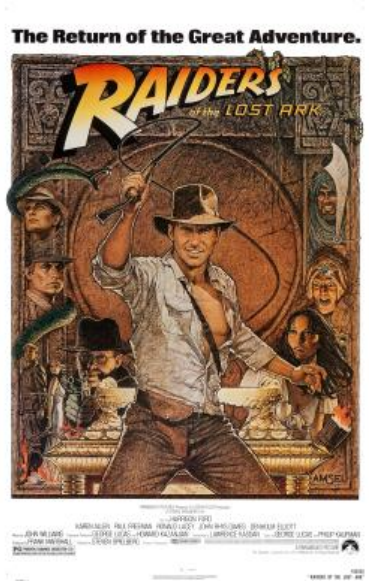
TUTORIAL

Handling within-subject/between-occasion variability in longitudinal data: Common Challenges and Practical Solutions



Paolo Denti

University of Cape Town

PAGE Meeting 2024, Rome, Italy

26 June 2024

Foreword…

Journal of Pharmacokinetics and Biopharmaceutics, Vol. 21, No. 6, 1993

PHARMACOMETRICS

The Importance of Modeling Intero
in Population Pharmacokinetic Ana

M. O. Karlsson[1,3] and L. B. Sheiner[1,2,4]

Received February 11, 1993—Final August 11, 1993

Individual pharmacokinetic parameters may change rando
of simulated data with NONMEM shows that ignoring su
result in biased population parameter estimates. Particula
which they are biased depend on study design and the
variability. Neglecting IOV also results in a high inci
period effects. Perhaps most important, ignoring IOV c
of the potential value of therapeutic drug monitoring. A
and its performance in the presence and absence of IO
well with respect to both model selection and populatio
studied. Analysis of two real data examples using this
eters for both drugs and supports the simulation find
dictable biases occur in parameter estimates and pre

KEY WORDS: interoccasion variability; interi
ability; pharmacokinetics; population analysis; N

Karlsson and Sheiner, **1993**, https://doi.org/10.1007/BF01113502

Outline of the tutorial

Introduction: layers of variability in PK/PD parameters

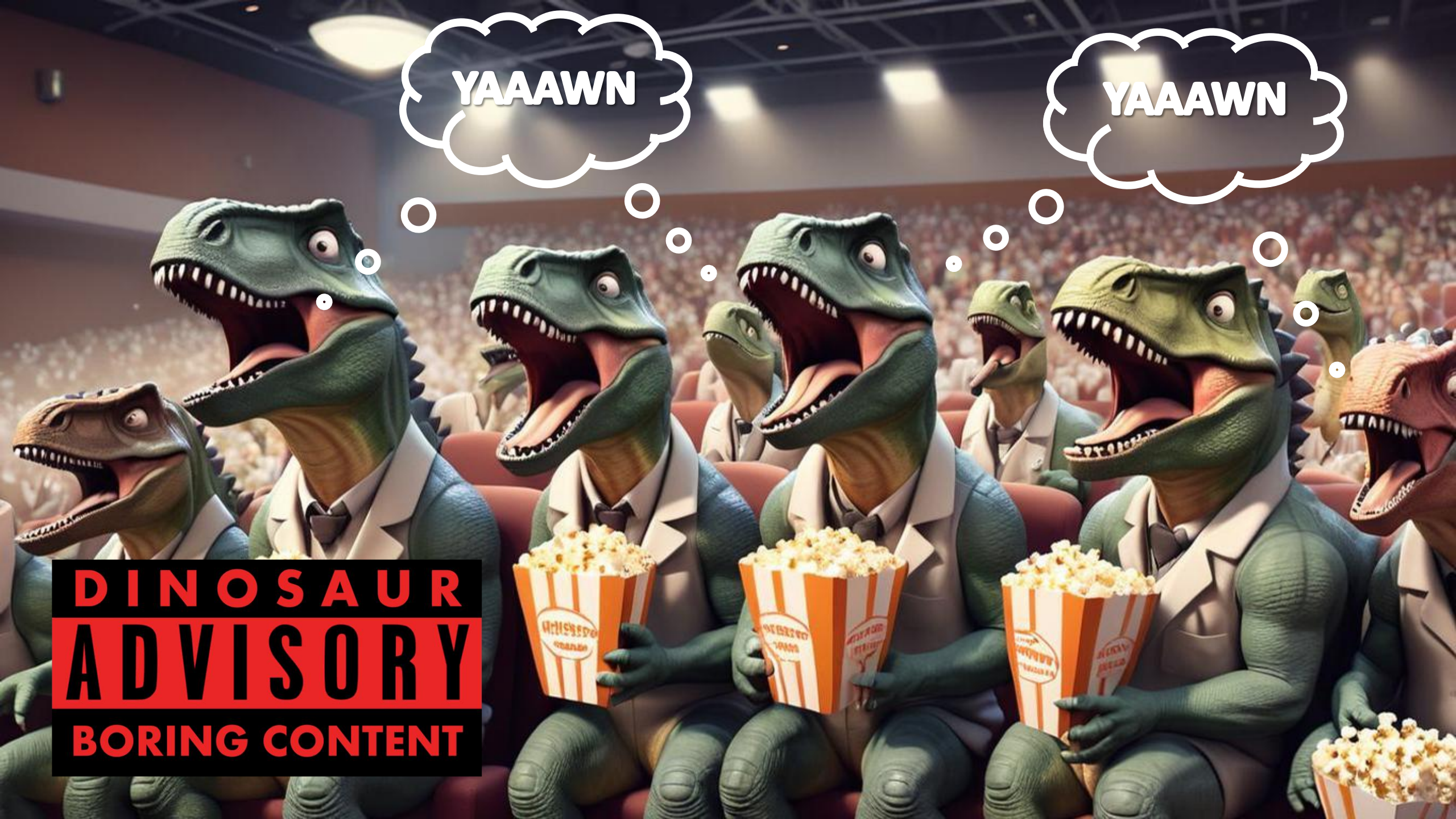
Case study, modelled with BSV only

Implementation of BOV in the dataset/model

Case study, now modelled with layers of variability

Idea: BOV as a tool to handle uncertain dosing history?

Conclusions/recommendations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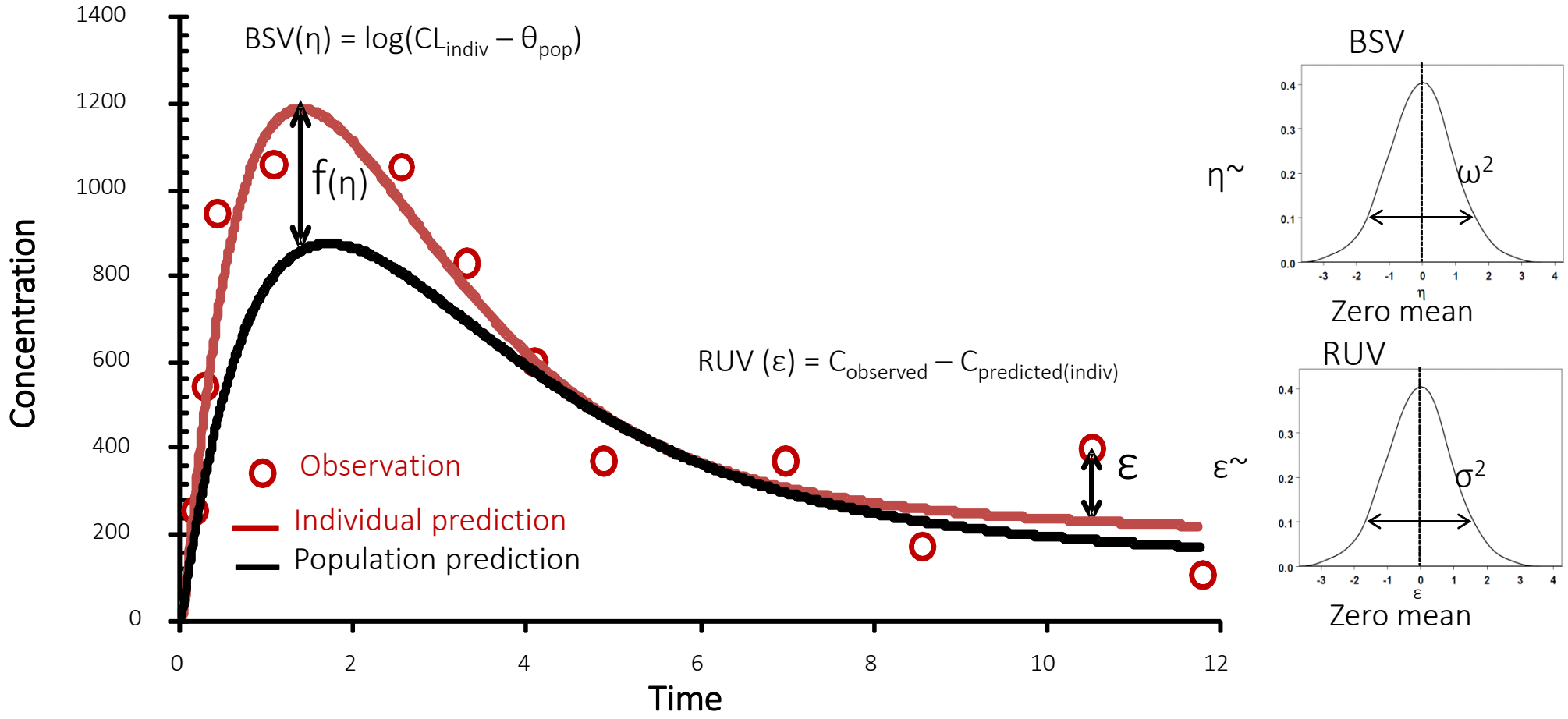
Stochastic variability in our models



