaPasqua[6], N Frey[3], B Hamrén[7], L Harnisch[1], F Ivanow[8], T Kerbusch[9], J Lippert[2], PA Milligan[1], S Rohou[10], A Staab[11], JL Steimer[12], C Tornøe[13] and SAG Visser[14]

This document was developed to enable greater consistency in the practice, application, and documentation of Model-Informed Drug Discovery and Development (MID3) across the pharmaceutical industry. A collection of ''good practice'' recommendations are assembled here in order to minimize the heterogeneity in both the quality and content of MID3 implementation and documentation. The three major objectives of this white paper are to: i) inform company decision makers how the strategic integration of MID3 can benefit R&D efficiency; ii) provide MID3 analysts with sufficient material to enhance the planning, rigor, and consistency of the application of MID3; and iii) provide regulatory authorities with substrate to develop MID3 related and/or MID3 enabled guidelines.


Learning
Confirming
Modeling
(Develop and Evaluate)
Utilize Established and
New Assumptions Based
on Pathology, Physiology
and Pharmacology
Data
- Disease Level
- Mechanism Level
- Compound Level
Generation of New
Experimental and
Trial Data
Test New
Assumptions
Knowledge
- Captured in the
Current Best Model
Inference
- Informed Conclusions
and Decision Making
Application of Current Best Model
Simulation and Prediction

Pop PKPD: the beginning

- **Continuous variables**
- **Short time scale**
- **Exploratory studies**
- **Early phases in drug development**

➢ **Mainly learning**

Pharmacometrics now

- **Clinical end points**
  - Longer time scale
  - Pivotal/confirming phases
  - Discrete variables and time to event
  - Disease progression
- **Results use for prediction / simulation**
  - Extrapolation
  - Planning / Design evaluation
  - Clinical trial simulation
  - Decision making…

➢ **More attention to model building / estimation / uncertainties in inference**

“I know nothing about statistics”

- A Pharmacometrician, yesterday

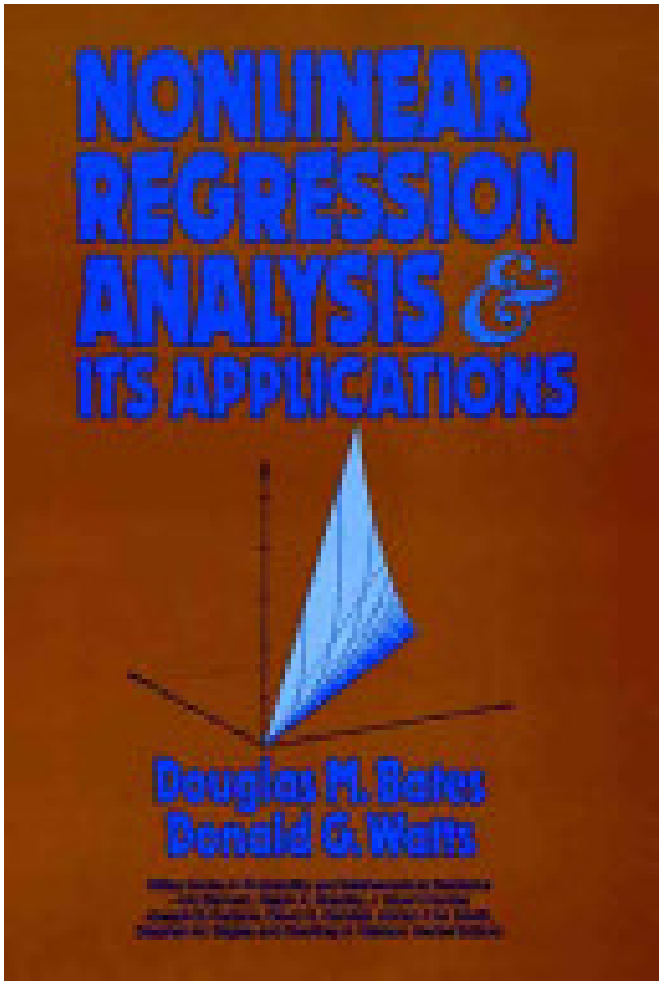
But you’re fitting **nonlinear mixed effect models** using maximum likelihood**, SAEM** or **MCMC,** using **likelihood ratio tests** to determine **significance**, **covariate search techniques**, considering collinearity, performing **model diagnostics**, **simulating new outcomes** , evaluating **decision criteria**, using **optimal design theory**…

Most of these topics would scare the living crap out of a graduate statistician.

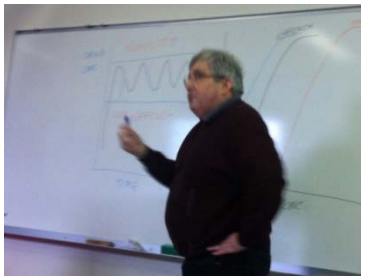
From Mike K Smith (Pfizer), ACOP7

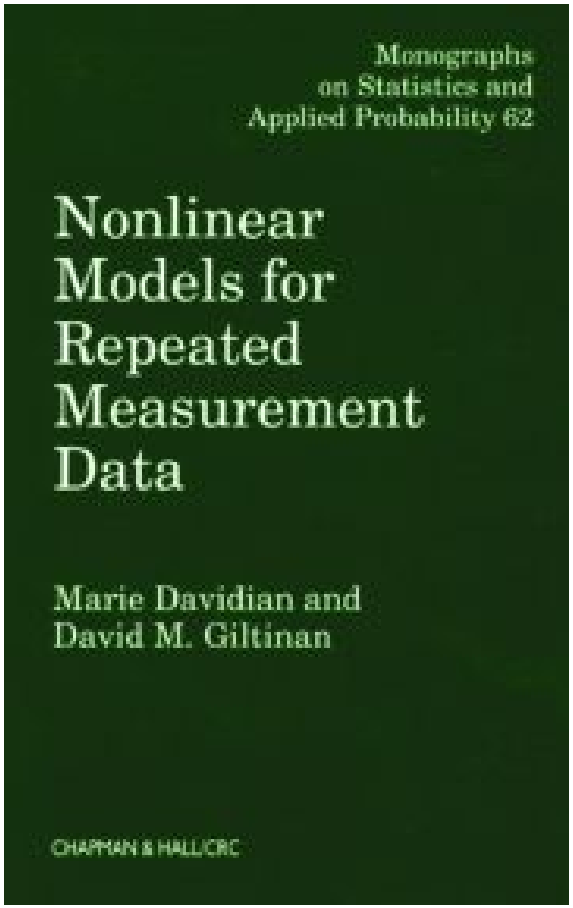
2. STATISTICIANS IN PHARMACOMETRICS

- **Estimation algorithms for NLMEM**
- **Statistical inference**
- **Model evaluation**
- **Optimal Design**
- **Decision making**
- **…**

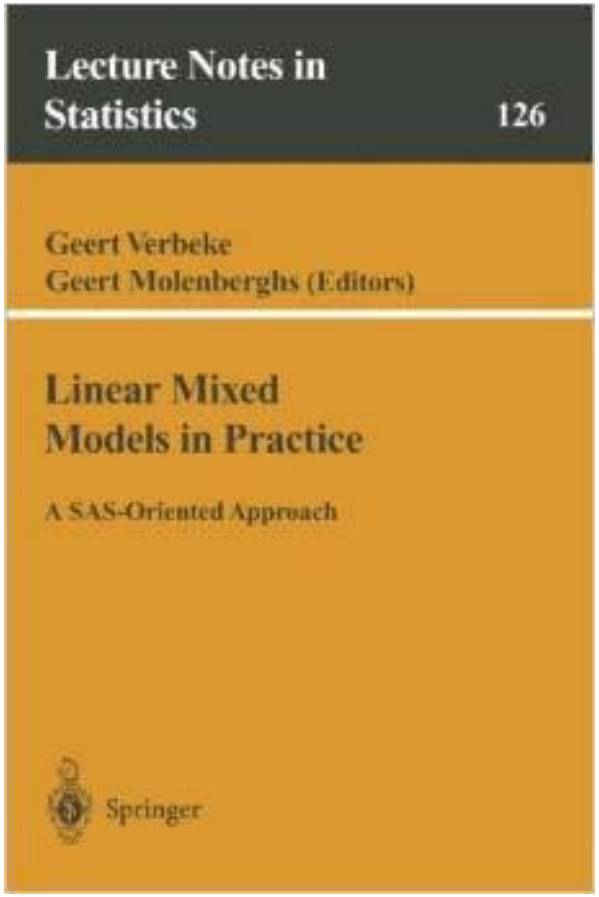

NONLINEAR
REGRESSION
ANALYSIS &
ITS APPLICATIONS
Douglas M. Bates
Donald G. Watts

1985

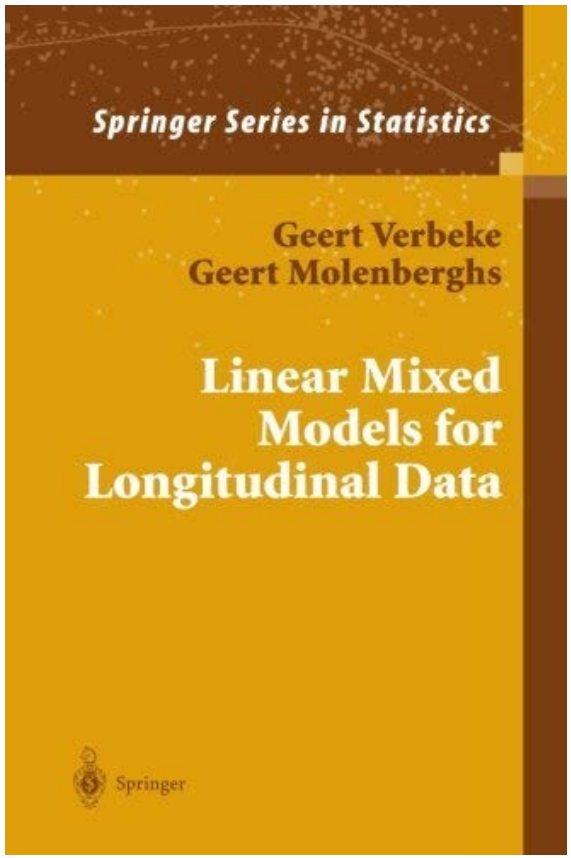


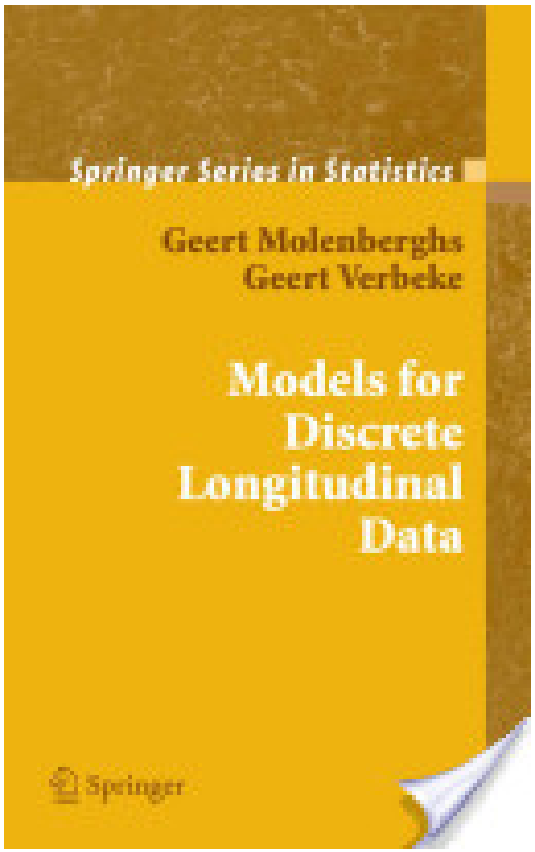

Monographs
on Statistics and
Applied Probability 62
Nonlinear
Models for
Repeated
Measurement
Data
Marie Davidian and
David M. Giltinan
CHAPMAN & HALL/CRC

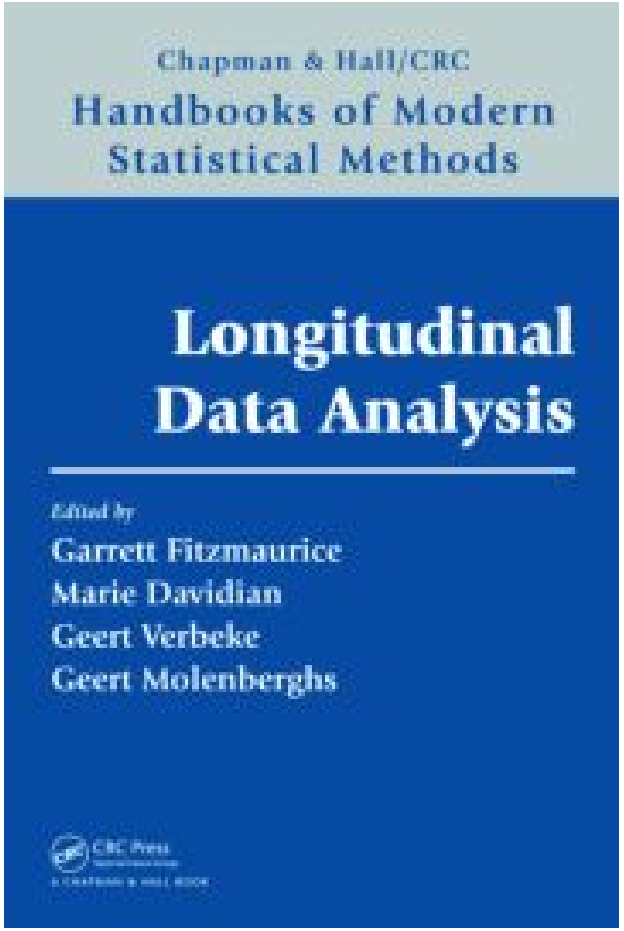
1995


Lecture Notes in
Statistics
126
Geert Verbeke
Geert Molenberghs (Editors)
Linear Mixed
Models in Practice
A SAS-Oriented Approach
Springer

1997



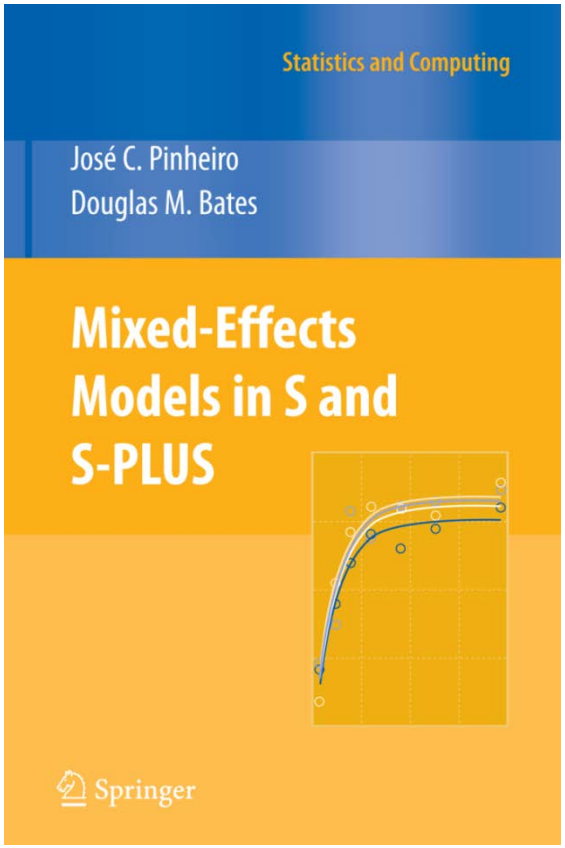


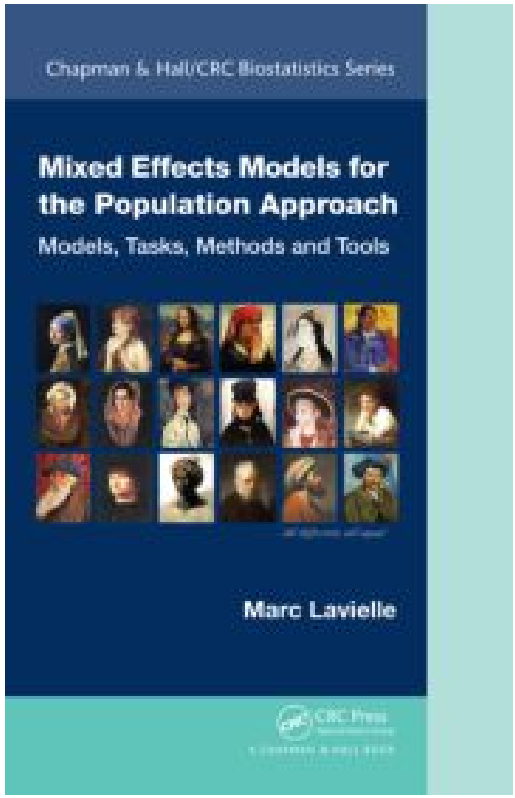


2000

2005

2008

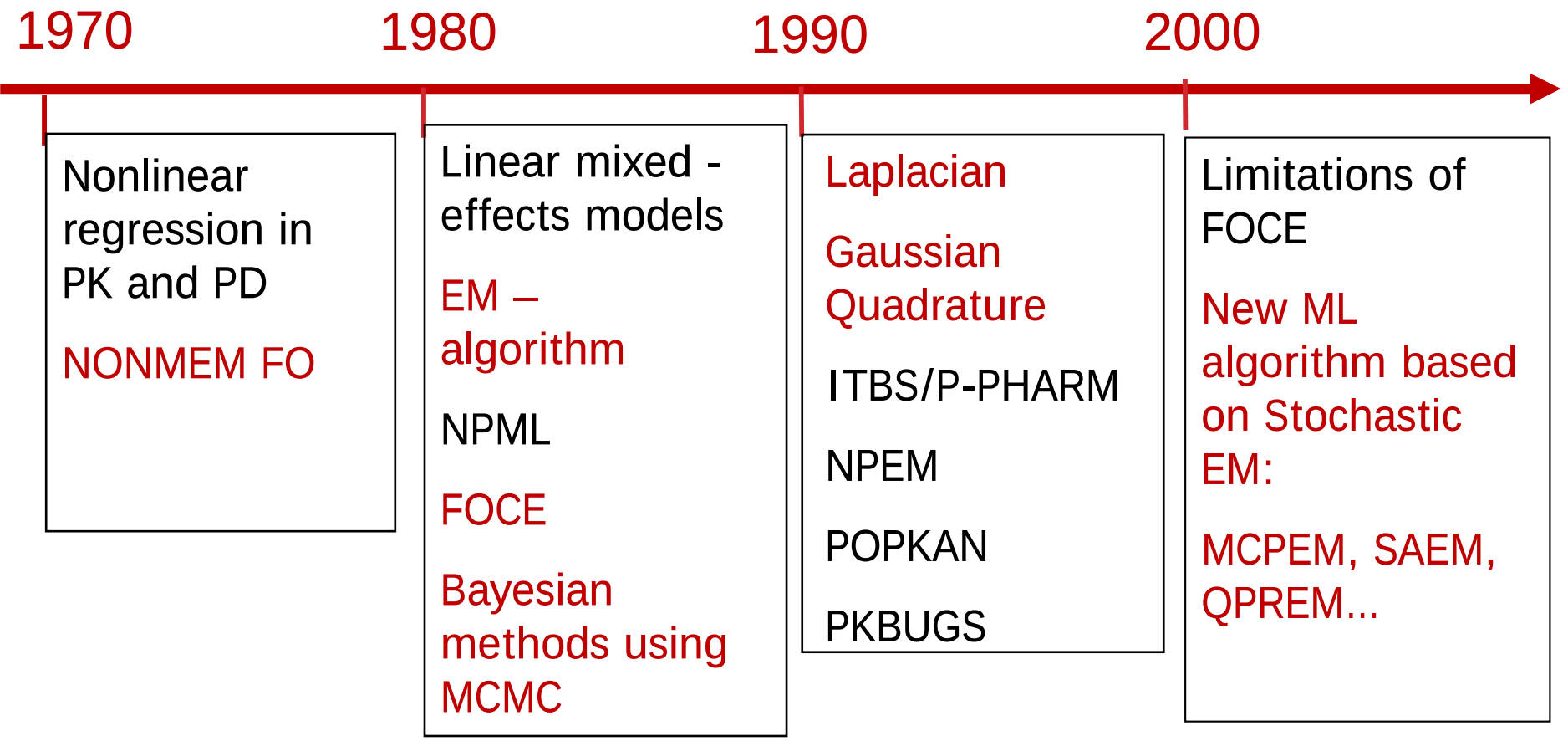

Statistics and Computing
José C. Pinheiro
Douglas M. Bates
Mixed-Effects Models in S and S-PLUS
Springer


Chapman & Hall/CRC Biostatistics Series
Mixed Effects Models for the Population Approach
Models, Tasks, Methods and Tools
Marc Lavielle

2009

2014

Development of estimation methods in NLMEM



Pillai, Mentré, Steimer (2005). Non-linear mixed effects modeling - from methodology and software development to driving implementation in drug development science. *J Pharmacokin Pharmacodyn*, 32:161-83.