Typical value

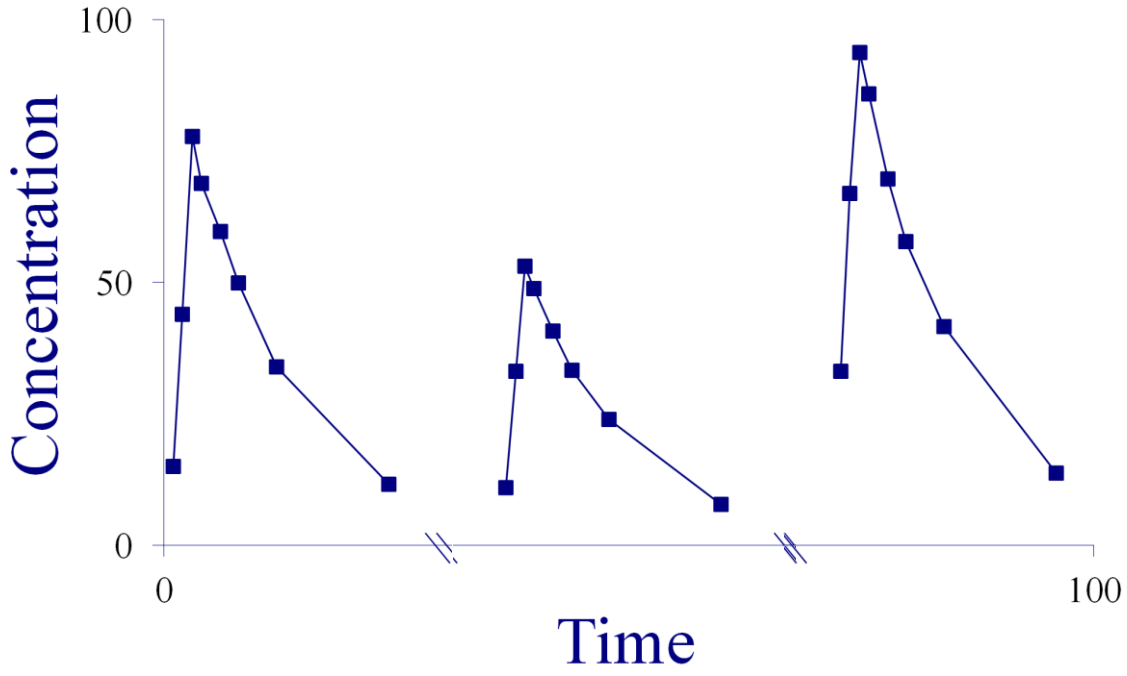
Inter-individual variability

Residual unexplained variability

$y = f(\vartheta)$ → $y = f(\vartheta,\eta)$ → $y = f(\vartheta,\eta)+\varepsilon$ → Experimental data

Slide courtesy of ???

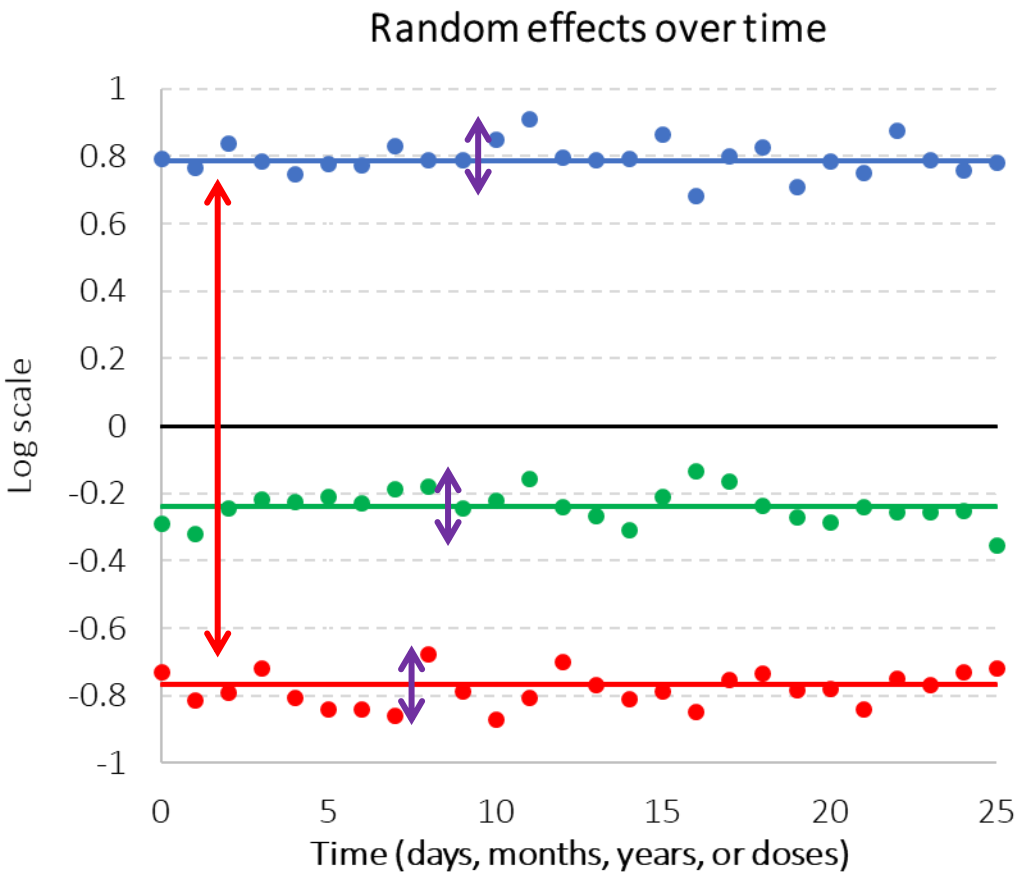
Within-subject variability

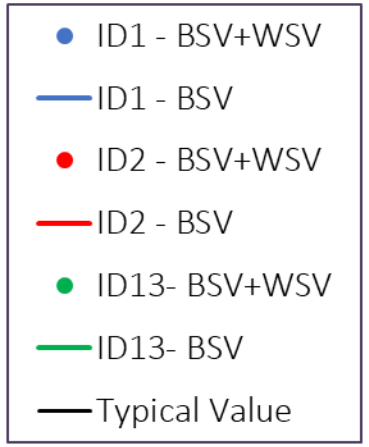


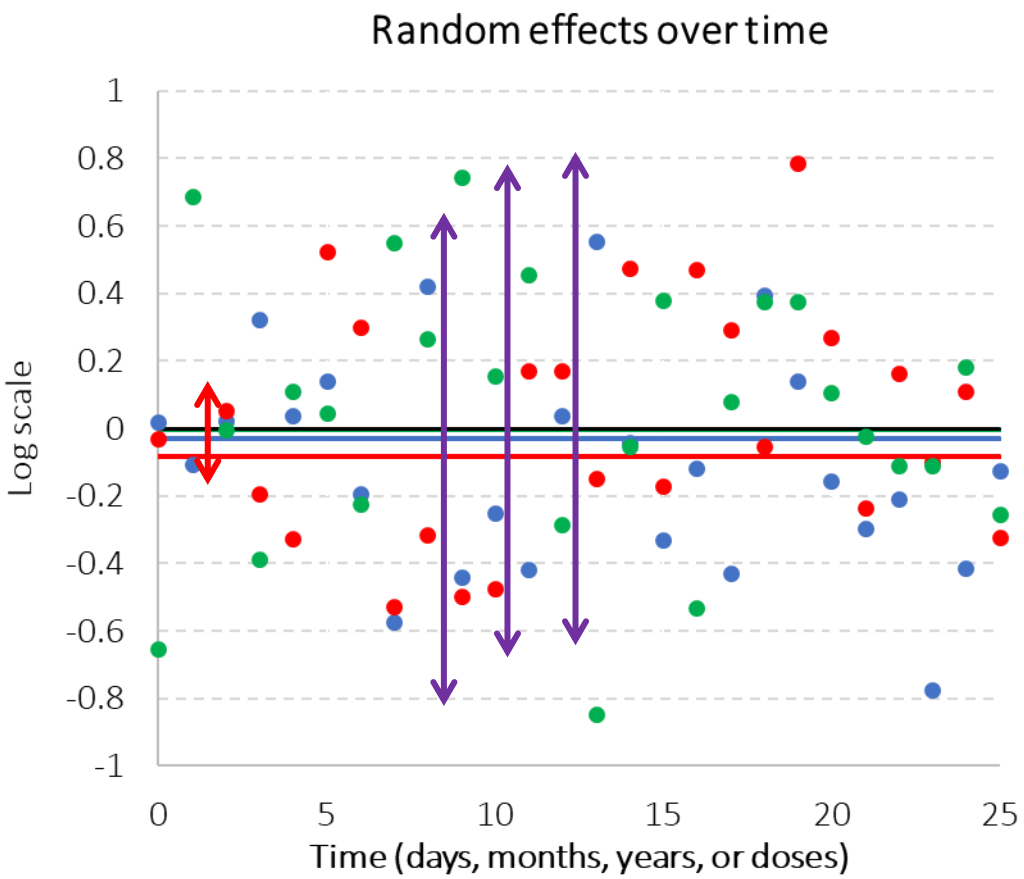
Separate layers of ETA variability

Between subject variability (BSV) >> Within-subject variability (WSV)

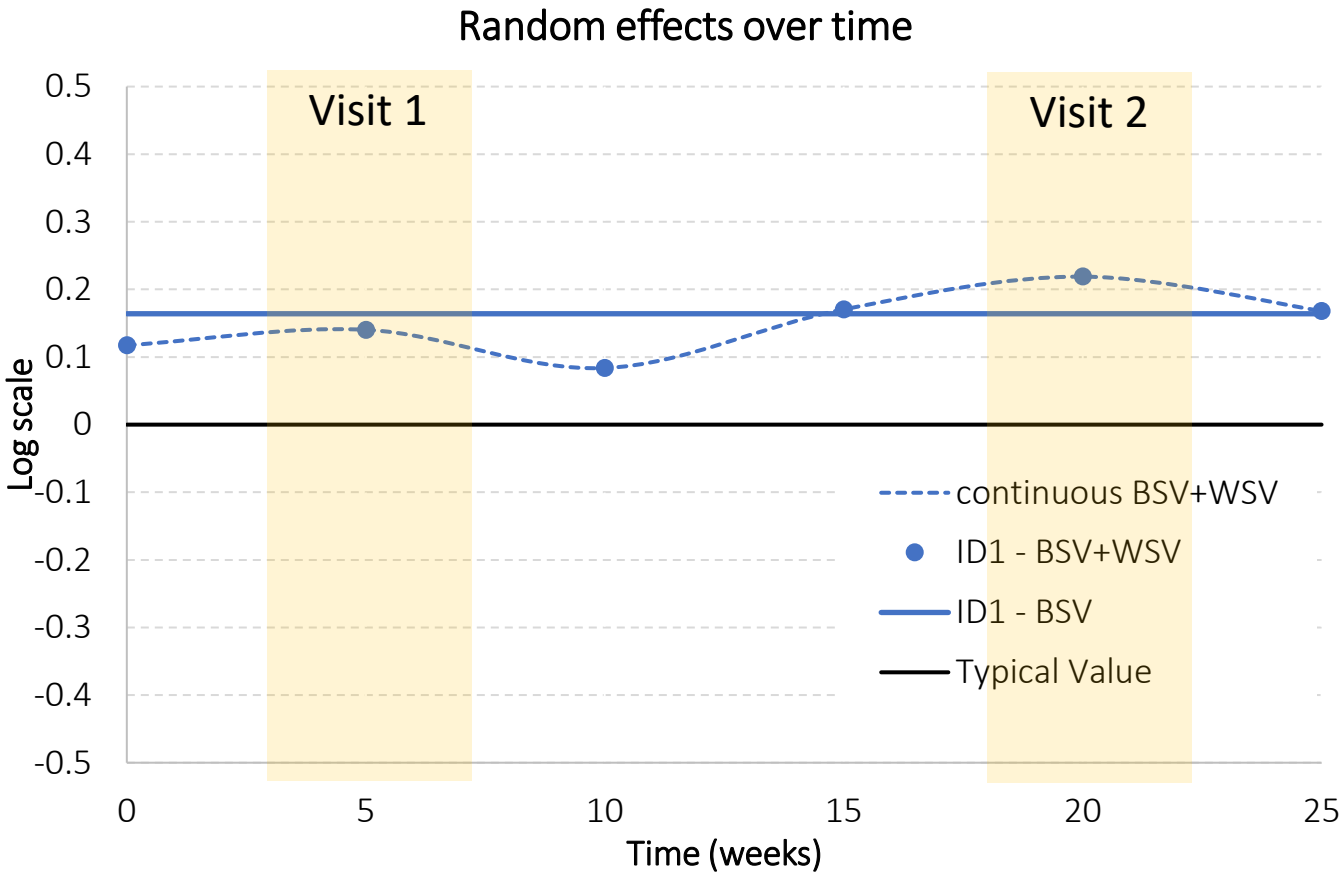
BSV << WSV







The time course of within-subject variability



Some parameters change **gradually**, sometimes quite slowly compared to the data (e.g. volume of distribution).

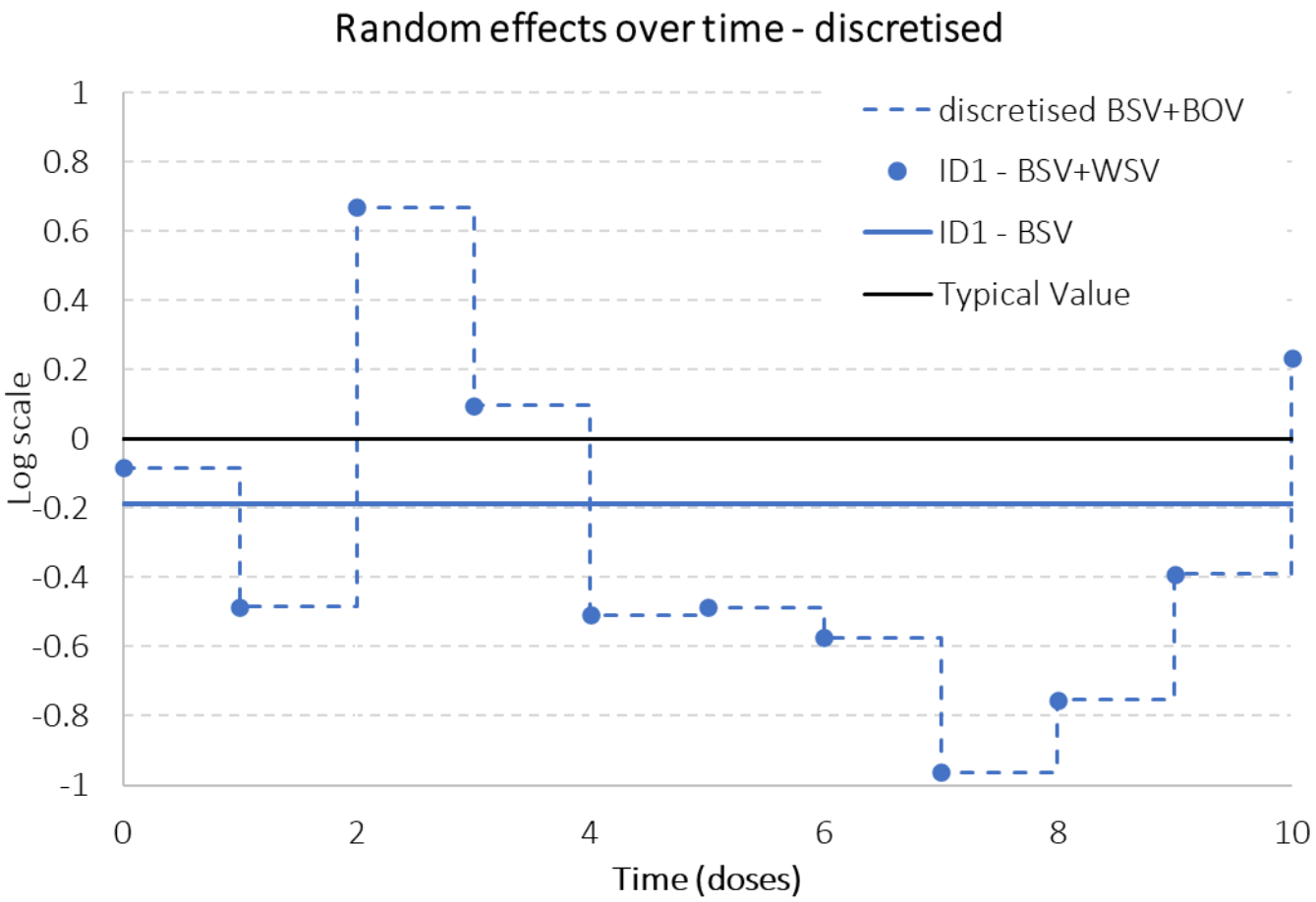
If these gradual changes are of interest, or important interpret the data, one may need to model them, for example **with stochastic differential equations**.

If not, one generally accepts the approximation that the parameters are **constant for the duration of the "visit".**

Deng et al., 2016, https://doi.org/10.1007/s10928-016-9473-1

Tornøe et al., 2005, https://10.1007/s11095-005-5269-5

WSV can be approximated into BOV



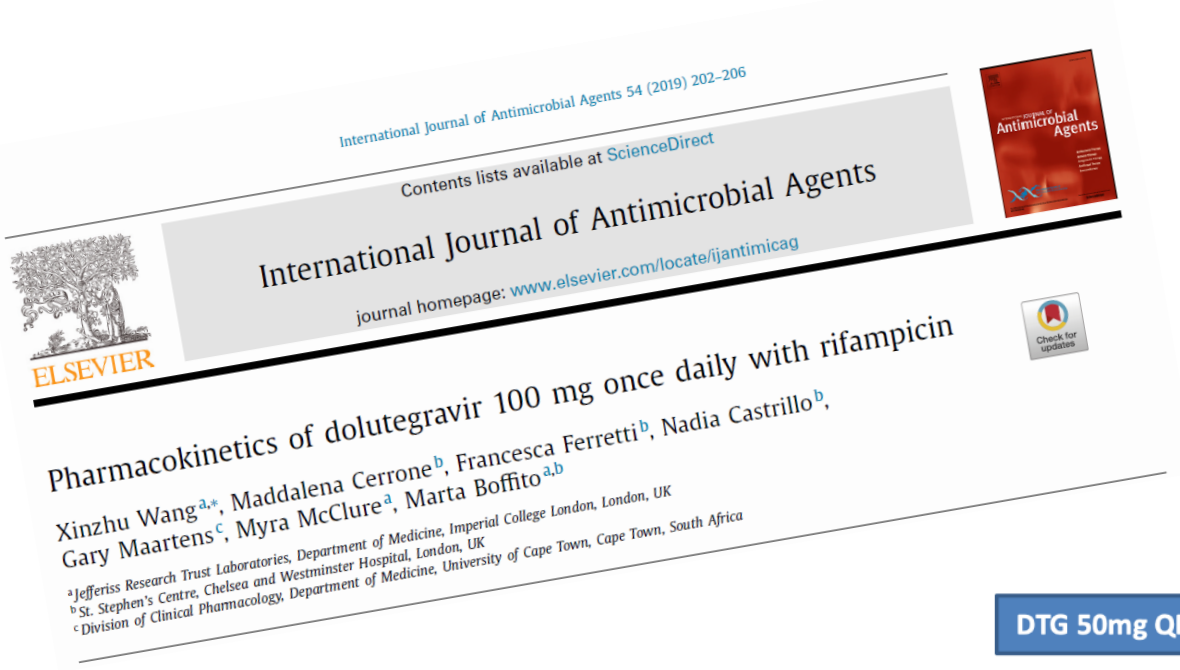
For other parameters (e.g. absorption) **changes can be quite sudden**.