Mould & Upton, **Basic concepts in population modeling, simulation and model-based drug development,** CPT: Pharmacomet Syst Pharmacol Pharm Sci 2012; 1:e6.

Table 4 Timeline for population modeling software development

Year	Event	Description
1972	Concept of "population pharmacokinetics"	The concept was published
1977	The first population pharmacokinetic analysis conducted	Application to digoxin data
1980	Announcement of NONMEM	An IBM-specific software for population pharmacokinetics
1984	NONMEM 77	A "portable" version of NONMEM
1989	NONMEM III	An improved user-interface with the NMTRAN front end. NONMEM Users Guide published
1989	BUGS software group forms	Different method: Markov chain Monte Carlo method
1991	USC*PACK	Different method: nonparametric population pharmacokinetic modeling (NPEM)
1992	NONMEM IV	New methods: FOCE

Mould & Upton, **Basic concepts in population modeling, simulation and model-based drug development,** CPT: Pharmacomet Syst Pharmacol Pharm Sci 2012; 1:e6.

Table 4 Timeline for population modeling software development

Year	Event	Description
1992	Publication with NPEM	First publication using NPEM method
1998	NONMEM V	New methods: mixture models
2001	Winbugs publication	First publication using Winbugs
2002	Publication with PKBUGs	Winbugs application designed for pharmacokinetic models
2003	Monolix Group Forms	Different method: stochastic approximation expectation maximization (SAEM)
2003	WinNonMix publication	Population modeling software with graphical user interface
2006	NONMEM VI	New methods: centering, HYBRID, nonparametric
2006	Monolix publications	First publications using Monolix
2009	Phoenix NLME	User-friendly GUI
2010	NONMEM 7	New methods: Bayes, SAEM, and others, parallel processing enabled
2012	Monolix 4.1	Full-script version (MLXTRAN, XML) and/or user-friendly GUI

Statisticians and estimation in NLMEM

Last decades

- **Development of good estimation methods and fast algorithms**

Present/ Future for estimation

- **More complex statistical models**
  - discrete data, RTTE, Markov model, joint models, dropouts, confounding, nonparametric, distributions, mixtures ….
- **More complex mechanistic models**
  - ODE, PDE, SDE….
- **Bayesian approaches** (HMC in STAN)
- **Better use of computers** (cloud, GPU,…)

➢ **Engineers, Computer scientists, Mathematicians, Statisticians….**

➢ **Enhanced (and new) software tools**

(Reseach) topics in statistics for NLMEM

- **Uncertainty estimation and propagation**
- **Model evaluation**
- **Covariate model building**
- **Optimal design**
- **Tests and inference for ‘small’ samples**
- **Model averaging**
- **Joint models: prediction of event from biomarker evolution**
- **Pooling data from various sources**
- **Multiplicity and type I error control**
- **…**

3. MODEL EVALUATION: A CORE SET OF GRAPHS

Citation: CPT Pharmacometrics Syst. Pharmacol. (2017) 6, 87–109; doi:10.1002/psp4.12161

TUTORIAL

Model Evaluation of Continuous Data Pharmacometric Models: Metrics and Graphics

THT Nguyen[1], M-S Mouksassi[2], N Holford[3], N Al-Huniti[4], I Freedman[5], AC Hooker[6], J John[7], MO Karlsson[6], DR Mould[8], JJ Pérez Ruixo[9], EL Plan[10], R Savic[11], JGC van Hasselt[12], B Weber[13], C Zhou[14], E Comets[1,15] and F Mentré[1]*
for the Model Evaluation Group of the International Society of Pharmacometrics (ISoP) Best Practice Committee

This article represents the first in a series of tutorials on model evaluation in nonlinear mixed effect models (NLMEMs), from the International Society of Pharmacometrics (ISoP) Model Evaluation Group. Numerous tools are available for evaluation of NLMEM, with a particular emphasis on visual assessment. This first basic tutorial focuses on presenting graphical evaluation tools of NLMEM for continuous data. It illustrates graphs for correct or misspecified models, discusses their pros and cons, and recalls the definition of metrics used.
CPT Pharmacometrics Syst. Pharmacol. (2017) **6**, 87–109; doi:10.1002/psp4.12161; published online 24 November 2016.

[1]INSERM, IAME, UMR 1137, Paris, France, Université Paris Diderot, Sorbonne Paris Cité, Paris, France; [2]Certara Strategic Consulting, Montréal, Canada; [3]Department of Pharmacology and Clinical Pharmacology, University of Auckland, Auckland, New Zealand; [4]Quantitative Clinical Pharmacology, AstraZeneca, Waltham, Massachusetts, USA; [5]Dr Immanuel Freedman Inc., Harleysville, Pennsylvania, USA; [6]Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden; [7]Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Washington, DC, USA; [8]Projections Research Inc., Phoenixville, Pennsylvania, USA; [9]The Janssen Pharmaceutical Companies of Johnson & Johnson, Belgium; [10]Pharmetheus, Uppsala, Sweden; [11]Department of Bioengineering and Therapeutic Sciences, University of California – San Francisco, San Francisco, California, USA; [12]Division of Pharmacology, Leiden Academic Centre for Drug Research, Leiden University, Leiden, Netherlands; [13]Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Connecticut, USA; [14]Genentech, San Francisco, California, USA; [15]INSERM CIC 1414, Rennes, France, University Rennes-1, Rennes, France. *Correspondence: F Mentré (france.mentre@inserm.fr)

- **ISOP best practice committee** has initiated a ‘Model Evaluation Group’ (chair France Mentré)
- **Series of tutorials** to provide detailed guidance for model evaluation in pharmacometrics
- **First tutorial:** Model evaluation for continuous data pharmacometric models
  - Target audience: beginner modellers
  - Focus on graphical uses of evaluation tools
  - Define metrics and graphs
  - Propose a core set of graphs

GRAPHS FOR EVALUATION OF CONTINOUS NLMEM

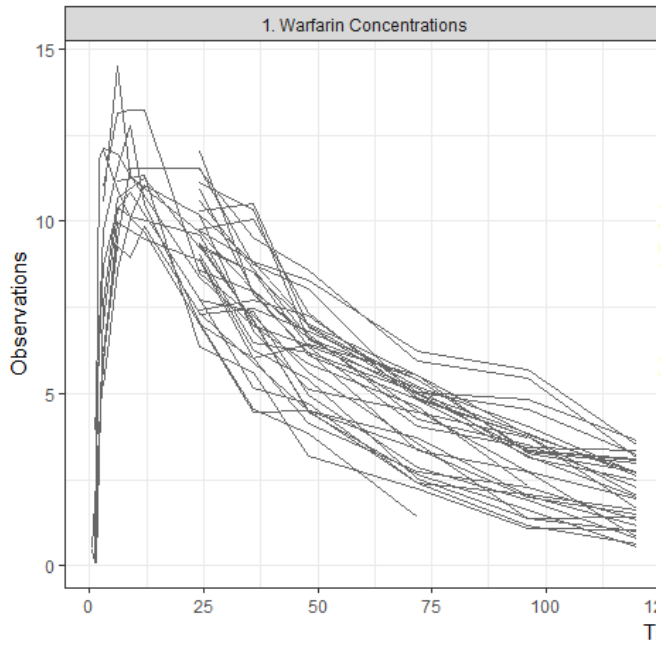
Table 1 Various evaluation graphs in nonlinear mixed effect model[a] and proposal for a core set of evaluation graphs

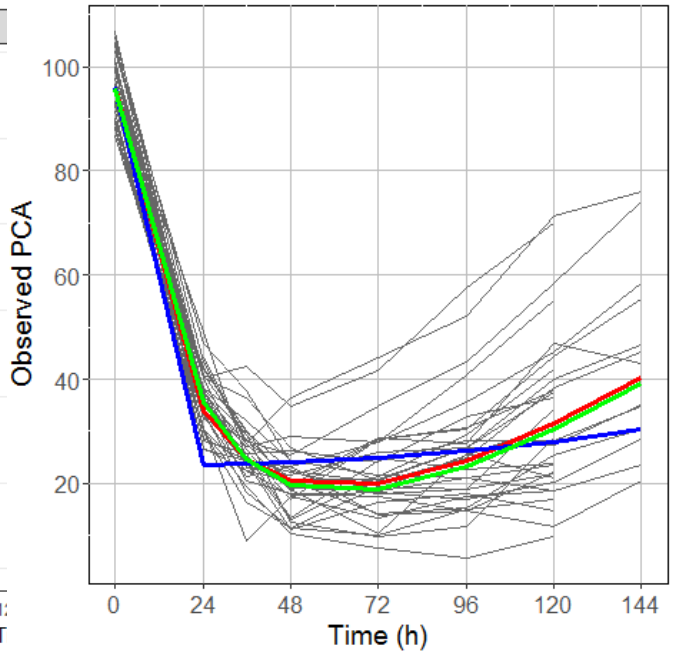
Graphs	In core set	What to expect if the model is correct?	What to do if the graph does not fulfill the requirements?
Evaluation graphs	**In core set**	**What to expect if the model is correct?**	**What to do if the graph does not fulfill the requirements?**
a. Basic goodness-of-fit plots	✓		
OBS vs xPRED, (x=C, P, I)	✓		
xWRES vs Time or xPRED	✓		
b. Individual fits	✓		
c. EBE-based graphs	✓		
d. Simulation-based graphs	✓		
VPC	✓		
NPD vs Time or PPRED	✓		

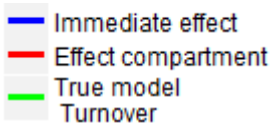
- Population predictions/ residuals: CPRED/CWRES or PPRED/PWRES
- Individual predictions/residuals: IPRED/IWRES
- EBE: Empirical Bayes estimates

MOTIVATING EXAMPLE: 3 MODELS FOR PKPD OF WARFARIN

- **PK model: One compartment model**
- **PD Model for PCA**
  - Misspecified: Immediate effect model
  - Misspecified: Effect compartment model
  - True: Turnover model