We can easily assume that **each dose constitutes a separate occasion.**

Example - RADIO study

Allan Kengo

Aida Kawuma



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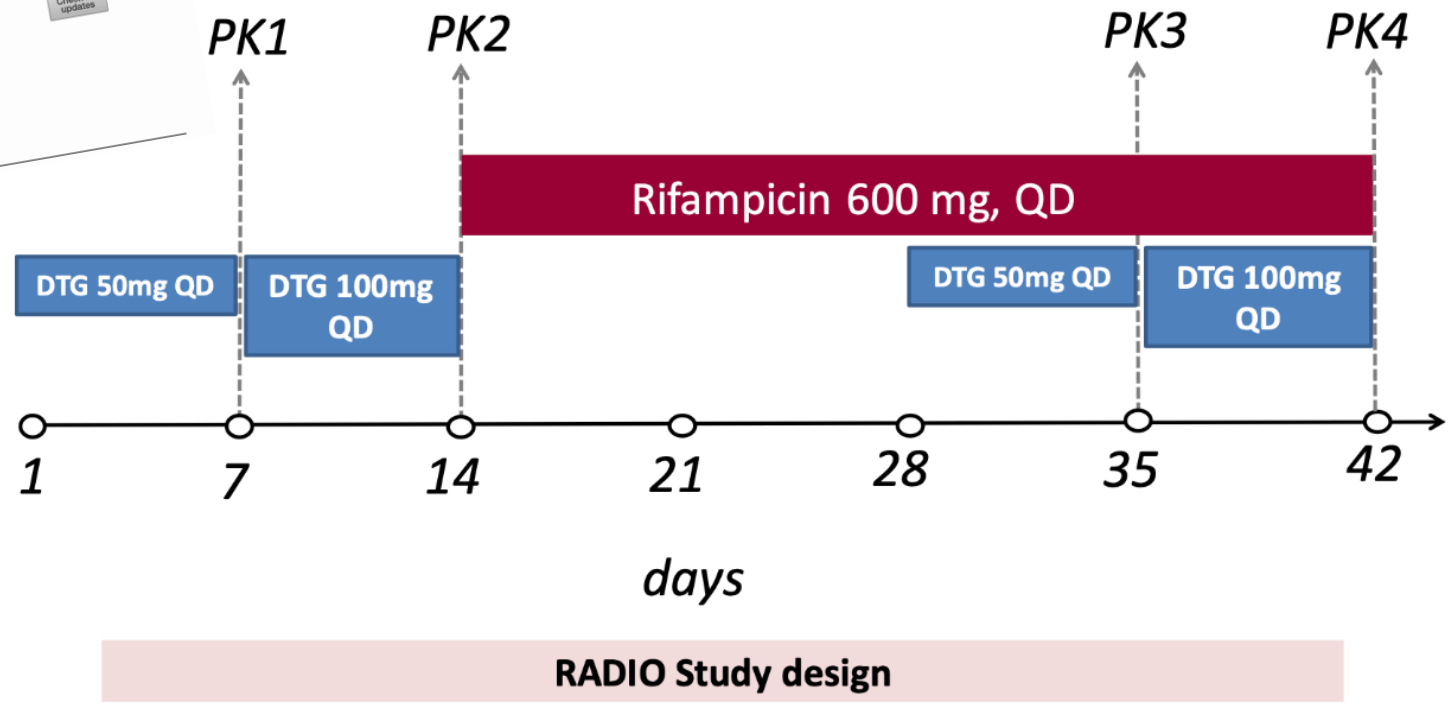
journal homepage: www.elsevier.com/locate/ijantimicag

Pharmacokinetics of dolutegravir 100 mg once daily with rifampicin

Xinzhu Wang[a,*], Maddalena Cerrone[b], Francesca Ferretti[b], Nadia Castrillo[b], Gary Maartens[c], Myra McClure[a], Marta Boffito[a,b]

[a] Jefferiss Research Trust Laboratories, Department of Medicine, Imperial College London, London, UK
[b] St. Stephen's Centre, Chelsea and Westminster Hospital, London, UK
[c] Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Cape Town, South Africa



RADIO Study design

Drug-drug interaction study

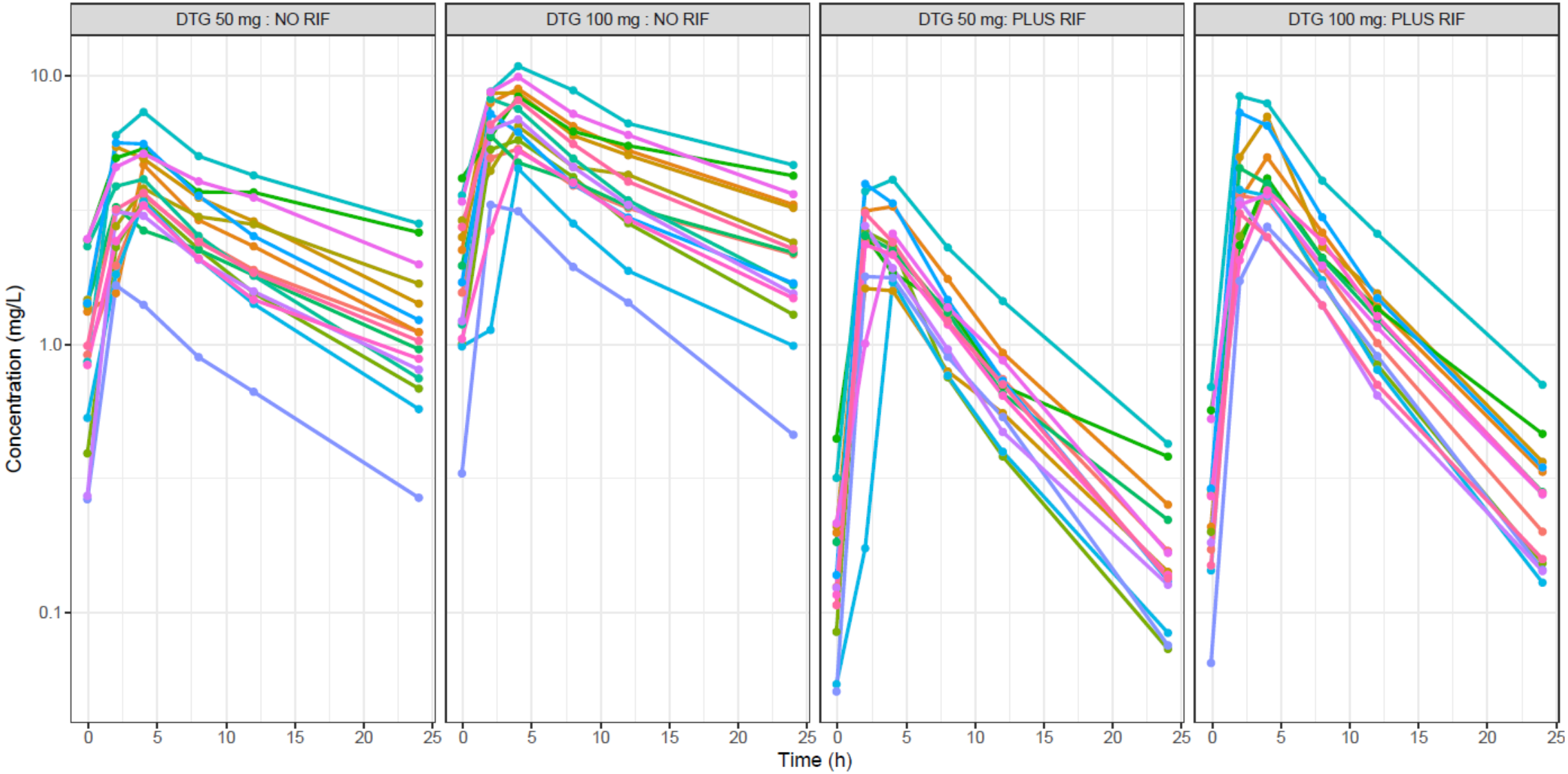
16 Healthy Volunteers

Sampled on 4 PK visits

Slide courtesy of Aida Kawuma

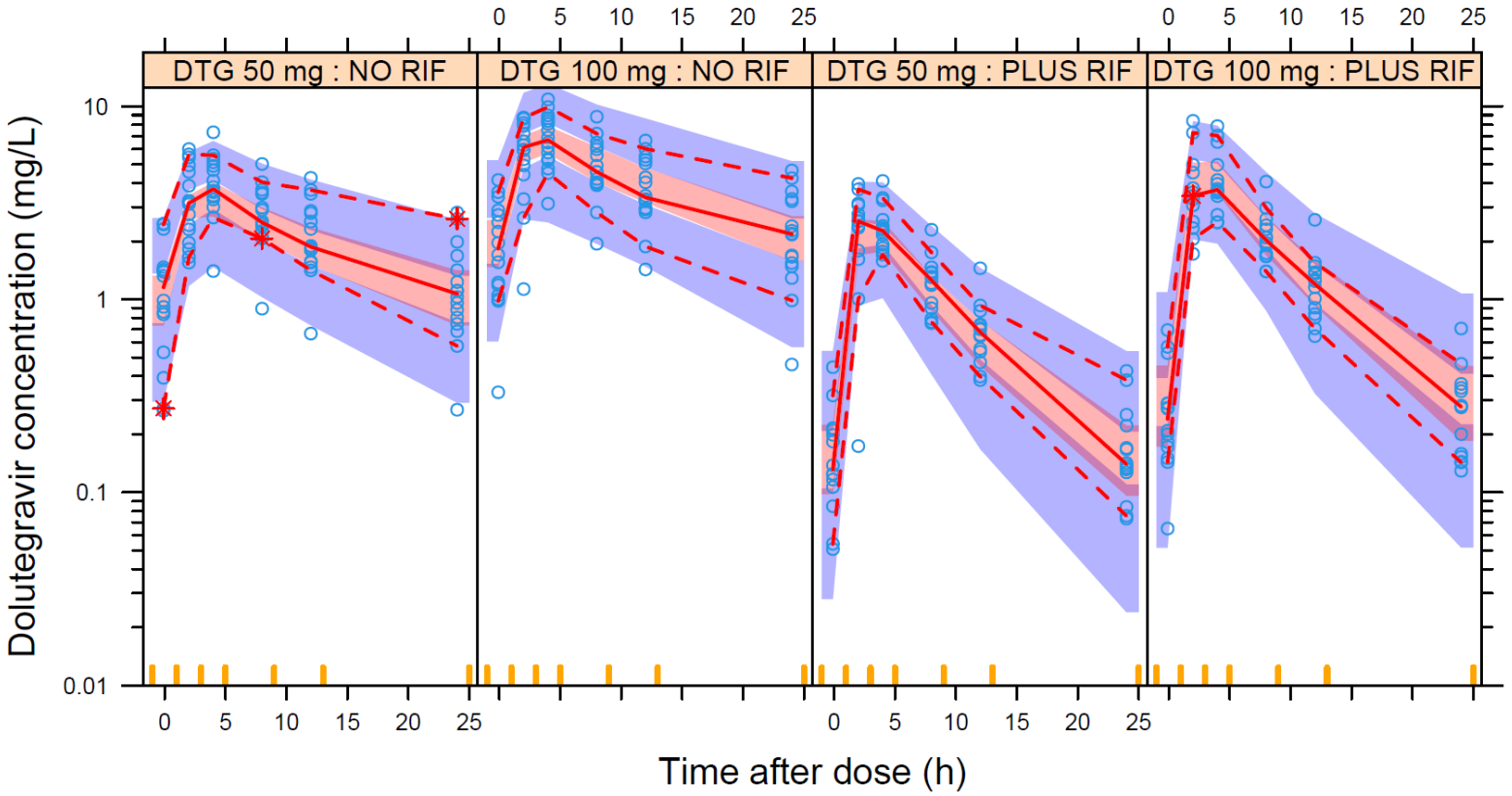
Xinzhu et al., 2019, https://doi.org/10.1016/j.ijantimicag.2019.04.009

RADIO study – Raw data



Best model with only BSV

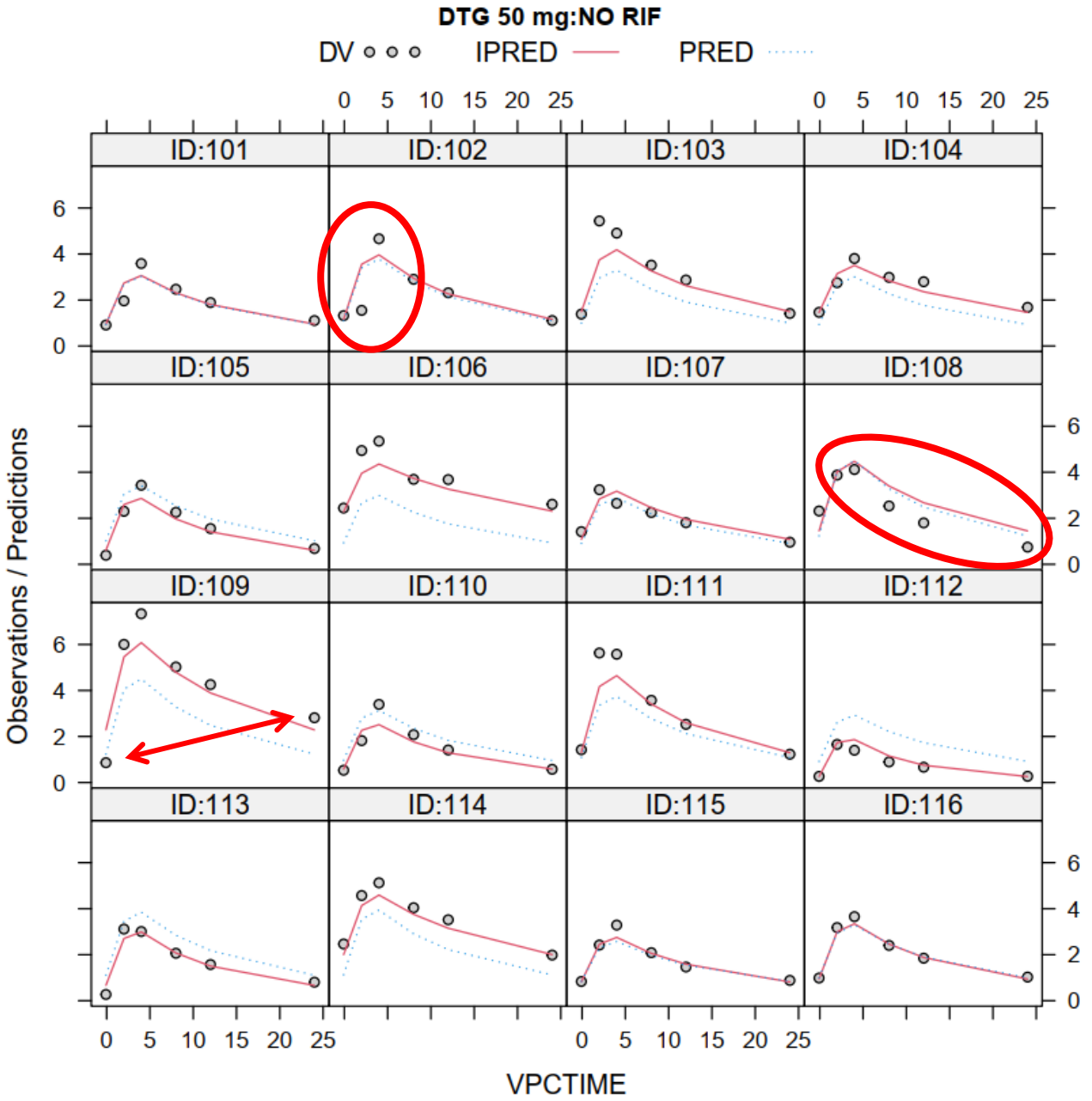
	BSV only	
dOFV	Ref	
	Value	RSE %
CL (L/h)	0.98	6
RIF on CL (fold-change)	2.47	2
Vc (L)	15.0	7
F (.)	1 FIX	-
Dose on F (%)	-	-
Tlag (h)	1.88	1
ka (1/h)	10 FIX	-
Q (L/h)	0.5	37
Vp (L)	3.3	22
Proportional error (%)	26%	4
Additive error (mg/L)	0.02 FIX	-
Btwn **SUBJECT** Var **CL**	24%	28
Btwn **VISIT** Var **CL**	-	
Btwn **SUBJECT** Var **Vc**	16%	35
Btwn **SUBJECT** Var **F**	-	-
Btwn **OCCASION** Var **F**	-	-
Btwn **SUBJECT** Var **ka**	-	-
Btwn **OCCASION** Var **ka**	-	-
Btwn **SUBJECT** Var **Tlag**	-	-
Btwn **OCCASION** Var **Tlag**	-	-



Main findings

- BSV in CL and V - No variability in absorption at ALL
- Proportional RUV ~26%
- 2 compartments was ~20 points OFV better than 1 compt, but KA needs to be fixed

Best model with BSV only



Some **variability in absorption** seems to be there…

Some patients with **IPRED worse than the PRED**!

Concentrations at **0 h quite different from 24 h** (not at steady state?)

Let's address these with other layers of ETA variability!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BOV in NONMEM – Model code

```
$PK
...
BSVKA = ETA(3)

BOVKA = 0
IF (OCC==1)  BOVKA = ETA(11) ; OCCASION 1
IF (OCC==2)  BOVKA = ETA(12) ; OCCASION 2
IF (OCC==3)  BOVKA = ETA(13) ; OCCASION 3
IF (OCC==4)  BOVKA = ETA(14) ; OCCASION 4

KA  = TVKA*EXP(BSVKA+BOVKA)
.....

$OMEGA  BLOCK(1) 0.1  ;    3 BSVKA
.....
$OMEGA  BLOCK(1) 0.1  ;  11 BOVKA
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
```

For **EACH occasion** and parameter with BOV, you need to add an **additional ETA.**

All the ETAs for a BOV, come from an **OMEGA with the SAME size**, so they are virtually all samples from the same distribution.

Considerations:

If even only 1 patient has **4 occasions**, NONMEM will estimate **4 ETAs** -> computational burden.