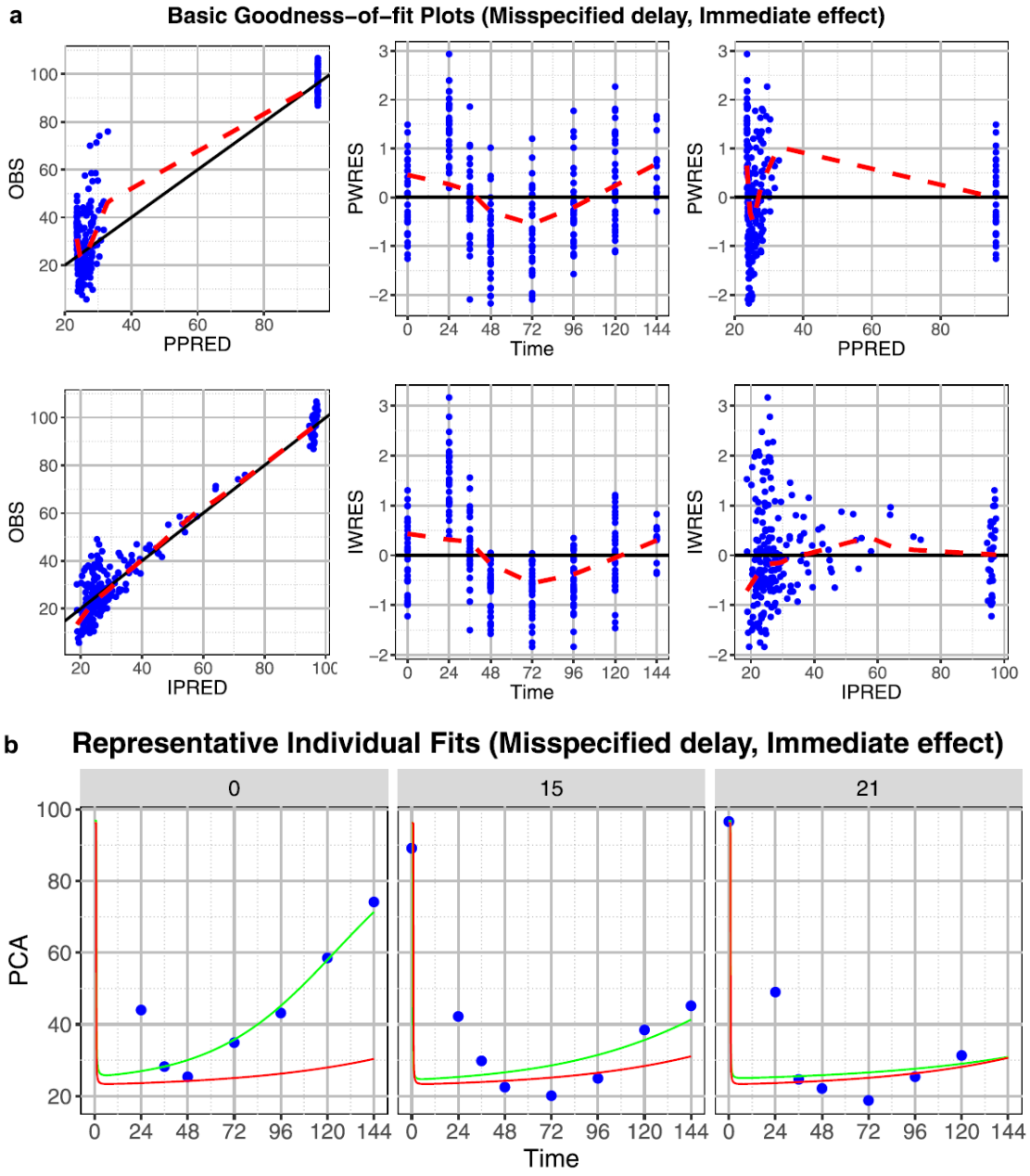






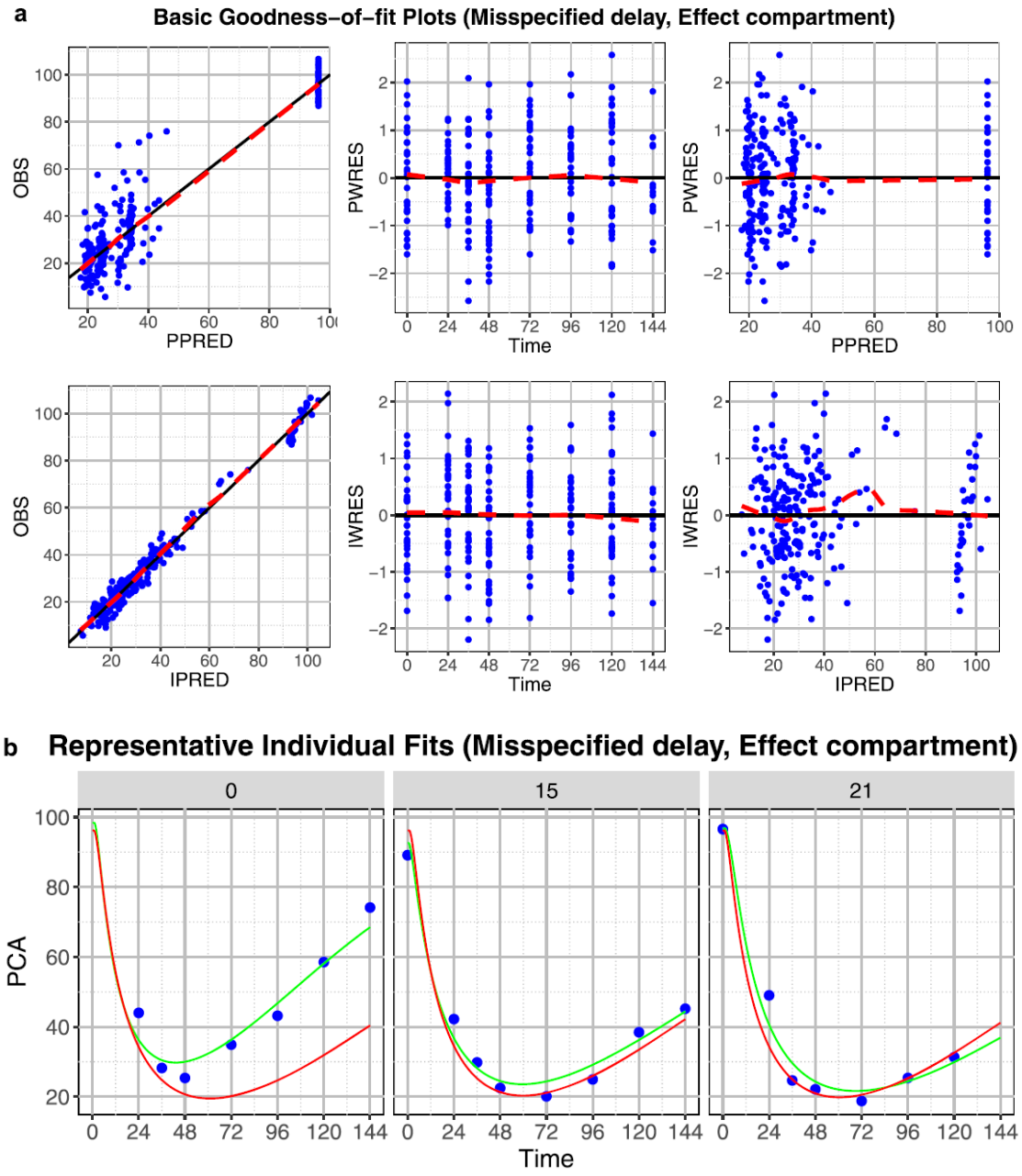
BASIC GOF PLOTS AND INDIVIDUAL FITS

Immediate effect model



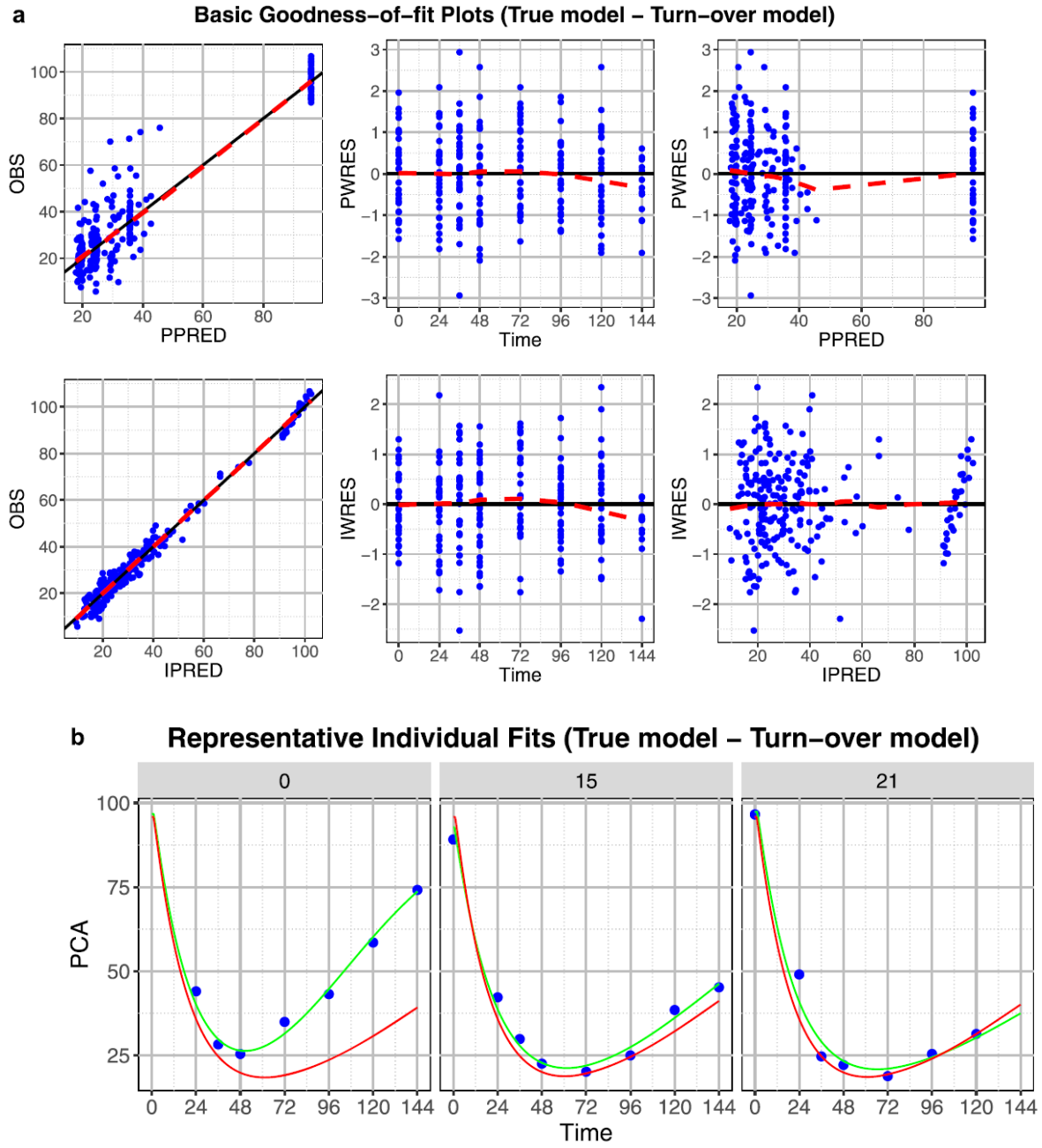
BASIC GOF PLOTS AND INDIVIDUAL FITS

Effect compartment model



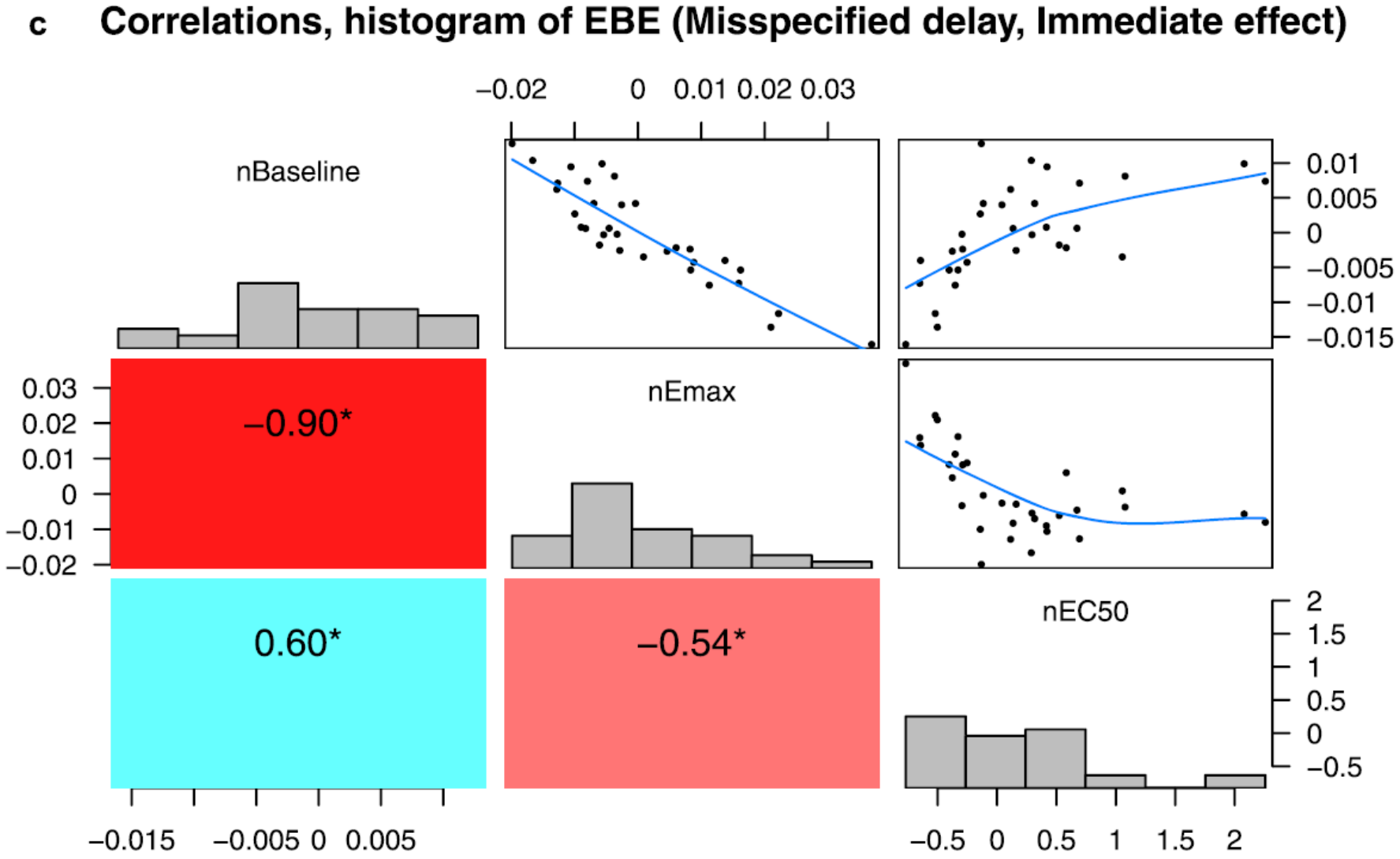
BASIC GOF PLOTS AND INDIVIDUAL FITS

Turnover model



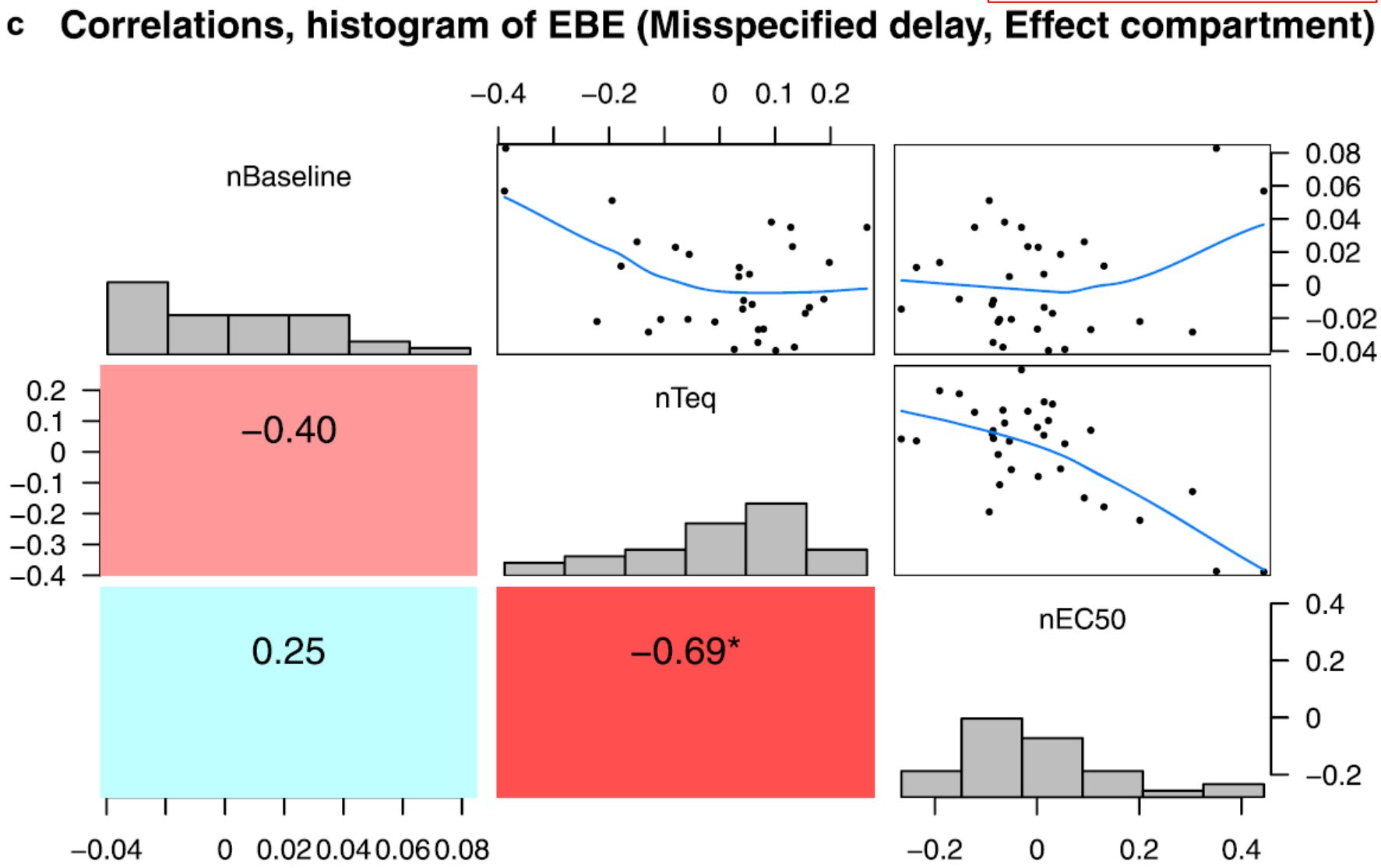
EBE-BASED GRAPHS

Immediate effect model



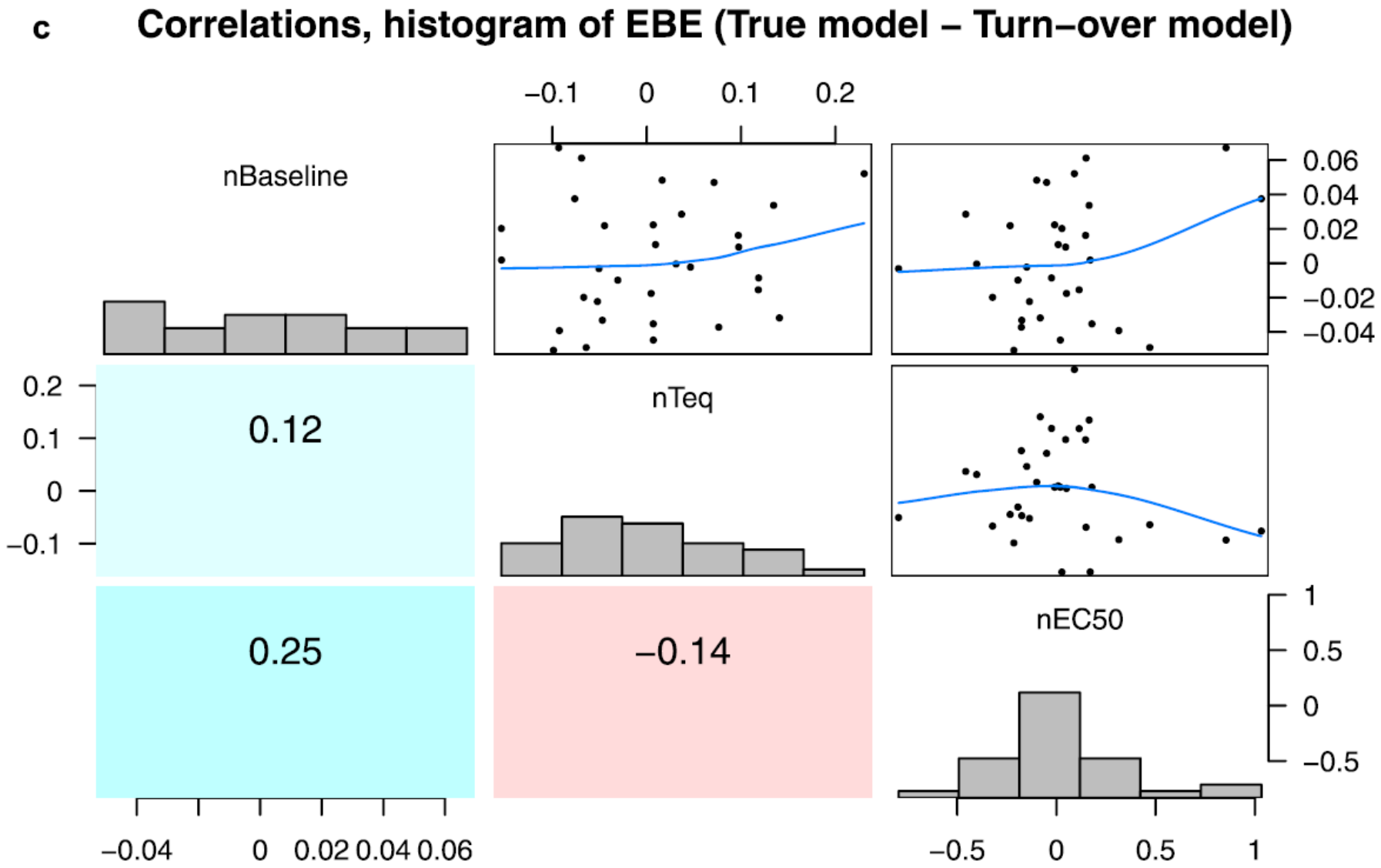
EBE-BASED GRAPHS

Effect compartment model



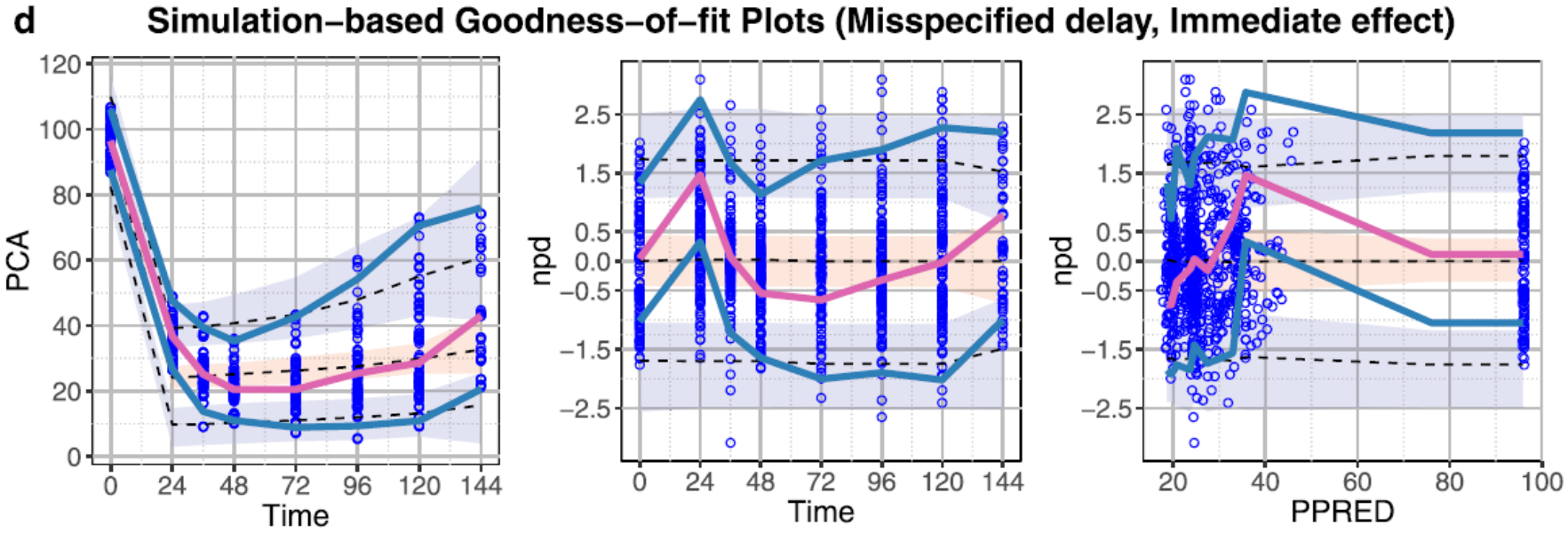
EBE-BASED PLOTS

Turnover model



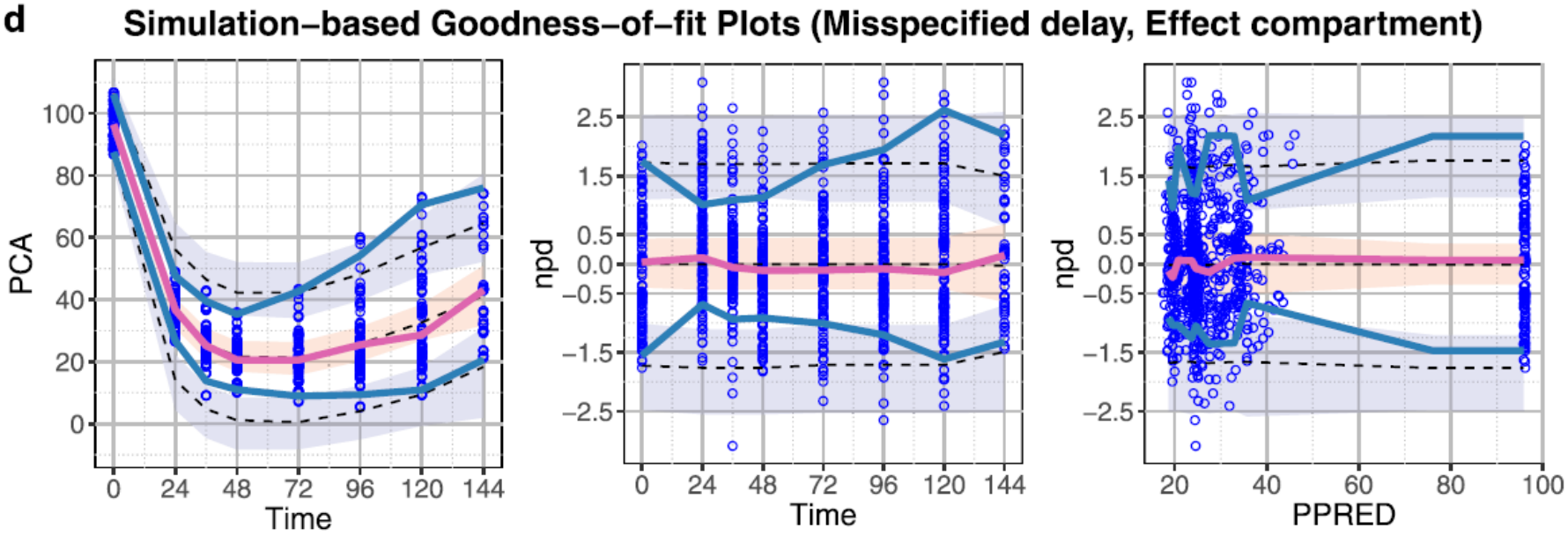
SIMULATION-BASED GRAPHS

Immediate effect model



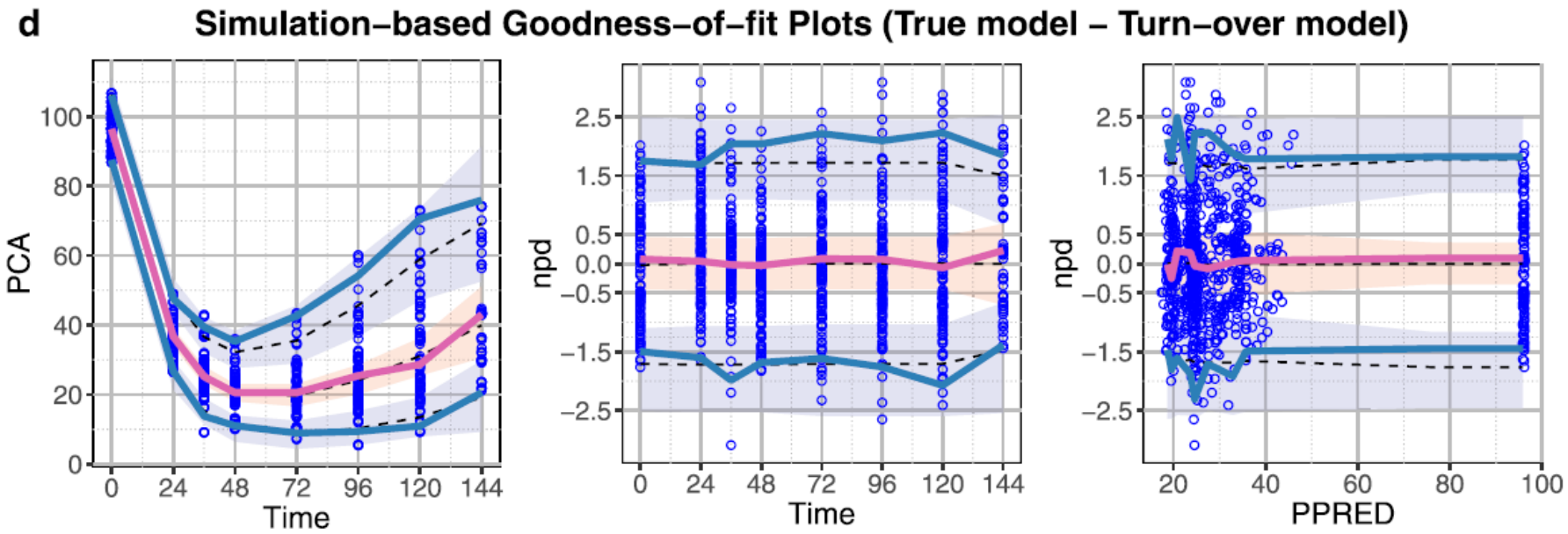
SIMULATION-BASED GRAPHS

Effect compartment model



SIMULATION-BASED GRAPHS

Turnover model



Discussion on model evaluation

- **To detect one type of misspecification, one evaluation graph may be sufficient**
- **To completely evaluate a model, a core set of evaluation graphs should be examined**
- **R script for graphs provided**

PERSPECTIVES

- **Two on-going tutorials about model evaluation**
  - for discrete data
  - time-to-event data

- **Other tutorials about advanced methods/problems in model evaluation (adaptive designs, censored data, etc.)**

4. DESIGNS IN PHARMACOMETRICS

- **Last decades: Several methods/software for maximum likelihood estimation of population parameters using NLMEM**

- **Problem beforehand: choice of 'population' design**
  - ➢ get precise estimates / adequate power
    - number of individuals?
    - number of sampling times/ individuals?
    - sampling times?
    - other design variables (doses, etc…)
  - ➢ Simulation (CTS): time consuming
  - ➢ Asymptotic theory: expected **Fisher Information Matrix**
    (Mentré, Mallet, Baccar, *Biometrika*, 1997)

NIH aims to beef up clinical trial design as part of new data sharing rules

By Jocelyn Kaiser | Sep. 16, 2016 , 12:00 PM

Drug companies and academic researchers will have to step up their public reporting of clinical trial results under new federal policies released today. The National Institutes of Health (NIH) in Bethesda, Maryland, also laid out a new plan for submitting clinical trial proposals that aims to beef up the rigor of the studies.

Researchers can no longer submit an unsolicited idea, but must respond to a request for applications that will include specific design requirements. The goal is to cut down on the number of "small crappy studies," that don't include sufficient numbers of patients or veer off from the original study plan, NIH staffers say. The agency wants to "reengineer the process by which clinical investigators develop ideas for new trials," NIH officials explain in a **commentary today in *The Journal of the American Medical Association*** (*JAMA*).

Software tools for population design

	PFIM	PFIM Int.	PkStaMP	PopDes	PopED	POPT
Authors	Mentré et al (Paris)	Mentré et al (Paris)	Leonov (US)	Ogungbenro (Manchester)	Hooker /Nyberg/Ueckert (Uppsala)	Duffull (Otago, NZ)
Language	R	R	Matlab CR	Matlab	Matlab and R	Matlab
Available on website	Yes	Yes	No	Yes	Yes	Yes
GUI	No	Yes	Yes	Yes	Yes	No
Library of models	Yes	Yes	Yes	Yes	Yes	Yes
User defined models	Yes	Yes	Yes	Yes	Yes	Yes

BJCP British Journal of Clinical Pharmacology

DOI:10.1111/bcp.12352

Methods in Clinical Pharmacology Series

Methods and software tools for design evaluation in population pharmacokinetics–pharmacodynamics studies