Important: OCC is NOT a reserved NONMEM variable, but just a **time-varying covariate** (this will cause drama later…)

NONMEM dataset – All doses manually one OCC each

ID	VISIT	**OCC**	TIME	WHAT=DROP	**AMT**	DV	MDV	EVID
1	1	**1**	0	dose1	**50**	.	1	1
1	1	**2**	24	dose2	**50**	.	1	1
1	1	**3**	48	dose3	**50**	.	1	1
1	1	**4**	72	dose4	**50**	.	1	1
1	1	**5**	96	dose5	**50**	.	1	1
1	1	**5**	119.5	0h(predose)	.	0.61	0	0
1	1	**6**	120	dose6(Pkvis)	**50**	.	1	1
1	1	**6**	120.5	0.5h	.	2.38	0	0
1	1	**6**	121	1h	.	3.12	0	0
1	1	**6**	122	2h	.	2.82	0	0
1	1	**6**	123	3h	.	2.52	0	0
1	1	**6**	124	4h	.	2.13	0	0
1	1	**6**	126	6h	.	1.65	0	0
1	1	**6**	128	8h	.	1.28	0	0
1	1	**6**	132	12h	.	1.03	0	0
1	1	**6**	144	24h	.	0.44	0	0

List **EACH dose** in the dataset with their **own OCC** value

List the pre-dose concentrations BEFORE the dose

Considerations:

Loooong dataset

EACH OCC will need an **ETA** for **EACH parameter** with BOV

- Loooots of ETAs and OMEGAs in the model code
- Veeeeery long run times

Are all these leading occasions doing much?

- They are so long before the observed data, little effect on the fit, estimates will have ~100% shrinkage

NONMEM dataset – Lumping occasions with no data

ID	VISIT	OCC	TIME	WHAT=DROP	AMT	DV	MDV	EVID
1	1	1	0	dose1	50	.	1	1
1	1	1	24	dose2	50	.	1	1
1	1	1	48	dose3	50	.	1	1
1	1	1	72	dose4	50	.	1	1
1	1	1	96	dose5	50	.	1	1
1	1	1	119.5	0h(predose)	.	0.61	0	0
1	1	2	120	dose6(Pkvis)	50	.	1	1
1	1	2	120.5	0.5h	.	2.38	0	0
1	1	2	121	1h	.	3.12	0	0
1	1	2	122	2h	.	2.82	0	0
1	1	2	123	3h	.	2.52	0	0
1	1	2	124	4h	.	2.13	0	0
1	1	2	126	6h	.	1.65	0	0
1	1	2	128	8h	.	1.28	0	0
1	1	2	132	12h	.	1.03	0	0
1	1	2	144	24h	.	0.44	0	0

ID	VISIT	OCC	TIME	WHAT=DROP	AMT	DV	MDV	EVID
1	1	0	0	dose1	50	.	1	1
1	1	0	24	dose2	50	.	1	1
1	1	0	48	dose3	50	.	1	1
1	1	0	72	dose4	50	.	1	1
1	1	1	96	dose5	50	.	1	1
1	1	1	119.5	0h(predose)	.	0.61	0	0
1	1	2	120	dose6(Pkvis)	50	.	1	1
1	1	2	120.5	0.5h	.	2.38	0	0
1	1	2	121	1h	.	3.12	0	0
1	1	2	122	2h	.	2.82	0	0
1	1	2	123	3h	.	2.52	0	0
1	1	2	124	4h	.	2.13	0	0
1	1	2	126	6h	.	1.65	0	0
1	1	2	128	8h	.	1.28	0	0
1	1	2	132	12h	.	1.03	0	0
1	1	2	144	24h	.	0.44	0	0

We can lump all occasions/doses with **NO observed data**. This saves ETAs in the model code as well!

We could merge all “historical doses” as OCC=1. However…

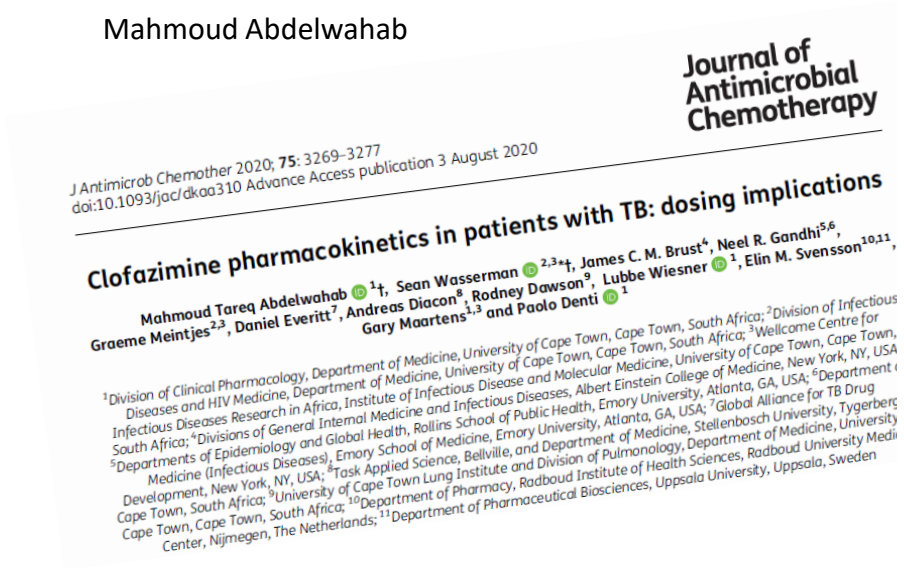
	History								Yesterday	Today
Separate OCC each	-31%	+65%	+26%	-85%	+59%	+0%	-14%	+33%	+41%	-42%
OCC=1	+41%	+41%	+41%	+41%	+41%	+41%	+41%	+41%	+41%	-42%
OCC=0	0	0	0	0	0	0	0	0	+41%	-42%

The **expected value of BOV is 0**, so over a long series, the net effect should average to 0.

But if we use the same OCC (and the same ETA) repeatedly, the **average will not be 0**.

NONMEM dataset – Compounding effect

Mahmoud Abdelwahab



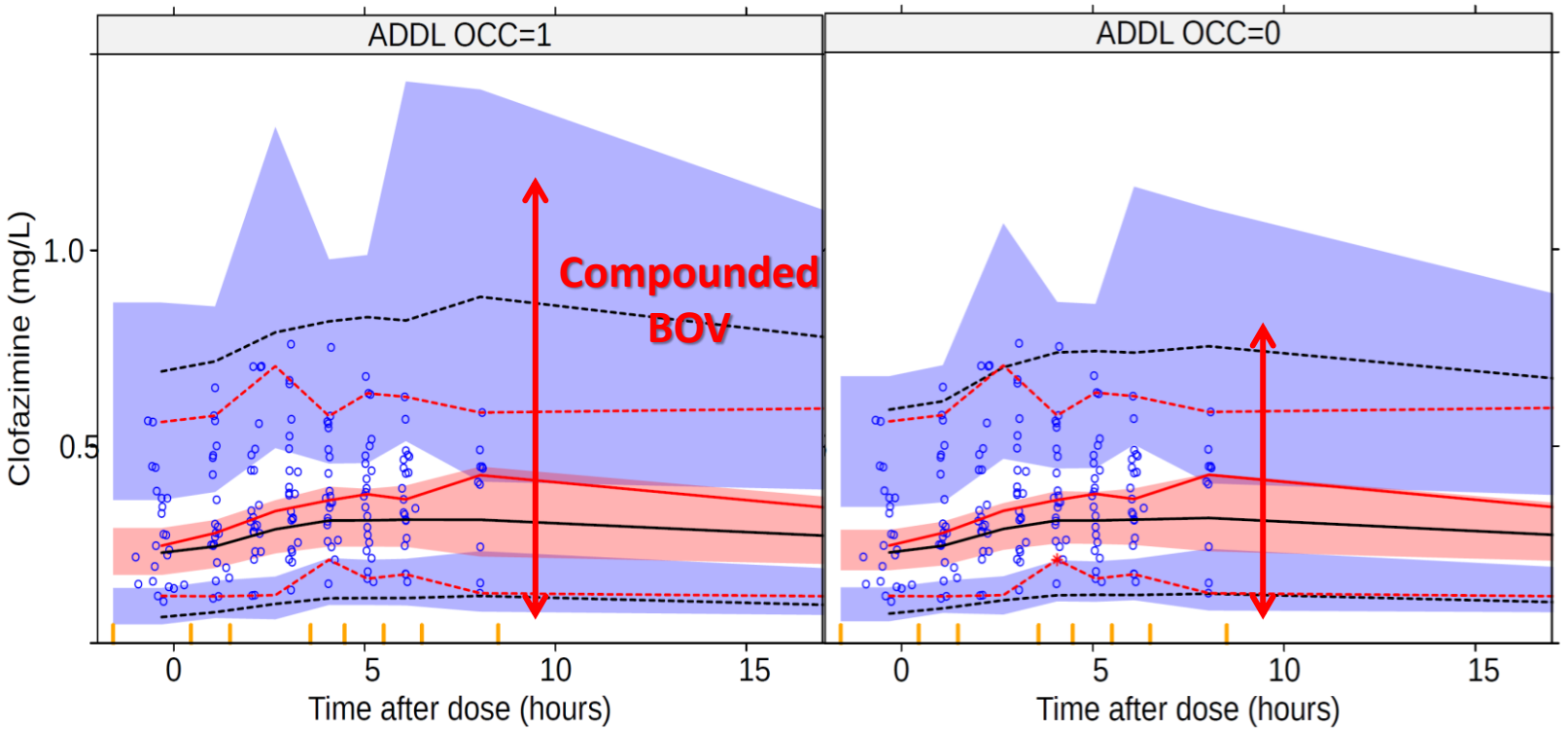
Journal of Antimicrobial Chemotherapy

J Antimicrob Chemother 2020; **75**: 3269–3277
doi:10.1093/jac/dkaa310 Advance Access publication 3 August 2020