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[1]Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden, [2]Laboratoire Jean Kuntzmann, Département Statistique, University of Grenoble, Grenoble, France, [3]Centre for Applied Pharmacokinetic Research, School of Pharmacy and Pharmaceutical Sciences, University of Manchester, Manchester, UK, [4]Institute for Systems Analysis, Russian Academy of Sciences, Moscow, Russia, [5]AstraZeneca, Wilmington, DE, USA, [6]School of Pharmacy, University of Otago, Dunedin, New Zealand and [7]INSERM U738 and University Paris Diderot, Paris, France

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Keywords
Fisher information matrix, nonlinear mixed effect models, optimal design, population design, population pharmacokinetics–pharmacodynamics

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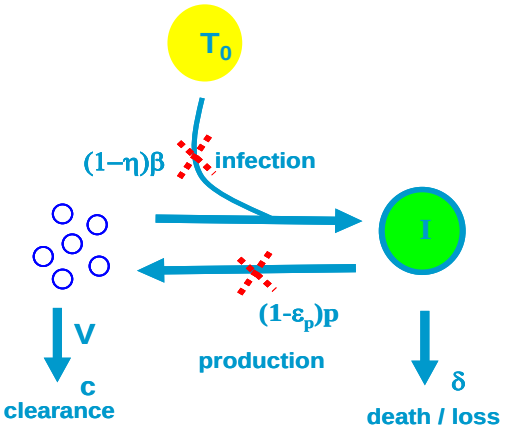
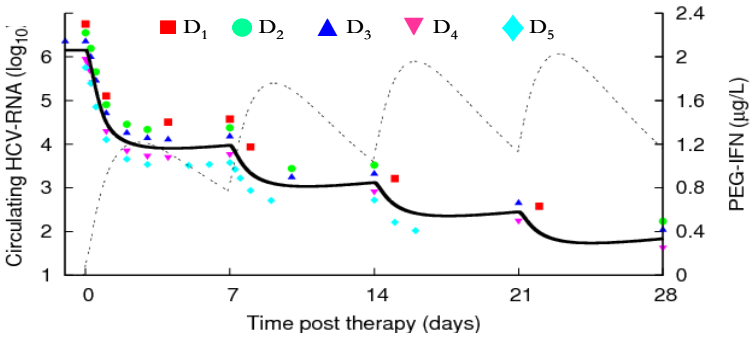
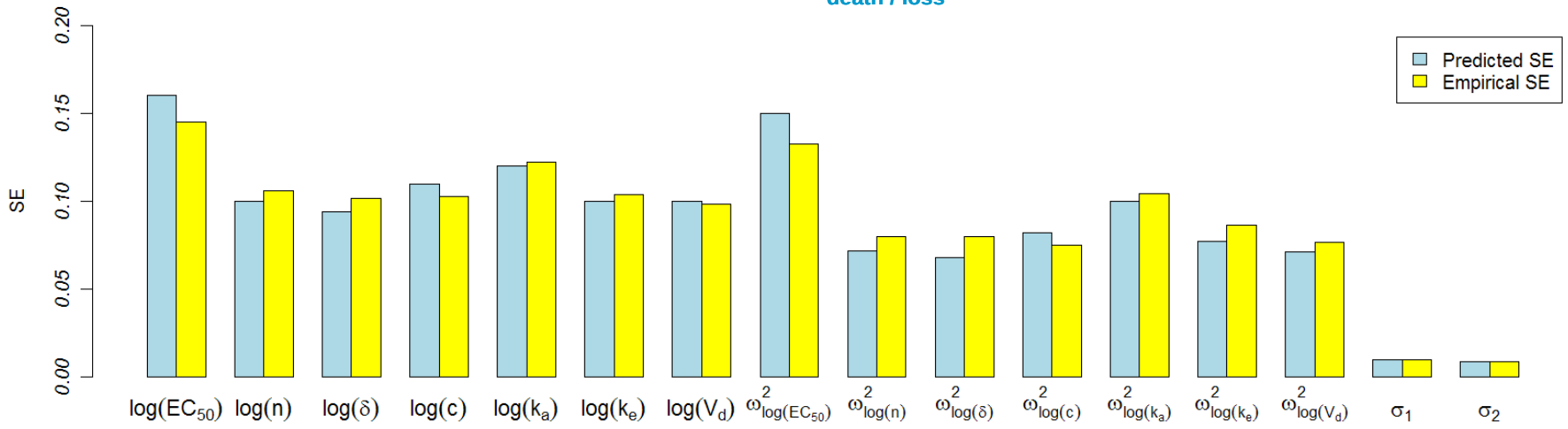
- For most PKPD models, using any of the available software tools will **provide meaningful results avoiding cumbersome simulation** and allowing design optimization

PKPD example in HCV

$$\begin{cases} \dfrac{dX}{dt} = D - k_a X \\ \dfrac{dA}{dt} = k_a X - k_e A \\ C(t) = \dfrac{A(t)}{V_d} \\ \dfrac{dT}{dt} = s - \beta(1-\eta)VT - dT \\ \dfrac{dI}{dt} = \beta(1-\eta)VT - \delta I \\ \dfrac{dV}{dt} = p\left(1 - \dfrac{C(t)^n}{C(t)^n + EC_{50}^n}\right) I - cV \end{cases}$$







- Good prediction of SE of all PKPD parameters
- Computing time
  - CTS = 5 days
  - Design evaluation with PFIM = 5 mins!

(Guedj, Bazzoli, Neumann, Mentré, *Stat Med,* 2011)

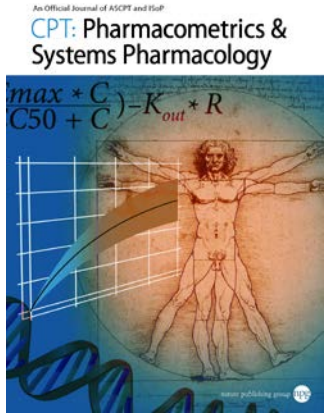
Citation: CPT: Pharmacometrics & Systems Pharmacology (2013) 2, e46; doi:10.1038/psp.2013.19

www.nature.com/psp

PERSPECTIVE

Current Use and Developments Needed for Optimal Design in Pharmacometrics: A Study Performed Among DDMoRe's European Federation of Pharmaceutical Industries and Associations Members

F Mentré[1], M Chenel[2], E Comets[1], J Grevel[3], A Hooker[4], MO Karlsson[4], M Lavielle[5] and I Gueorguieva[6]



- Optimal design methodology has been **quickly adopted within the industry**, especially in early phases where PKPD is more important
- **High priority** given to further development of **adaptive optimal design in NLMEM** with optimization not only of sampling times but of other design variables (e.g., doses)

Using HMC for robust designs in NLMEM with discrete data

- **Optimal design depends on knowledge on model and parameters**
  - Local planification: given a model and a priori values for population parameter
  - Widely used criterion: D-optimality (determinant of FIM)

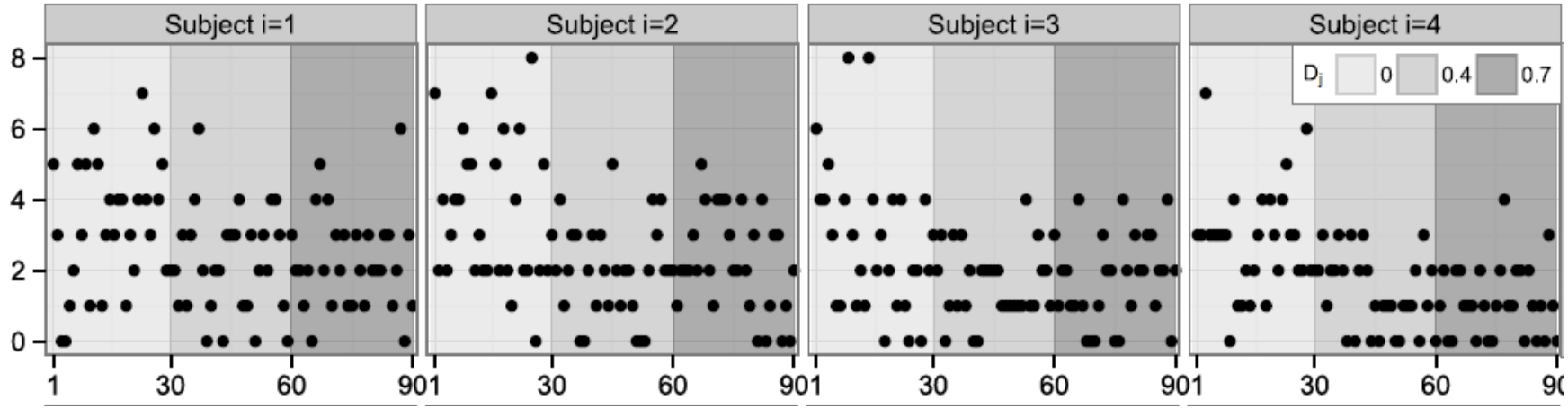
- **Alternative: Robust designs**
  - Taking into account uncertainty on parameters (prior distribution)
  - Over a set of candidate models (as in MCP-MOD)

- **Using HMC in Stan in an extension of R package MXFIM**

(Rivière, Ueckert, Mentré, *Biostatistics*, 2016)

Application to robust designs for repeated count data

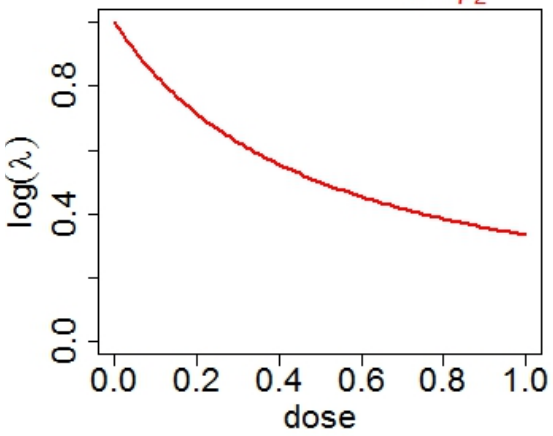
- Exemple: Daily count of events that we want to prevent
- Poisson model for repeated count response $P(\mathrm{y} = \mathrm{k}|\mathrm{b}) = \frac{\lambda^{\mathrm{k}}\, \mathrm{e}^{-\lambda}}{\mathrm{k!}}$
- Each patient observed at 3 dose levels (one placebo) during x days



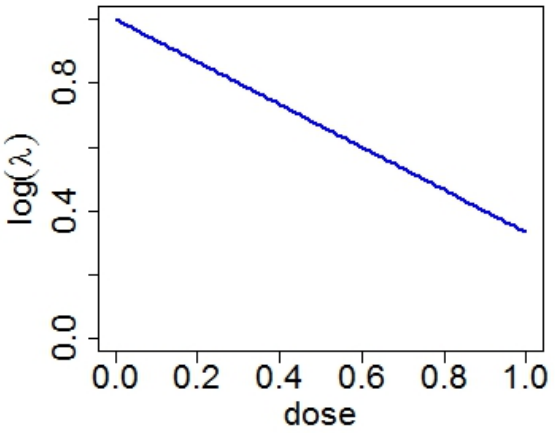
- Several candidate models for the link between log(λ) and dose
- λ: mean number of events / day

Five models of effect of dose on decreasing Poisson parameter

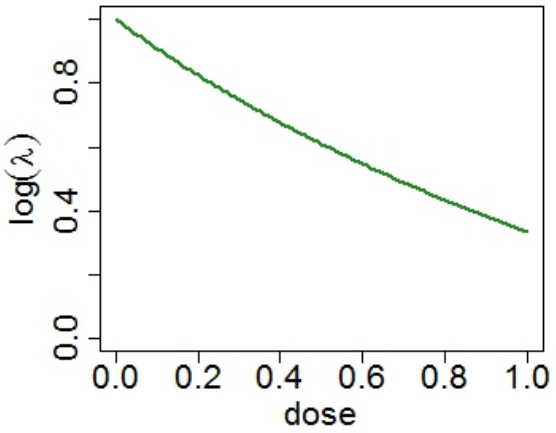
M1: $\log(\lambda)=\beta_1(1-\frac{d}{d+\beta_2})$



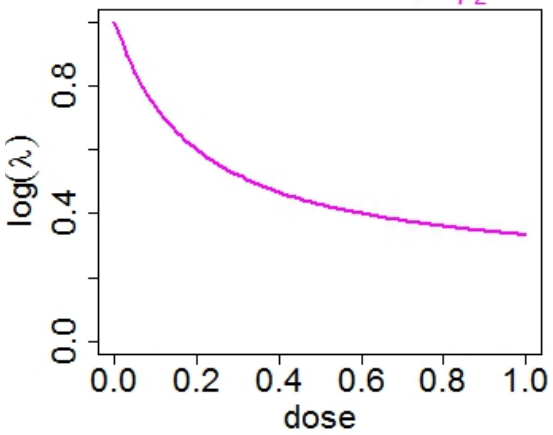
M2: $\log(\lambda)=\beta_1(1-\beta_2 d)$



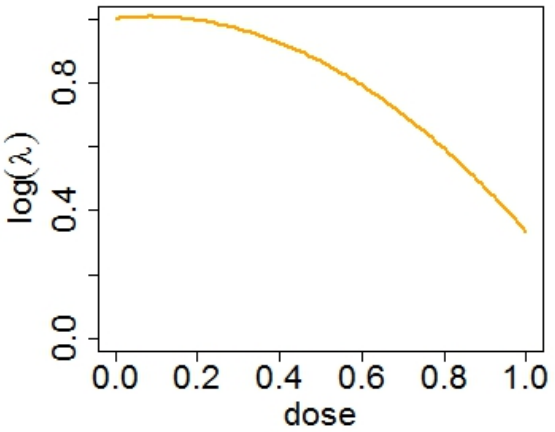
M3: $\log(\lambda)=\beta_1(1-\beta_2\log(d+1))$



M4: $\log(\lambda)=\beta_1(1-\frac{\beta_3 d}{d+\beta_2})$



M5: $\log(\lambda)=\beta_1(1-\beta_2 d-\beta_3 d^2)$

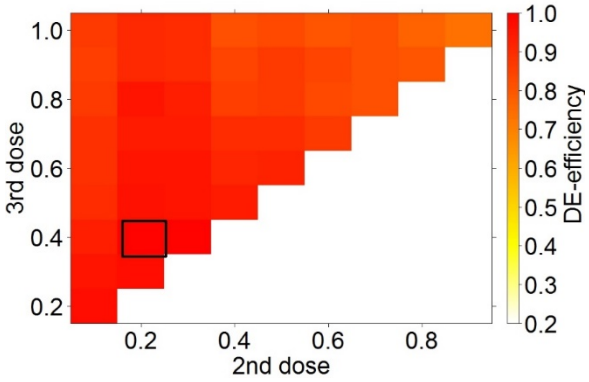


1. Full Emax
2. Linear
3. Log-Linear
4. Emax
5. Quadratic

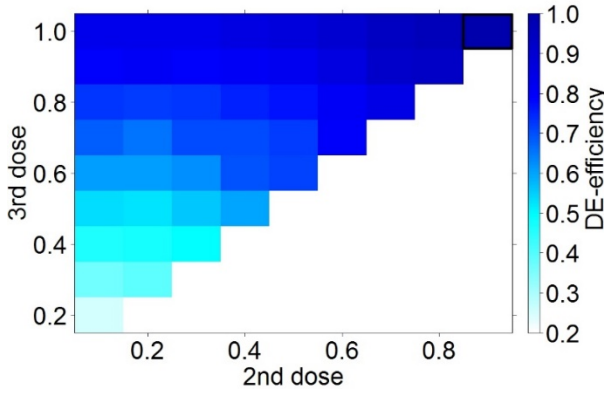
Design optimisation

Methods		
Constraints	Number of subjects	N = 60
	Number of days	n = 10 days / dose
	Number of doses	3 doses / patients
	Choice of doses	d_1= 0 (placebo) d_2, d_3 from 0.1 to 1 (step 0.1, no replication)
Combinatorial Optimization	Evaluation of FIM for all possible designs	5000 MC 200 HMC
	For each model	DE-criterion on robust FIM (averaging for uncertainty on parameters)
	Over 5 models	Compound DE-criterion (averaging for uncertainty on models and parameters)

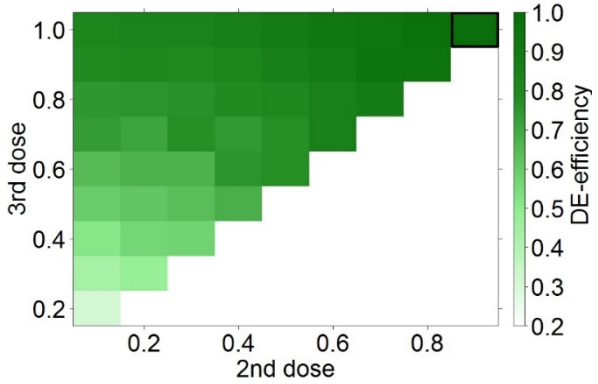
Results: robust optimal design for each model



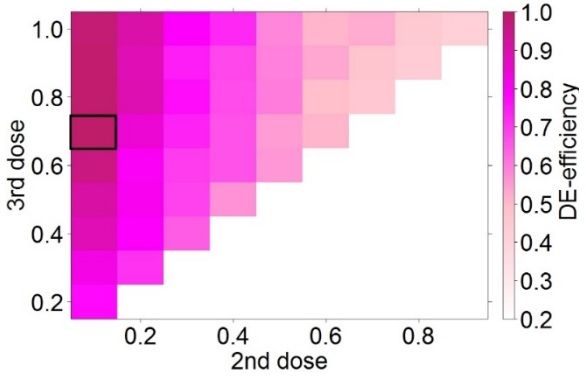
$\xi_{M1}=(0,\mathbf{0.2},\mathbf{0.4})$



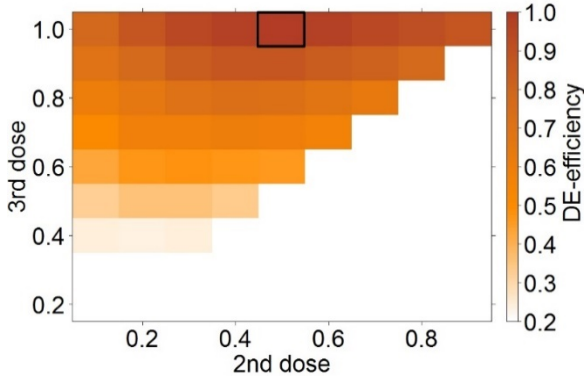
$\xi_{M2}=(0,\mathbf{0.9},\mathbf{1})$



$\xi_{M3}=(0,\mathbf{0.9},\mathbf{1})$



$\xi_{M4}=(0,\mathbf{0.1},\mathbf{0.7})$



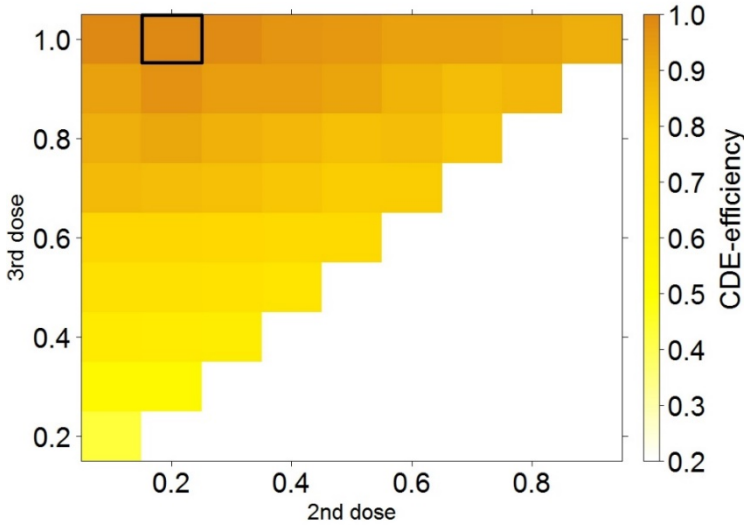
$\xi_{M5}=(0,\mathbf{0.5},\mathbf{1})$

1. Full Emax
2. Linear
3. Log-Linear
4. Emax
5. Quadratic

Results: loss of efficiency if wrong model

	M1 Full Emax	M2 Linear	M3 Log-Linear	M4 Emax	M5 Quadratic
$\xi_{M1}=(0,0.2,0.4)$	100%	**47%**	57%	78%	**24%**
$\xi_{M2}=(0,0.9,1)$	73%	100%	100%	**44%**	87%
$\xi_{M3}=(0,0.9,1)$	73%	100%	100%	**44%**	87%
$\xi_{M4}=(0,0.1,0.7)$	89%	68%	74%	100%	51%
$\xi_{M5}=(0,0.5,1)$	83%	88%	90%	59%	100%
$\xi_{all}=(0,0.2,1)$	91%	84%	84%	85%	83%

Efficiency greater than 80% for all models



Optimal design over 5 models
$\xi_{all}=(0,\mathbf{0.2,1})$

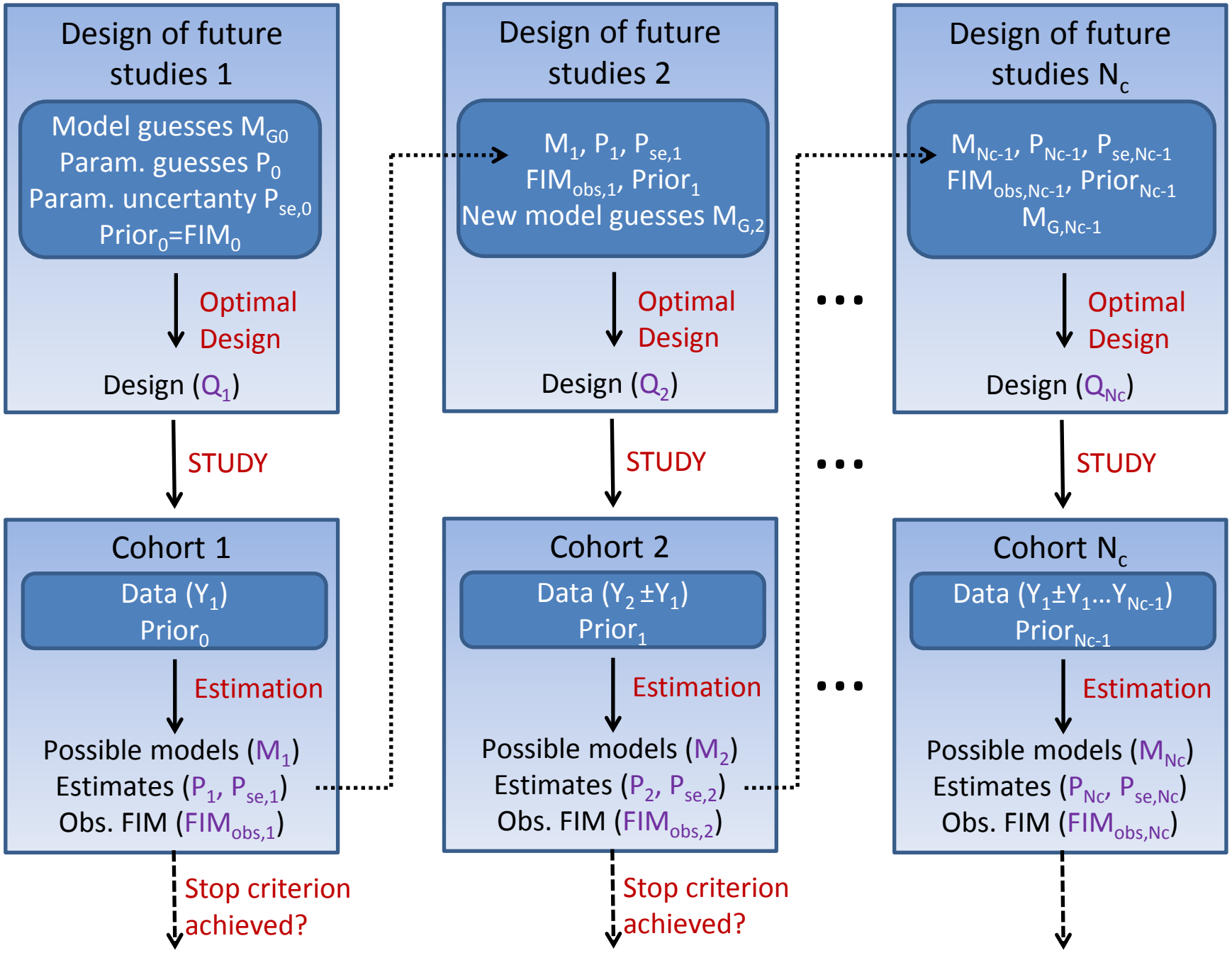
Discussion on designs in pharmacometrics

- Evaluation and comparison of population designs without simulation using statistical approach
- Designs may CONSIDERABLY affects precision of estimation
- Results of population PKPD analyses increasingly used
  - ➢ Informative studies with small estimation errors needed

SPARSE-SAMPLING DESIGN = BEST INFORMATION IS NEEDED

COMPLEX MODELS = DIFFICULT TO 'GUESS' GOOD DESIGNS

- **Several software tools available: no excuses!**
  - Define good population designs (ethical/financial reasons)
  - Anticipate ‘fatal’ population designs
  - Careful: lower bound (nonlinearity, small sample size)
    → CTS for key designs
- **Ongoing work by statisticians & pharmacometricians**
  - Model based adaptive designs



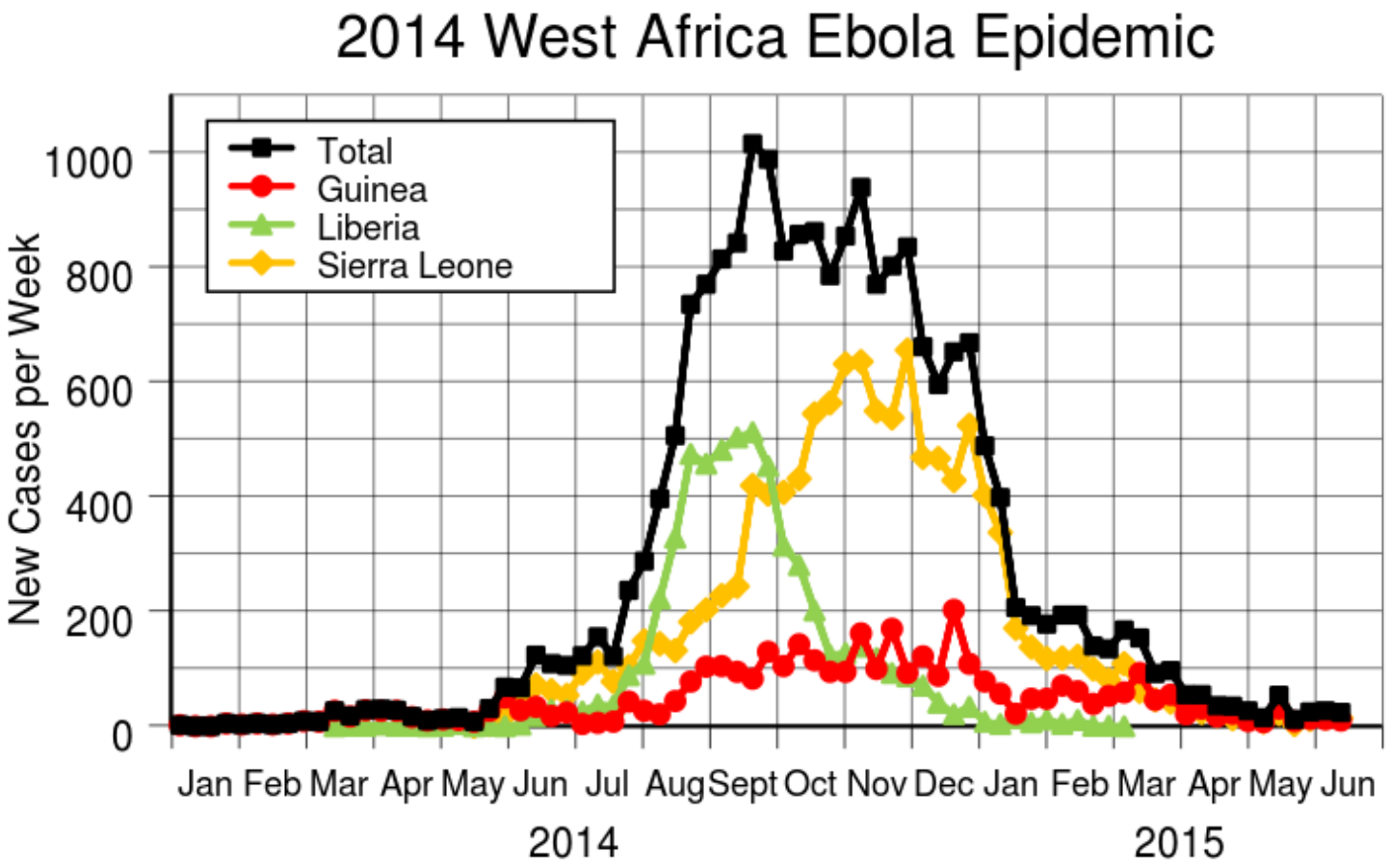
- **MBAOD prototype in R** (developed by Andrew Hooker, Uppsala University)

Outline

1. **Pharmacometrics**
2. **Statisticicians in pharmacometrics**
3. **Model evaluation: a core set of graphs**
4. **Design in pharmacometrics**
5. **Dose of favipiravir in Ebola infection**
6. **Bridging the gap between statisticians and pharmacometricians**

5. DOSE OF FAVIPIRAVIR FOR EBOLA INFECTION

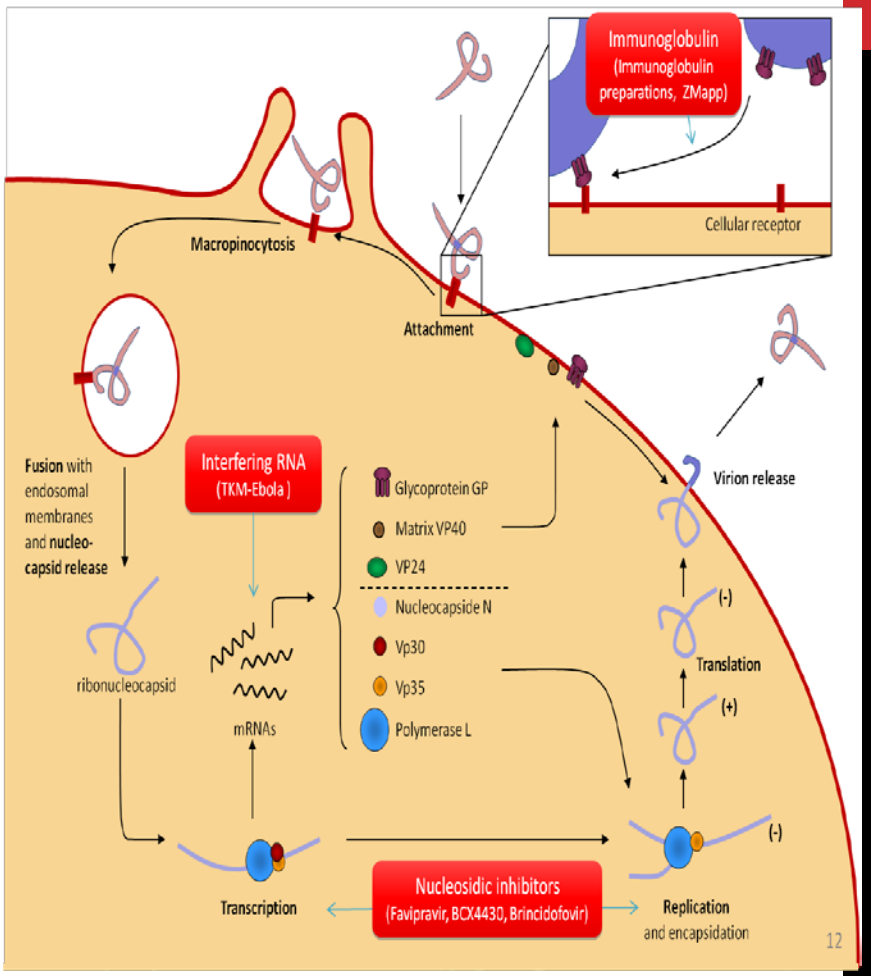
- **2014: largest outbreak of Ebola infection in West Africa**
  - 29 000 cases, 11 000 deaths
- **5 therapeutic trials were launched**