Clofazimine pharmacokinetics in patients with TB: dosing implications

Mahmoud Tareq Abdelwahab[1†], Sean Wasserman[2,3*†], James C. M. Brust[4], Neel R. Gandhi[5,6], Graeme Meintjes[2,3], Daniel Everitt[7], Andreas Diacon[8], Rodney Dawson[9], Lubbe Wiesner[1], Elin M. Svensson[10,11], Gary Maartens[1,3] and Paolo Denti[1]

[1]Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Cape Town, South Africa; [2]Division of Infectious Diseases and HIV Medicine, Department of Medicine, University of Cape Town, Cape Town, South Africa; [3]Wellcome Centre for Infectious Diseases Research in Africa, Institute of Infectious Disease and Molecular Medicine, University of Cape Town, Cape Town, South Africa; [4]Divisions of General Internal Medicine and Infectious Diseases, Albert Einstein College of Medicine, New York, NY, USA; [5]Departments of Epidemiology and Global Health, Rollins School of Public Health, Emory University, Atlanta, GA, USA; [6]Department of Medicine (Infectious Diseases), Emory School of Medicine, Emory University, Atlanta, GA, USA; [7]Global Alliance for TB Drug Development, New York, NY, USA; [8]Task Applied Science, Bellville, and Department of Medicine, Stellenbosch University, Tygerberg, Cape Town, South Africa; [9]University of Cape Town Lung Institute and Division of Pulmonology, Department of Medicine, University of Cape Town, Cape Town, South Africa; [10]Department of Pharmacy, Radboud Institute of Health Sciences, Radboud University Medical Center, Nijmegen, The Netherlands; [11]Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden



Clofazimine has a terminal **half-life of MONTHS**

Abdelwahab *et al.*, 2020, https://doi.org/10.1093/jac/dkaa310

Nearly there!

ID	VISIT	OCC	TIME	WHAT=DROP	AMT	DV	MDV	EVID
1	1	0	0	dose1	50	.	1	1
1	1	0	24	dose2	50	.	1	1
1	1	0	48	dose3	50	.	1	1
1	1	0	72	dose4	50	.	1	1
1	1	1	96	dose5	50	.	1	1
1	1	1	119.5	0h(predose)	.	0.61	0	0
1	1	2	120	dose6(Pkvis)	50	.	1	1
1	1	2	120.5	0.5h	.	2.38	0	0
1	1	2	121	1h	.	3.12	0	0
1	1	2	122	2h	.	2.82	0	0
1	1	2	123	3h	.	2.52	0	0
1	1	2	124	4h	.	2.13	0	0
1	1	2	126	6h	.	1.65	0	0
1	1	2	128	8h	.	1.28	0	0
1	1	2	132	12h	.	1.03	0	0
1	1	2	144	24h	.	0.44	0	0

OCC is **NOT a reserved variable in NONMEM**, but a user-defined variable.

When using **$DES (custom differential equations)**, for all user-defined variables, NONMEM used the value **NEXT record in the dataset! This will affect OCC!**

Between TIME 72 and 96, the doses will have Fn, ALAGn, and Dn from the initial dose (OCC=0), BUT for any other parameter (such as KA), NONMEM will already use the value for OCC=1

Similarly, between TIME 119.5 and 120, NONMEM will already use the parameters from OCC=2.

We must find a way to “protect” the change in the value of OCC...

Introducing dummy records

ID	VISIT	OCC	TIME	WHAT=DROP	AMT	DV	MDV	EVID
1	1	0	0	dose1	50	.	1	1
1	1	0	24	dose2	50	.	1	1
1	1	0	48	dose3	50	.	1	1
1	1	**0**	**72**	dose4	50	.	1	1
1	1	**1**	**96**	dose5	50	.	1	1
1	1	**1**	**119.5**	0h(predose)	.	0.61	0	0
1	1	**2**	**120**	dose6(Pkvis)	50	.	1	1
1	1	2	120.5	0.5h	.	2.38	0	0
1	1	2	121	1h	.	3.12	0	0
1	1	2	122	2h	.	2.82	0	0
1	1	2	123	3h	.	2.52	0	0
1	1	2	124	4h	.	2.13	0	0
1	1	2	126	6h	.	1.65	0	0
1	1	2	128	8h	.	1.28	0	0
1	1	2	132	12h	.	1.03	0	0
1	1	2	144	24h	.	0.44	0	0

ID	VISIT	OCC	TIME	WHAT=DROP	AMT	DV	MDV	EVID
1	1	0	0	dose1	50	.	1	1
1	1	0	24	dose2	50	.	1	1
1	1	0	48	dose3	50	.	1	1
1	1	0	72	dose4	50	.	1	1
1	**1**	**0**	**96**	**dummy**	**.**	**.**	**1**	**2**
1	**1**	**1**	**96**	**dose5**	**50**	**.**	**1**	**1**
1	1	1	119.5	0h(predose)	.	0.61	0	0
1	**1**	**1**	**120**	**dummy**	**.**	**.**	**1**	**2**
1	**1**	**2**	**120**	**dose6(Pkvis)**	**50**	**.**	**1**	**1**
1	1	2	120.5	0.5h	.	2.38	0	0
1	1	2	121	1h	.	3.12	0	0

We can introduce extra records (i.e. **DUMMY records**)

- with **EVID=2** (other event)
- with the same **TIME as the NEXT record** at which OCC changes
- with the value of **OCC from the PREVIOUS record**

But what if we have 1 month of leading doses?
Do we have to enter each dose as a separate record?

NONMEM dataset – ADDL – The Dark Lord has returned…

NONMEM dataset - ADDL

ID	OCC	TIME	WHAT=DROP	AMT	ADDL	II	DV	MDV	EVID
1	0	0	dose	600	10	24	.	1	4
1	1	97	day4_1h	.	.	.	6.45	0	0
1	1	100	day4_4h	.	.	.	2.40	0	0
1	2	170	day7_2h	.	.	.	8.42	0	0
1	2	172	day7_4h	.	.	.	3.65	0	0
1	3	241	day10_1h	.	.	.	0.56	0	0
1	3	244	day10_4h	.	.	.	3.24	0	0

ID	OCC	TIME	WHAT=DROP	AMT	ADDL	II	DV	MDV	EVID
1	0	0	dose	600	10	24	.	1	4
1	?	24	addl_dose1	600	.	.	.	1	1
1	?	48	addl_dose2	600	.	.	.	1	1
1	?	72	addl_dose3	600	.	.	.	1	1
1	?	96	addl_dose4	600	.	.	.	1	1
1	1	97	day4_1h	.	.	.	6.45	0	0
1	1	100	day4_4h	.	.	.	2.40	0	0
1	?	120	addl_dose5	600	.	.	.	1	1
1	?	144	addl_dose6	600	.	.	.	1	1
1	?	168	addl_dose7	.	.	.	.	1	1
1	2	170	day7_2h	.	.	.	8.42	0	0
1	2	172	day7_4h	.	.	.	3.65	0	0
1	?	192	addl_dose8	600	.	.	.	1	1
1	?	216	addl_dose9	600	.	.	.	1	1
1	?	240	addl_dose10	600	.	.	.	1	1
1	3	241	day10_1h	.	.	.	0.56	0	0
1	3	244	day10_4h	.	.	.	3.24	0	0

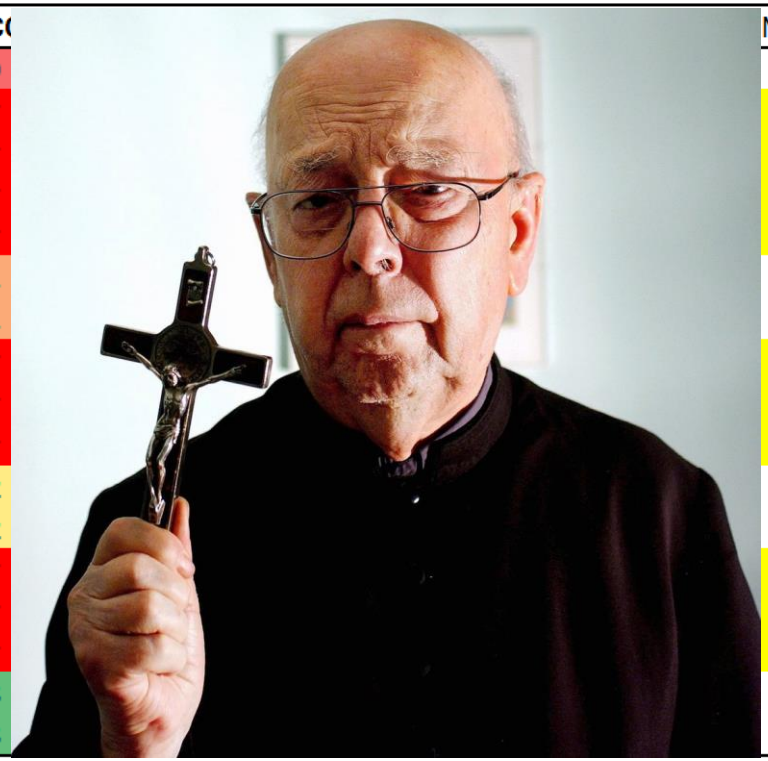
ADDL introduces a **series of doses, each delayed by II**

ALL additional doses **share the same values** of ALAGn, Dn, and Fn (lag time, infusion duration, and bioavailability)
No BOV is present for these parameters!
https://nmhelp.tingjieguo.com/addl.htm

It gets worse… 😈
The value of all user-defined variables (including OCC) is the one from NEXT record (same as before the dummy records).
So, for all the other parameters, NONMEM will skip ahead and already use the value from the OCC of the NEXT record!
This will happened for $DES model, but maaaaaybe, also for pre-coded models if CALLFL=-2
https://nmhelp.tingjieguo.com/$bind.htm