Favipiravir: a direct acting antiviral

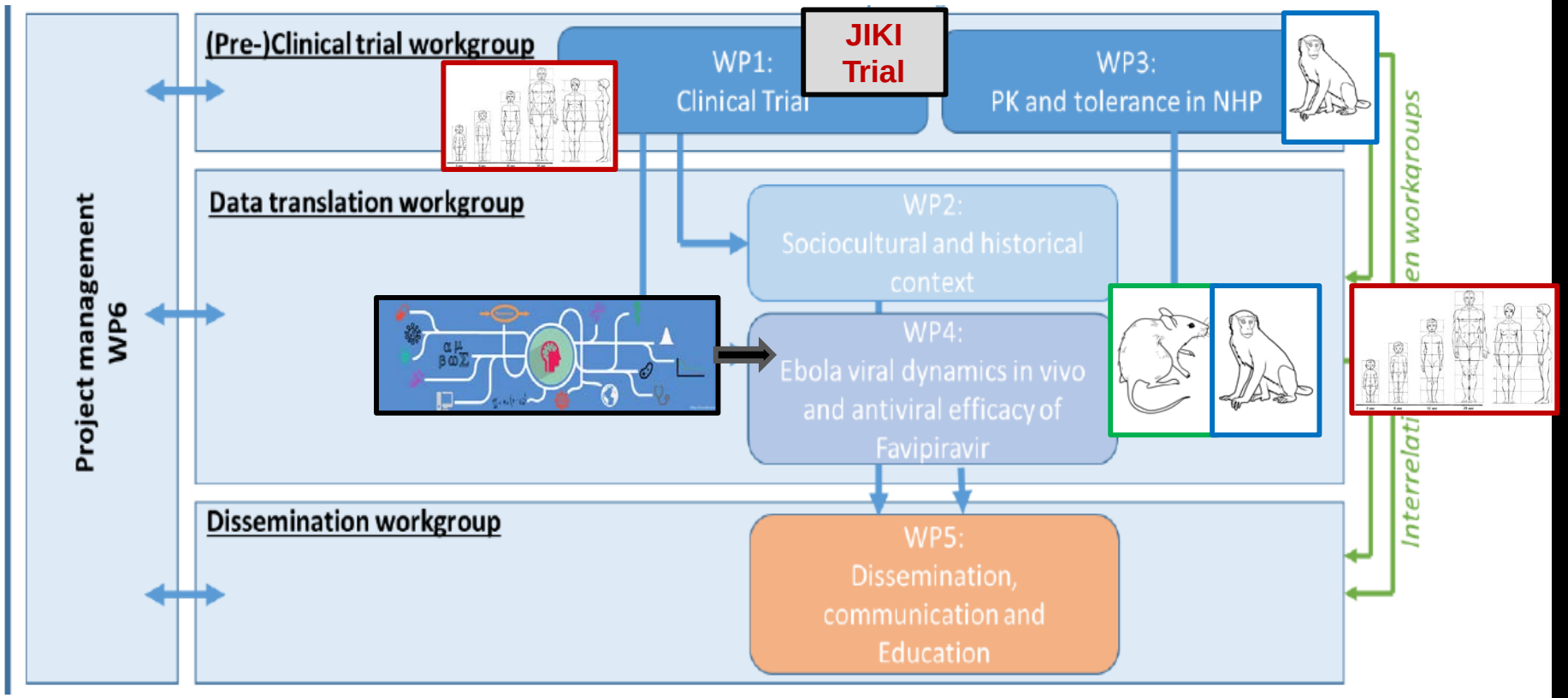
- **Nucleoside polymerase inhibitor**
- **Approved for influenza**
- **Developed by Toyama Chemicals**
- **Good tolerance**
- **Prioritized by WHO in 2014**
- **In Ebola infected mice treated with favipiravir: 100% survival vs 0% (untreated)**

(Oesterreich et al, *Antivir Res,* 2014)

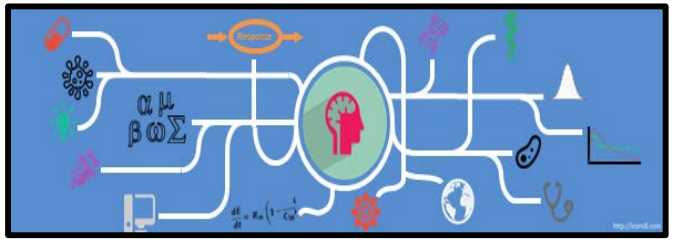


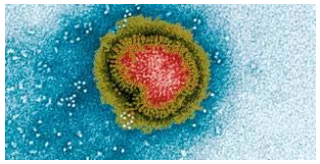
Evaluation of efficacy and antiviral activity of favipiravir in non-human primates for Ebola virus (EBV)

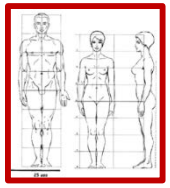
PI: Hervé Raoul, BSL4, INSERM,France



Dose of favipiravir in EBV-infected patients?







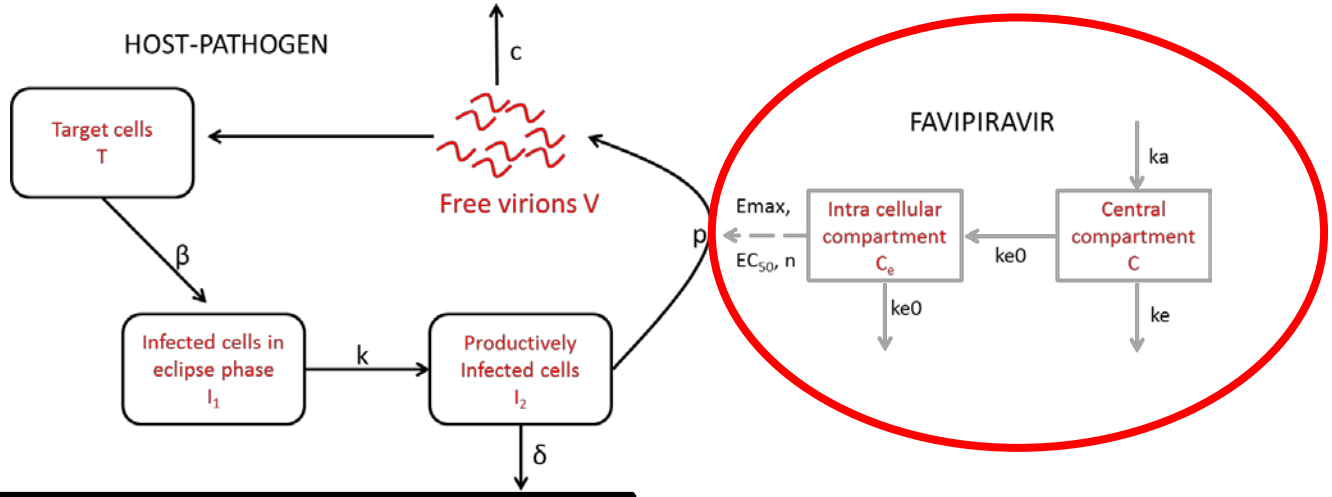
Additional PK data asked to Toyama Chemicals

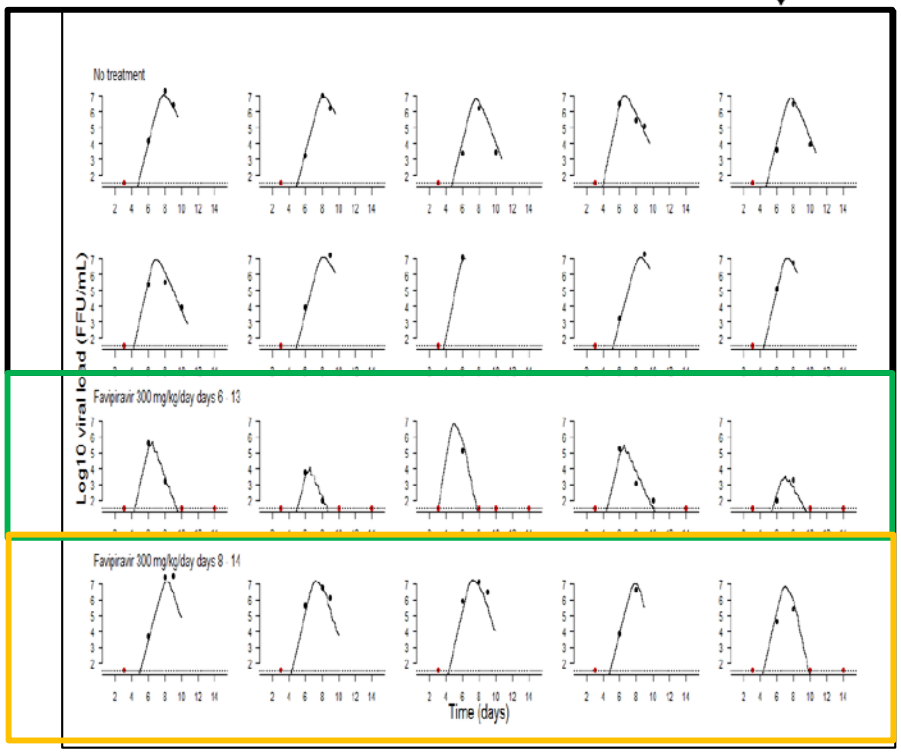
Toxicokinetics data in mice with same dose

Population PK in Phase 3 US studies

PKVK Model for favipiravir in mice

Model for EBOV replication



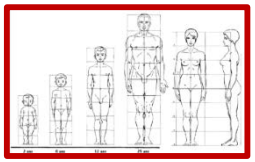


- High steady-state effectiveness of favipiravir in blocking viral production (99.6%)
- A single infected cell could produce ~9 new productive infections

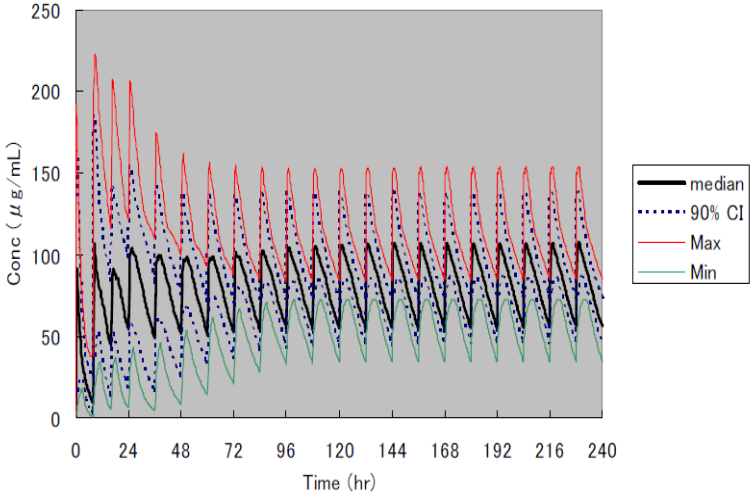
Madelain, Oestereich, Graw, Nguyen, de Lamballerie, Mentré, Günther, Guedj. Ebola virus dynamics in mice treated with favipiravir. *Antiviral Research* (2015)

Dose of favipiravir for EBV-infected patients

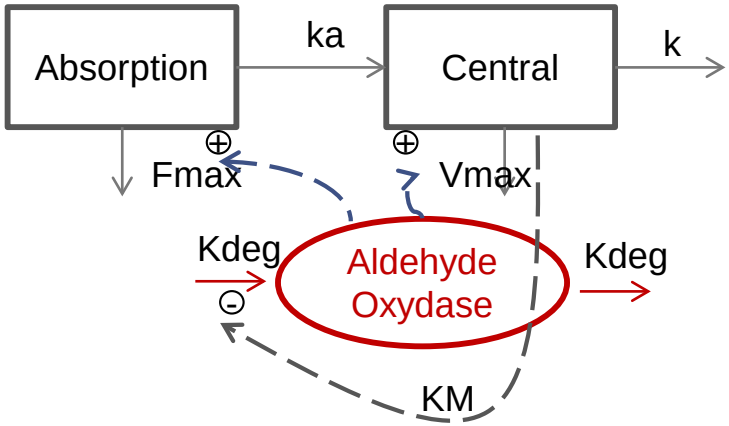
→ 50% higher than for influenza



D1: 2400/ 2400/ 1200 mg
D2-D10: 1200 mg BID

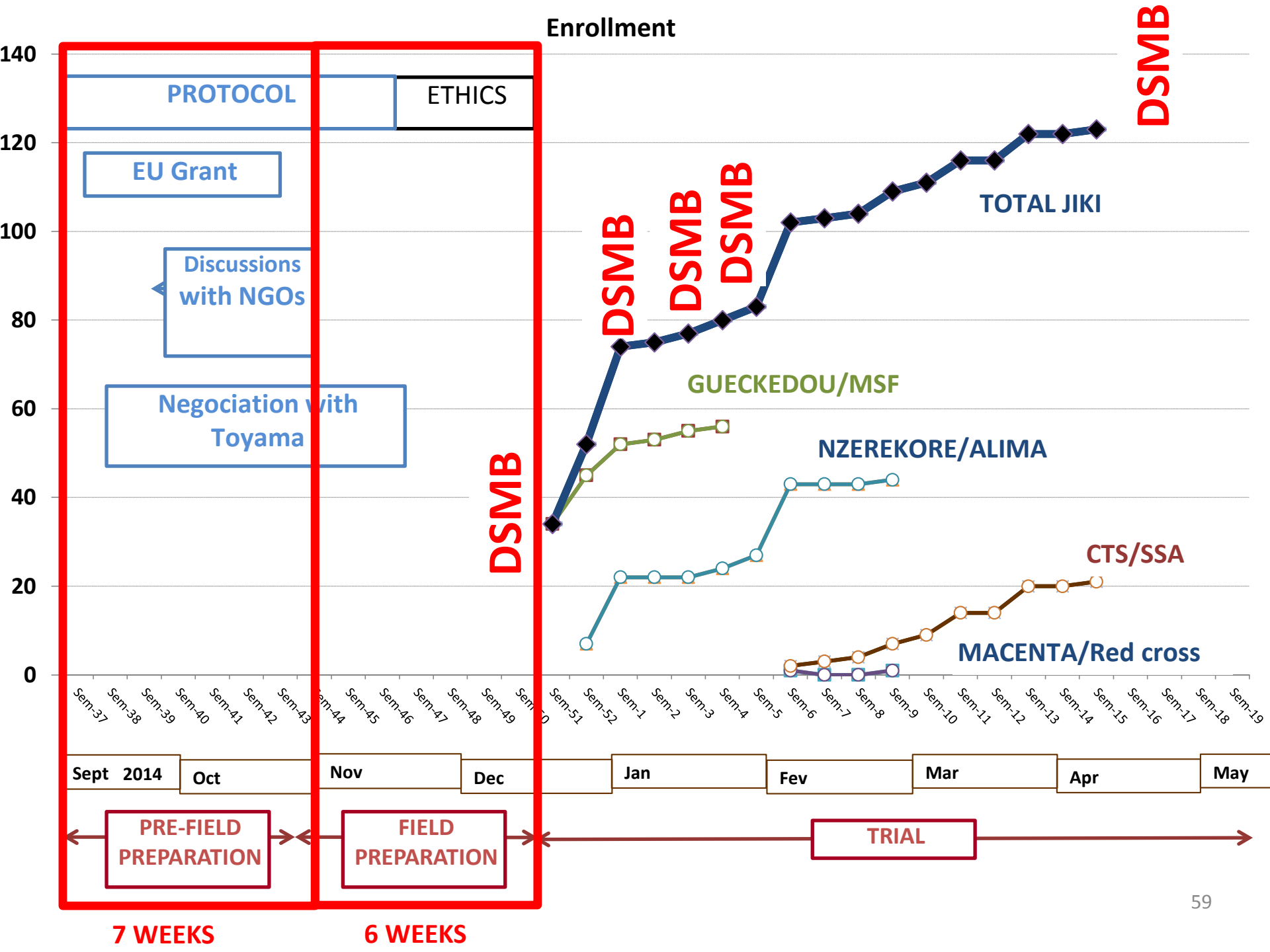


Population PK model (US phase 3 influenza)



Mentré, Taburet, Guedj, Anglaret, Keïta, de Lamballerie, Malvy. Dose regimen of favipiravir for Ebola virus disease, *The Lancet Infectious Diseases* (2015)

Bouazza, Treluyer, Foissac, Mentré, Taburet , Guedj, Anglaret, de Lamballerie, Keïta, Malvy, Frange. Favipiravir for Children with Ebola, *Lancet* (2015)


Enrollment
PROTOCOL
ETHICS
EU Grant
Discussions with NGOs
Negociation with Toyama
DSMB
DSMB
DSMB
DSMB
DSMB
TOTAL JIKI
GUECKEDOU/MSF
NZEREKORE/ALIMA
CTS/SSA
MACENTA/Red cross
140
120
100
80
60
40
20
0
Sept 2014
Oct
Nov
Dec
Jan
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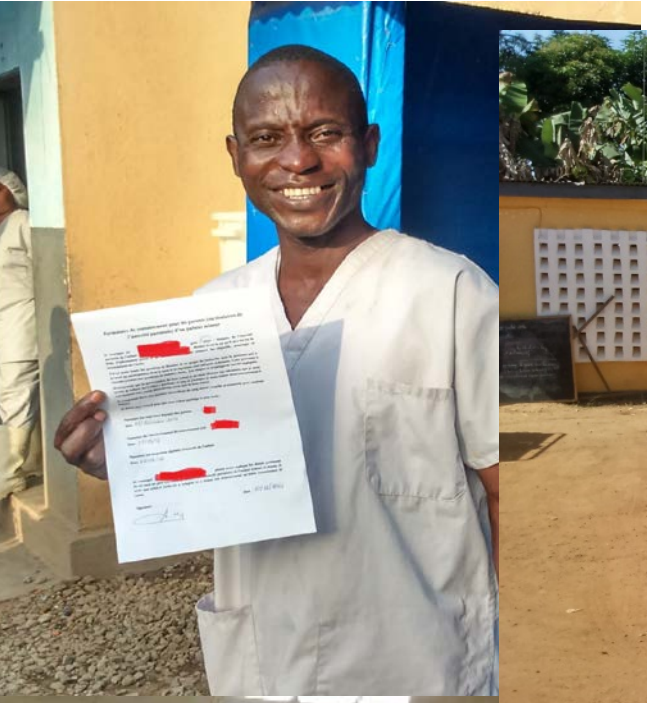
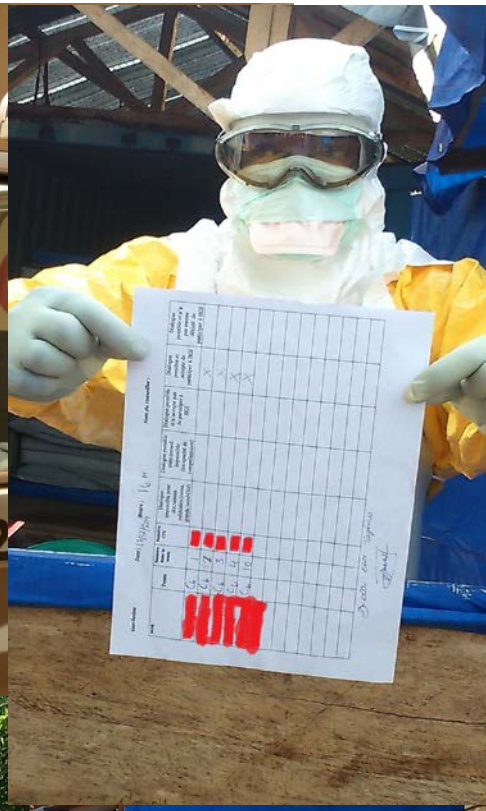
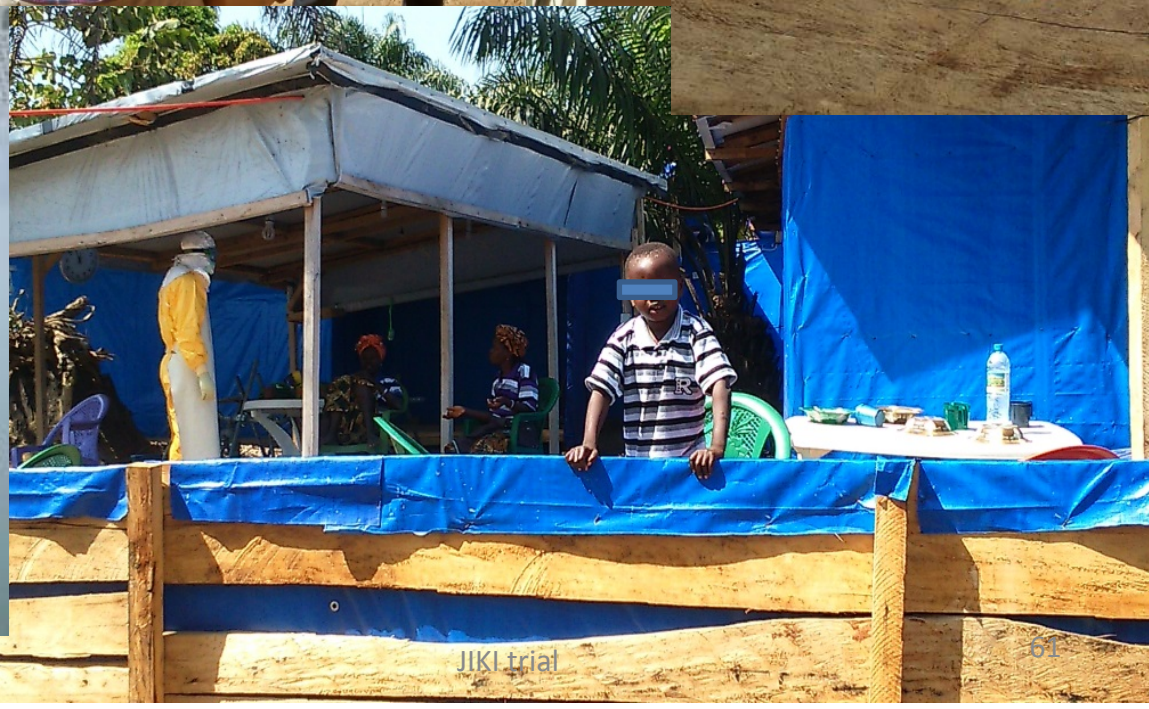
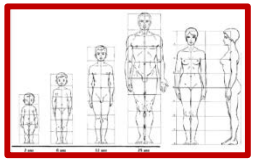
Mar
Apr
May
PRE-FIELD PREPARATION
FIELD PREPARATION
TRIAL
7 WEEKS
6 WEEKS


CENTRE DE TRAITEMENT
EBOLA









PLOS | MEDICINE

PLOS Medicine | DOI:10.1371/journal.pmed.1001967 March 1, 2016

RESEARCH ARTICLE

Experimental Treatment with Favipiravir for Ebola Virus Disease (the JIKI Trial): A Historically Controlled, Single-Arm Proof-of-Concept Trial in Guinea

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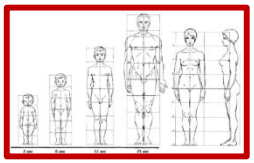
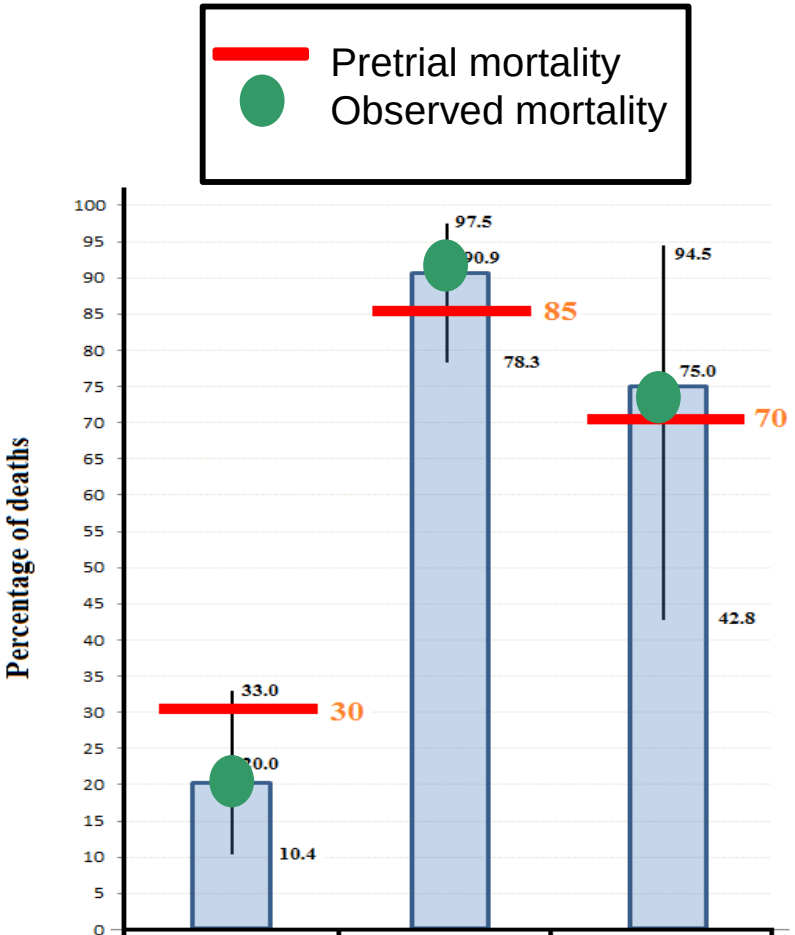
JIKI Results (111 patients)



- **No conclusion on the efficacy of the drug**
- **Encouraging conclusions on tolerance**
- **Favipiravir merits further studies**
- **Higher doses?**
- **Combination therapy?**



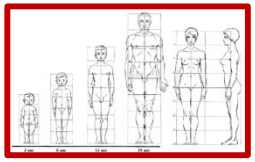
	Adults and adolescents Ct ≥20	Adults and adolescents Ct < 20	Young children
Number of patients	55	44	12
Number of deaths	11	40	9

Moderate & High viral load

Very High viral load
Severe disease

PLOS | NEGLECTED TROPICAL DISEASES

PLOS Neglected Tropical Diseases | DOI:10.1371/journal.pntd.0005389 February 23, 2017

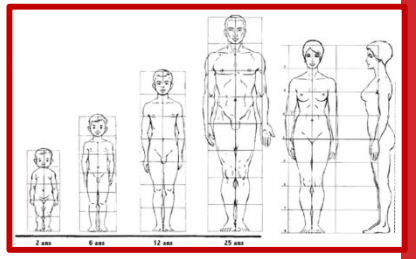


RESEARCH ARTICLE

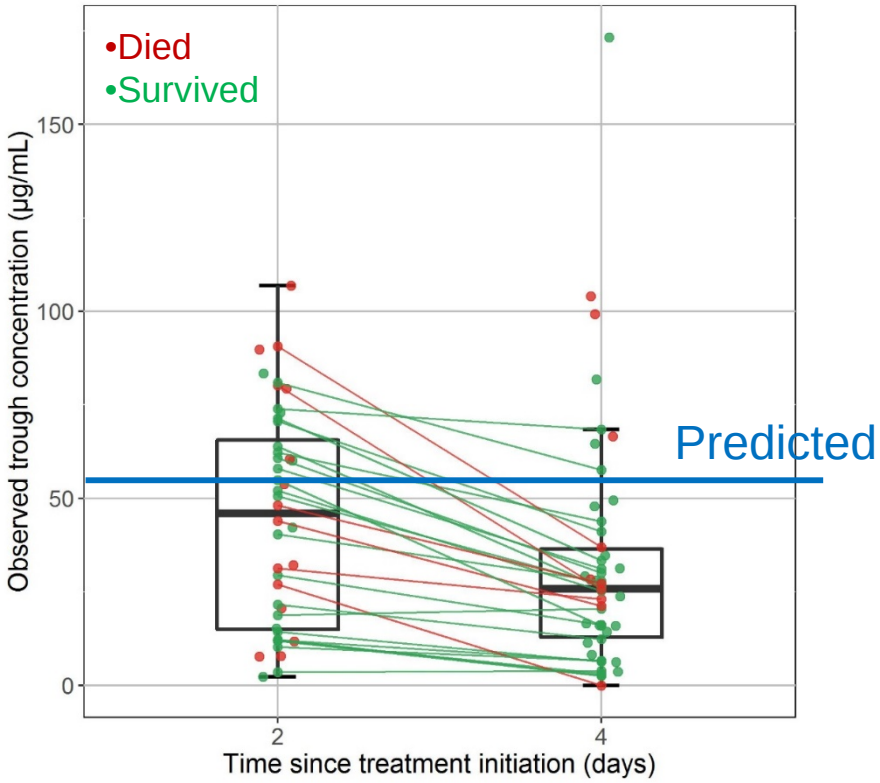
Favipiravir pharmacokinetics in Ebola-infected patients of the JIKI trial reveals concentrations lower than targeted

Thi Huyen Tram Nguyen[1], Jérémie Guedj[1], Xavier Anglaret[2,3], Cédric Laouénan[1,4], Vincent Madelain[1,4], Anne-Marie Taburet[5], Sylvain Baize[6], Daouda Sissoko[2,7], Boris Pastorino[8], Anne Rodallec[8], Géraldine Piorkowski[8], Sara Carazo[9], Mamoudou N. Conde[10], Jean-Luc Gala[11,12,13,14], Joseph Akoi Bore[15,16,17], Caroline Carbonnelle[18], Frédéric Jacquot[18], Hervé Raoul[18], Denis Malvy[2,7], Xavier de Lamballerie[8], France Mentré[1,4]*, on behalf of the JIKI study group[¶]

PK data from JIKI trial (2016)



Trough concentrations (8 to 9 AM) at Day 2 and Day 4 in 66 patients

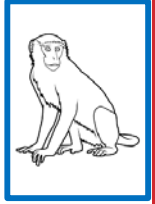


- **Drop in concentration between D2 and D4**
- **D4 concentrations lower than expected**

➢ **Concentrations in JIKI trial too low to strongly inhibit viral replication**

- EC_{50} for EBV = 10.5 µg/mL (Mayinga 1976)
  = 31-63 µg/mL (Kikwit 1995/E718)
- Protein binding 50%

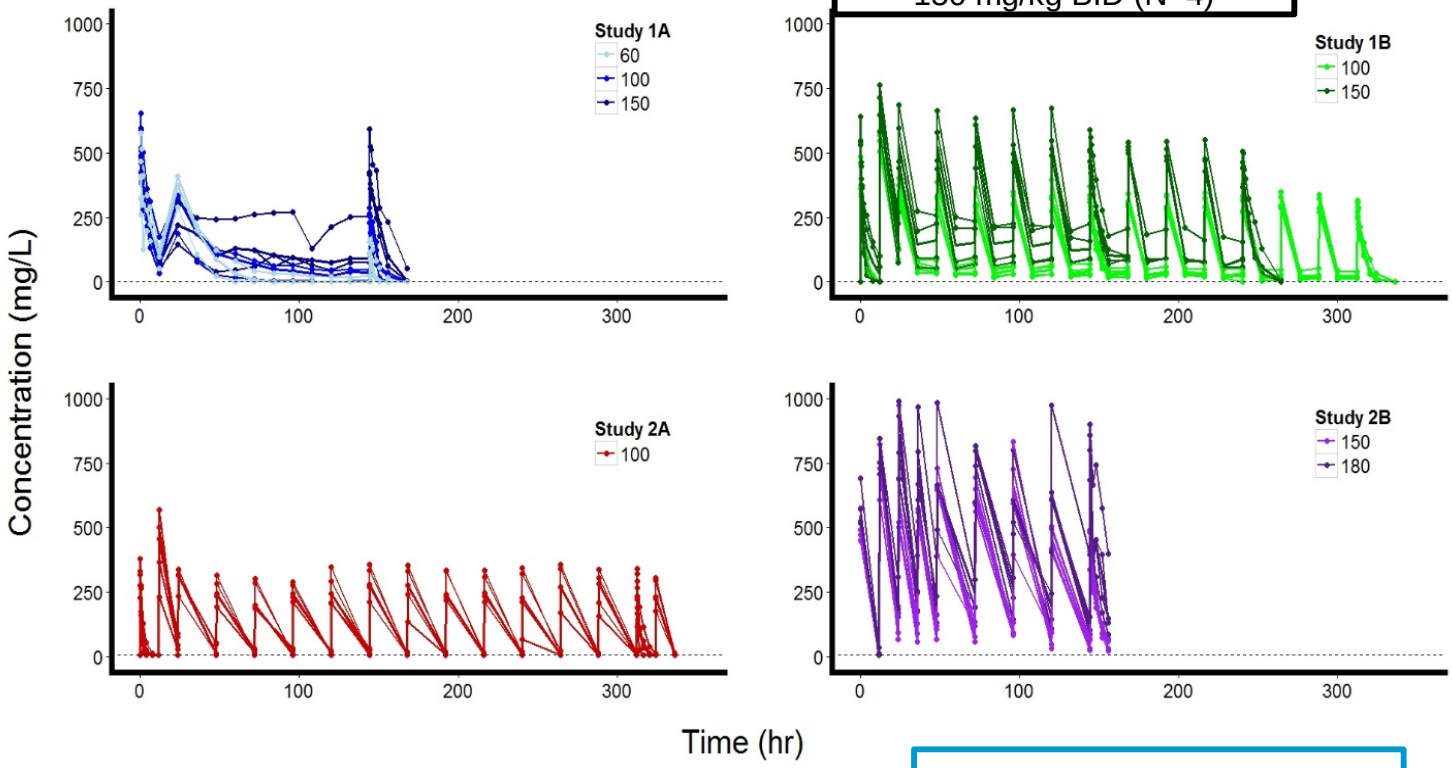
PK model for high dose of favipiravir in NHP



Study 1A (Toyama)
Non anesthetized Male Chinese Cynomolgus treated for 7 days
60 mg/kg BID (N=3)
100 mg/kg BID (N=3)
150 mg/kg BID (N=3)

Study 1B (Toyama)
Anesthetized Female Chinese Cynomolgus treated for 14 days

100 mg/kg BID (N=4)
150 mg/kg BID (N=4)



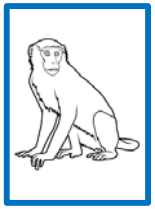
Study 2A (Reaction)
Anesthetized Female Mauritian Cynomolgus treated for 14 days

100 mg/kg BID (N=5)

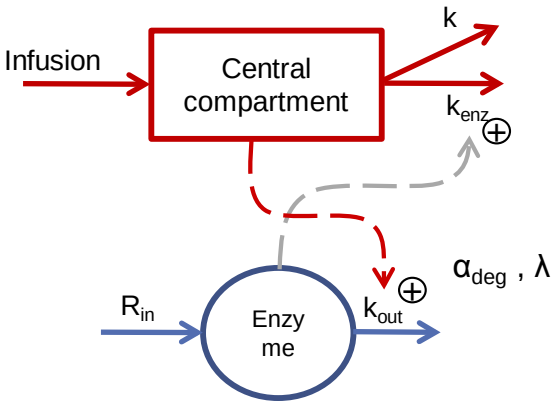
Study 2B (Reaction)
Anesthetized Female Mauritian Cynomolgus treated for 7 days

150 mg/kg BID (N=4)
180 mg/kg BID (N=4)

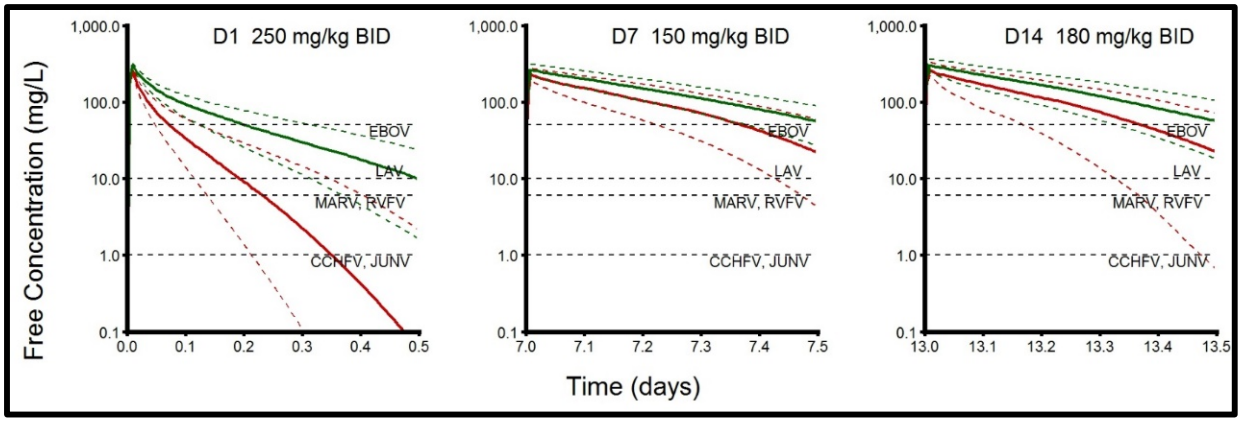
PKVK Model for favipiravir in NHP



- Model accounts for concentration dependent aldehyde oxidase inhibition
- Enzyme dependent elimination rate increased over time and was higher in NHPs from Mauritian than from Chinese origin

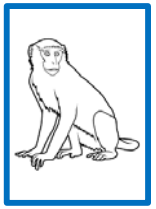


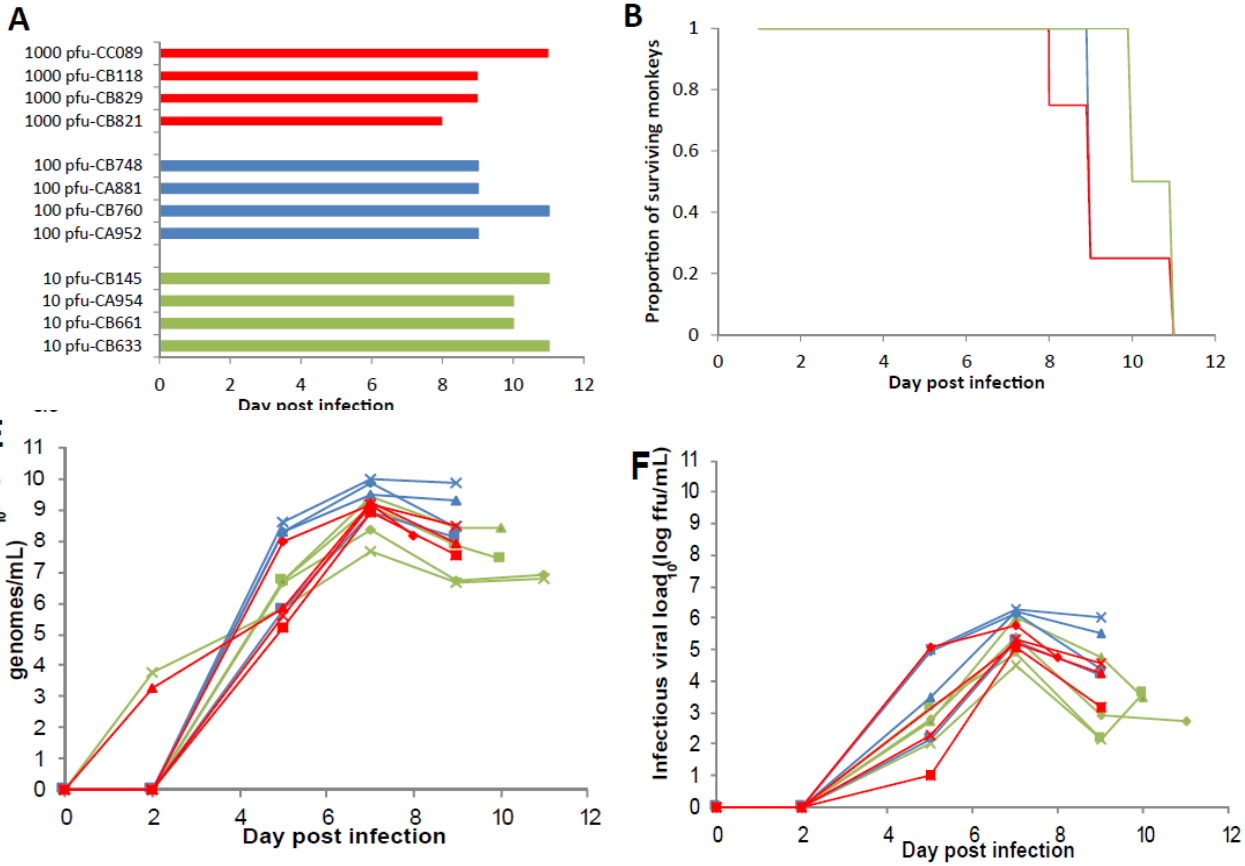
➢ **Proposed doses for BSL4 studies (Mauritian NHP): 250/150/180 mg/kg BID**



Madelain, Guedj, Mentré, Nguyen, Jacquot, Oestereich, Kadota, Yamada, Taburet, de Lamballerie, Raoul. Favipiravir pharmacokinetics in non-human primates: insights for future efficacy studies of haemorrhagic fever viruses, *Antimicrobial Agents Chemotherapy (2016)*

NHP model in French BSL4 (untreated)





Piorkowsky, Jacquot, Quérat, Carbonnelle, Pannetier, Mentré, Raoul, de Lamballerie. Implementation of a non-human primate model of Ebola disease: Infection of Mauritian cynomolgus macaques and analysis of virus population, *Antiviral Research (2017)*

- **Studies ongoing in EBV-infected NHP in BSL4 in France with various doses of favipiravir**

Discussion on dose of favipiravir in Ebola

- Complex PK of favipiravir: concentration and time dependent aldehyde oxidase inhibition & genetic polymorphism
- High EC50 for EBV: Higher doses needed and longer treatment
- Trials in patients before NHP studies and before PK studied in healthy volunteers with high doses
- Combination studies in NHP in preparation

➢ **Be ready for next outbreak of Ebola Virus** (and other hemorrhagic fevers)

Will There Be a Cure for Ebola?

Anthony P. Cardile, Travis K. Warren, Karen A. Martins, Ronald B. Reisler, and Sina Bavari

US Army Medical Research Institute of Infectious Diseases, Frederick, Maryland 21702; email: anthony.p.cardile.mil@mail.mil

Annu. Rev. Pharmacol. Toxicol. 2017. 57:329–48

First published online as a Review in Advance on December 7, 2016

The *Annual Review of Pharmacology and Toxicology* is online at pharmtox.annualreviews.org

This article's doi: 10.1146/annurev-pharmtox-010716-105055

Keywords

BCX4430, brincidofovir, favipiravir, GS-5734, ZMapp, convalescent plasma

Abstract

Despite the unprecedented Ebola virus outbreak response in West Africa, no Ebola medical countermeasures have been approved by the US Food and Drug Administration. However, multiple valuable lessons have been learned about the conduct of clinical research in a resource-poor, high risk–pathogen setting. Numerous therapeutics were explored or developed during the outbreak, including repurposed drugs, nucleoside and nucleotide analogues (BCX4430, brincidofovir, favipiravir, and GS-5734), nucleic acid–based drugs (TKM-Ebola and AVI-7537), and immunotherapeutics (convalescent plasma and ZMapp). We review Ebola therapeutics progress in the aftermath of the West Africa Ebola virus outbreak and attempt to offer a glimpse of a path forward.

5. BRIDGING THE GAP between Pharmacometricians and Biostatisticians

STATE OF THE ART

nature publishing group

Statisticians and Pharmacokineticists: What They Can Still Learn From Each Other

S Senn[1]

Examples are given of how the practice of statistics could be improved if statisticians showed a greater awareness of pharmacokinetic and pharmacodynamic modeling. Some examples are also given where a wider appreciation of statistical theory would improve current approaches to pharmacometrics. Areas in which the two disciplines are in agreement but have failed to have as much influence on others in drug development as they ought are also considered. It is concluded that there would be much benefit in increasing collaboration between these disciplines.

VOLUME 88 NUMBER 3 | SEPTEMBER 2010 | www.nature.com/cpt

‘The battle lines were clear’

On the one side were the forces of light:

those who liked models used biological insights, generally welcomed data from disparate sources and were not afraid to try various bold and ingenious strategies for putting models and data together

Bridging the gap

On the other side were the forces of darkness:

a bunch of dice throwers and hypothesis testers with an inane obsession with intention to treat

Statisticians and Pharmacokineticists: What They Can Still Learn From Each Other, S Senn, Clinical Pharmacology and Therapeutics (2010) 88: 328–334

Pitfalls in pharmacometrics

- **Handling of data (per protocol, ITT, missing, dropout)**
  - problem especially in confirmatory analysis
- **Multiple testing in model building, covariates analysis …**
  - Lack of control of type I error
- **Model evaluation, checking assumptions**
  - No standard procedure
- **Often lacking model based analysis plan**
- **Design / sample size (uncertainty…)**

From Stacey Tannenbaum (Astellas Pharma), WCoP 2016

Pitfalls in biostatistics

- **‘Stuck’ to standard linear or standard empirical models**
- **Like few assumption models**
  - whereas PKPD based on centuries of physiology in pharmacology
- **Reluctance to use new software/ tools, and not totally pre-specified analysis**
  - ‘fear’ for NLMEM

Tension between PMX and Stats

Kowalski (2015), "**My Career as a Pharmacometrician and Commentary on the Overlap Between Statistics and Pharmacometrics in Drug Development**", *Statistics in Biopharmaceutical Research*, 7:148-159.

- Mechanistic versus empirical models
- Adequacy of the model fit and predictive performance
- Exposure-response relationships
- Exposure versus dose
- Inadequate understanding of statistics
- Use of assumption-rich models
- Drawing confirmatory conclusions from exploratory data analysis

From Stacey Tannenbaum (Astellas Pharma), WCoP 2016

Benefits: evolution of both groups

- **More standardization in pharmacometrics**
- **More modelling in biostatistics (analysis of longitudinal data in clinical trials)**

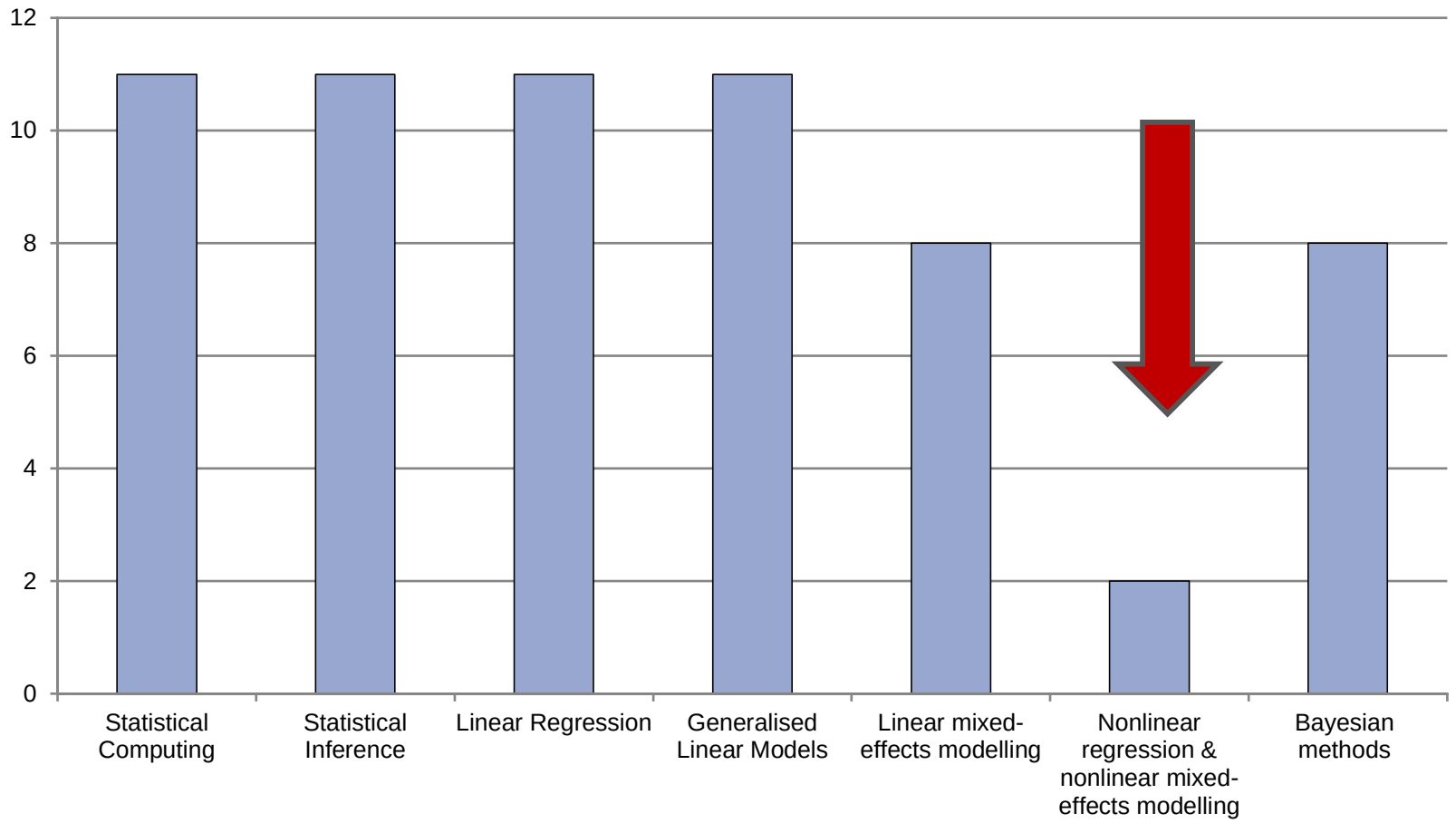
➢ **Education and teaching**

Top 16 universities for Clinical, Pre-clinical and Health 2015-16

Rank	Institution	Country	Master of Biostatistics	Master of Pharmacometrics	Master of Computational Biology
1	University of Oxford	UK	√ (MSc Applied Stats)	X	X
2	Harvard University	USA	√	X	√
3	University of Cambridge	UK	X	X	√
4	University College London	UK	√	X	X
=5	University of California, Berkeley	USA	√	X	√ **(1st year PhD)**
=5	Imperial College London	UK	X	X	X
7	Stanford University	USA	√ **(1st year PhD)**	X	√ **(1st year PhD)**
8	King's College London	UK	X	X	X
9	Johns Hopkins University	USA	√	X	X
10	Columbia University	USA	√	X	X
11	University of Toronto	Canada	√	X	X (undergraduate training)
12	University of Edinburgh	UK	X	X	X
13	Karolinksa Institute	Sweden	X	X	X
14	Duke University	USA	√	X	√ **(1st year PhD)**
=15	University of California, Los Angeles	USA	√	X	√ **(MSc Biomathematics)**
=15	University of Melbourne	Australia	√	X	X

From Julie Simpson (University of Melbourne), WCoP 2016

Master of Biostatistics (11 Universities): Skill set for PK-PD modelling?



Time for Quantitative Clinical Pharmacology: A Proposal for a Pharmacometrics Curriculum

N Holford[1] and MO Karlsson[2]

Table 2 Topics for an advanced pharmacometrics course

Week	Lecture topic
1	Optimal design of PKPD studies
2	Model building strategies
3	Model diagnostics
4	Evaluation methods such as bootstrapping, predictive checks
5	Hypothesis testing based on randomization tests
6	Differential equation defined models
7	Non-continuous data analysis (binomial, categorical, frequency, time to event)
8	Bayesian estimation
9	Mixed effect methods
10	Disease Progression models
11	Advanced PKPD models
12	Simulation methods (deterministic and stochastic)

PKPD, pharmacokinetic-pharmacodynamic.

ASA Statistics and Pharmacometrics Interest Group (SxP)

AMERICAN STATISTICAL ASSOCIATION
Promoting the Practice and Profession of Statistics®

ISOP INTERNATIONAL SOCIETY OF PHARMACOMETRICS

- SxP: Special Interest Group created in 2016

➢ Promote collaboration between Statisticians and Pharmacometricians

- to enable each discipline to learn and grow from the other
- to develop innovative approaches to model informed drug development

- Steering Committee
  - Co-chairs: Bret Musser (Merck) & Matt Rotelli (Lilly)
  - Fred Balch (U Utah), Rob Bies (U Buffalo), Brian Corrigan (Pfizer), Kevin Dykstra (qPhametra), Manolis Efthymios (EMA), Jonathan French (Metrum), Lena Friberg (U Uppsala), Alan Hartford (Abbvie), France Mentre (U Paris Diderot & INSERM), Jose Pinheiro (J&J), Dionne Price (FDA), Garry Rosner (Johns Hopkins), Vikram Sinha (FDA), Brian Smith (Novartis), Jing Su (Merck), Neelima Thaneer (BMS), Jingtao Wu (Takeda)

- Membership open to everyone
- Join http://community.amstat.org/sxp/home

Topic	Users	Replies	Views	Activity
About the Pharmacometrics with ASA (PASA) category [image] The Statistics and Pharmacometrics Interest Group (SxP) was named in 2016 and is chartered by both the American Statistical Association (ASA) and International Society of Pharmacometrics (ISOP). This Interest ... read more		0	415	Aug '16
When is a result worth noting? A quick thought on pharmacometrics and multiplicity		5	463	1h
Variability, Uncertainty, and Error		2	125	2d
Optimal PK sampling shedule		5	246	2d
What are the sticking points between statistics and pharmacometrics?		4	251	4d
Survey to Help in Planning		0	12	5d
2016 ASA Biopharmaceutical Section Regulatory-Industry Statistics Workshop		0	141	Oct '16
Announcing SxP (Statistics and Pharmacometrics Interest Group)		0	318	Jun '16
My Career as a Pharmacometrician and Commentary on the Overlap Between Statistics and Pharmacometrics in Drug Development		0	569	Feb '16

There are no more Statistics and Pharmacometrics (SxP) topics.

SxP organizes sessions in both statistics & pharmacometrics conferences

- **PAGE (June 2016):** First announcement of SxP
- **ACOP7 (Oct 2016):** Meet the ASA/ISoP Stat SIG
- **Joint Statistical Meeting (July 2016):** A mixer on SxP SIG

- **WCoP 2016 (August 2016)**

  Session: Bridging the gap between pharmacometricians and statisticians
- **ASA/FDA Regulatory-Industry Statistics Workshop (Sept 2016)**

  Panel session: Moving pharmacometrics and statistics beyond a marriage of convenience - Improving discipline synergy and drug development decision making
- **ASCPT (March 2017)**

  Symposium: Using biomarkers to predict registration endpoints: a look inside the crystal ball
- **Joint Statistical Meeting (July 2017)**

  Session: Pharmacometric Programming
- **Joint Conference on Biometrics & Biopharmaceutical Statistics (August 2017)**

  Session: Collaboration space between statistics and pharmacometrics: Opportunity and Challenges
- **ACOP8 (Oct 2017)**

  Symposium: Integrating quantitative disciplines - Making model-informed discovery and drug development (MID3) work in practice
- .....

Personal perspectives & hopes ....

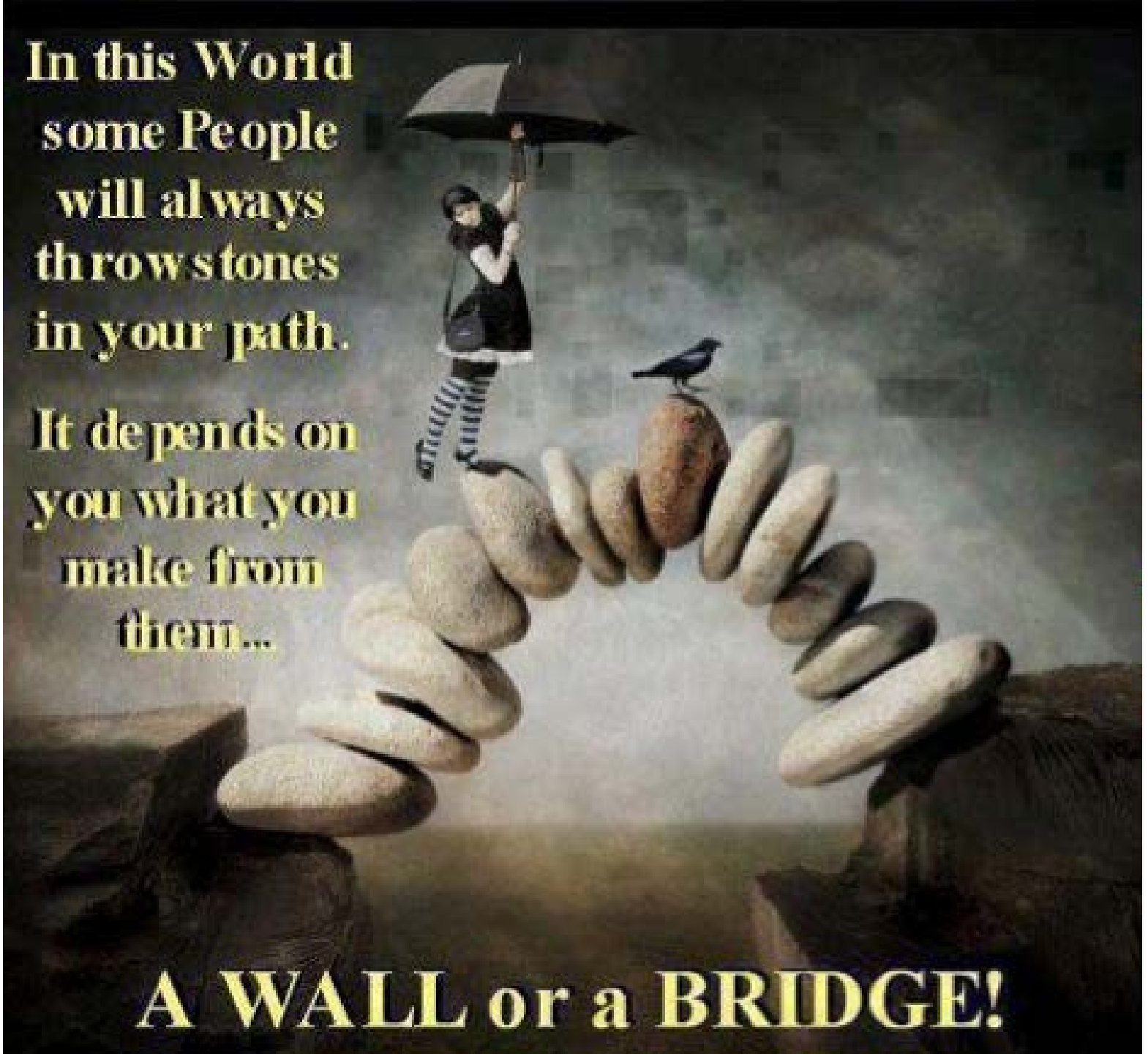
1. **Model-based analysis of pivotal trials in drug development and academic research**
2. **Model-based treatment personalization**
3. **Model-based evaluation of treatments in the developing world**

Pharmacometricians AND

(Bio)Statisticians

➢ **Help decrease disease burden in the world**

- better drugs/ treatments
- better targeted to each patient


In this World some People will always throw stones in your path.
It depends on you what you make from them...
A WALL or a BRIDGE!


We build too many walls
and not enough bridges.
~ Isaac Newton