NONMEM dataset - ADDL

ID	OCC	MDV	EVID
1	0	1	4
1	?	1	1
1	?	1	1
1	?	1	1
1	?	1	1
1	1	0	0
1	1	0	0
1	?	1	1
1	?	1	1
1	?	1	1
1	2	0	0
1	2	0	0
1	?	1	1
1	?	1	1
1	?	1	1
1	3	0	0
1	3	0	0



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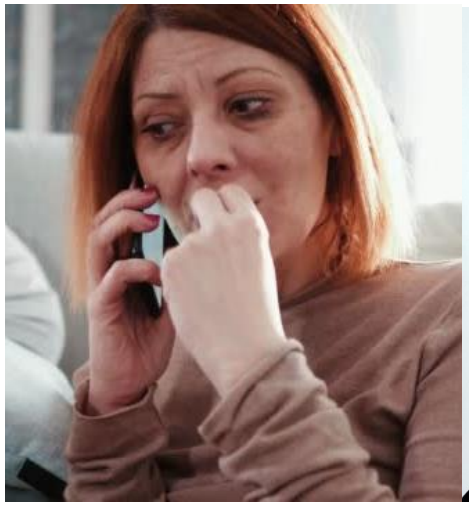
So, for all the other parameters, NONMEM will skip ahead and already use the value from the OCC of the NEXT record!
This will happened for $DES model, but maaaaaybe, also for pre-coded models if CALLFL=-2
https://nmhelp.tingjieguo.com/$bind.htm

NONMEM dataset - Summary

This was a bit more difficult than one would have thought, right?



In summary:

- Assign an OCC value to each "**relevant**" occasion (at least one observation or very close to one)
- All other occasions/doses without observations, should be **lumped together as OCC==0** (so that they don't get a BOV ETA assigned to them)
- If using $DES (ADVAN6, 8, 13, etc) – but maybe a good idea anyway - every time OCC changes without a reset, you need a **dummy record** to "protect" the change of value
- Preferably avoid dose series such as SS and ADDL
  - If you do use SS or ADDL, make sure they have OCC=0 and there is no overlap with changes in OCC (or any other time-changing covariate)

Implementation in other software

nlmixr2

BOV implementation currently available similarly to NONMEM (use OMEGAs constrained to have the same values)
https://github.com/nlmixrdevelopment/nlmixr/issues/93

Regarding ADDL and dummy records, occasions should not suffer from the same issues as NONMEM

Monolix

In Monolix **Occasion** is reserved variable/setting, not a time changing covariate

One can theoretically include as many OCC as one wants (also in Simulx), even on different levels (dose vs visit) without worsening computation.

ADDL with occasions is problematic, similar to NONMEM

OK, done with the boring stuff…

Back to RADIO – Now with multiple layers of ETA variability

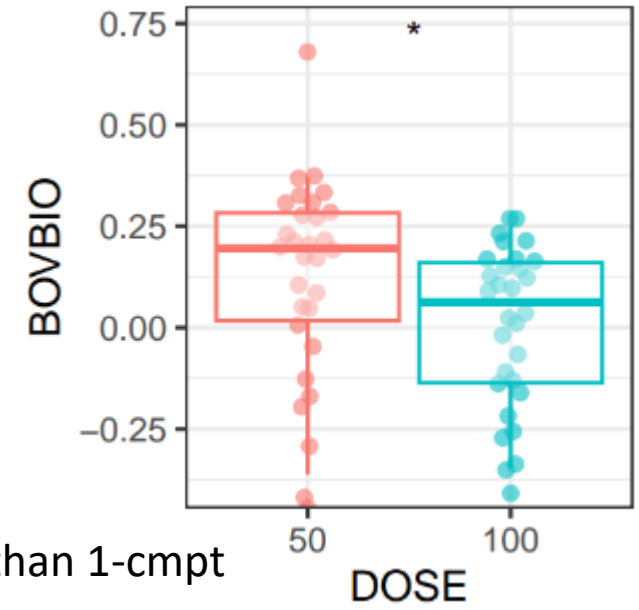
	BSV only		Any variability	
dOFV	Ref		-267	
	Value	RSE %	Value	RSE %
CL (L/h)	0.98	6	1.12	7
RIF on CL (fold-change)	2.47	2	2.44	3
Vc (L)	15.0	7	16.4	6
F (.)	1 FIX	-	1 FIX	-
Dose on F (%)	-	-	-12.2	37
Tlag (h)	1.88	1	1.69	3
ka (1/h)	10 FIX	-	3.53	20
Q (L/h)	0.5	37	1.1	29
Vp (L)	3.3	22	4.1	12
Proportional error (%)	26%	4	9%	7
Additive error (mg/L)	0.02 FIX	-	0.02 FIX	-
Btwn **SUBJECT** Var **CL**	24%	28	21%	15
Btwn **VISIT** Var **CL**	-		9%	15
Btwn **SUBJECT** Var **Vc**	16%	35	-	-
Btwn **SUBJECT** Var **F**	-	-	-	-
Btwn **OCCASION** Var **F**	-	-	32%	9
Btwn **SUBJECT** Var **ka**	-	-	-	-
Btwn **OCCASION** Var **ka**	-	-	-	-
Btwn **SUBJECT** Var **Tlag**	-	-	-	-
Btwn **OCCASION** Var **Tlag**	-	-	8%	17

Changes:
Each dose with data is a **separate OCC**
Each PK profile (>1 week apart) is a **separate VISIT**

Test **BOV on all absorption** parameters (possibly instead of BSV)
Test adding Between Visit Variability **(BVV) in CL**

Improvements:
Better OFV: -267
Lower RUV: From 26% to 9%
Variability in absorption

Dose on F (time-varying covariate) previously hard to detect!

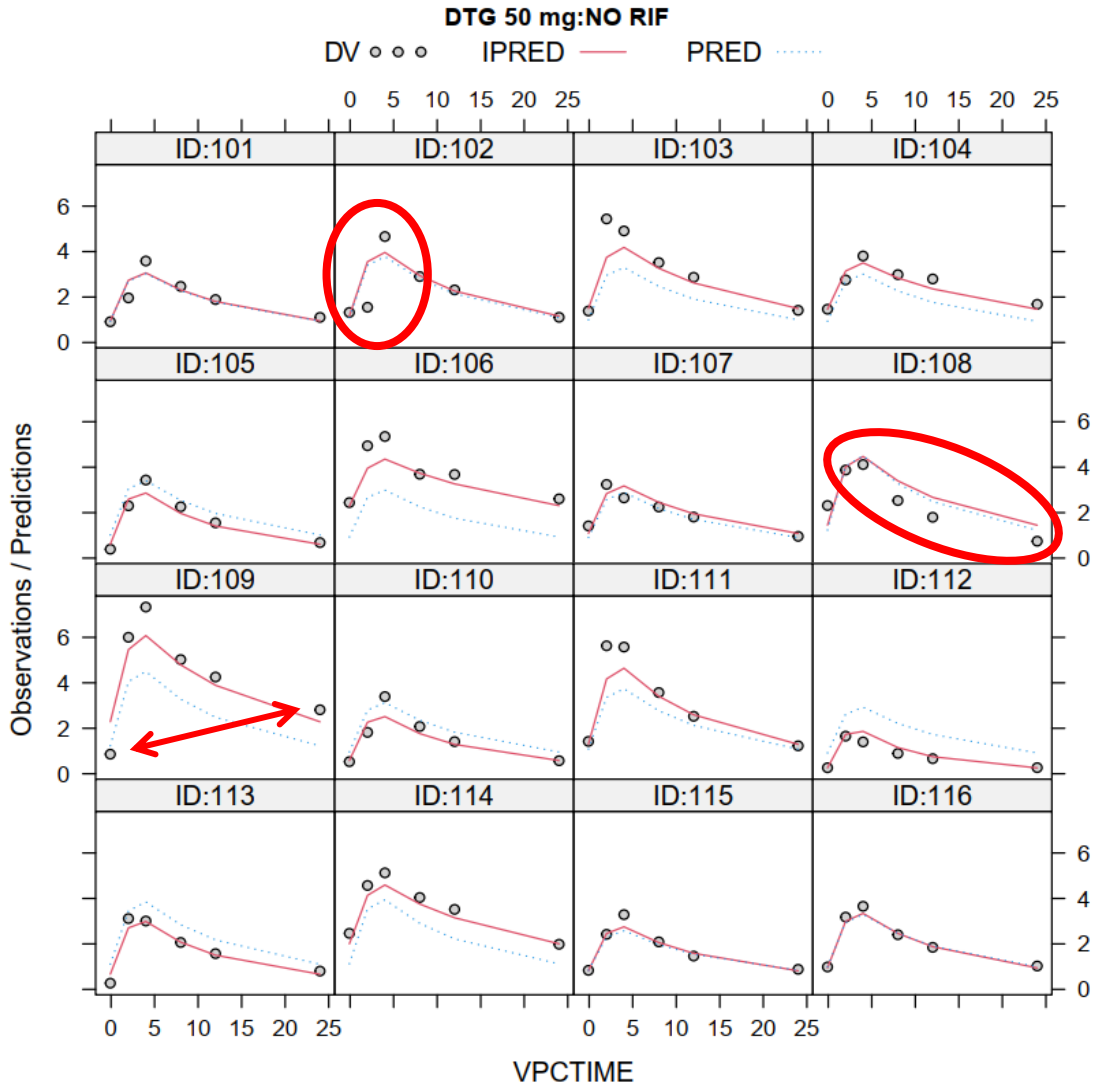


2 cmpt is now 87 points OFV better than 1-cmpt

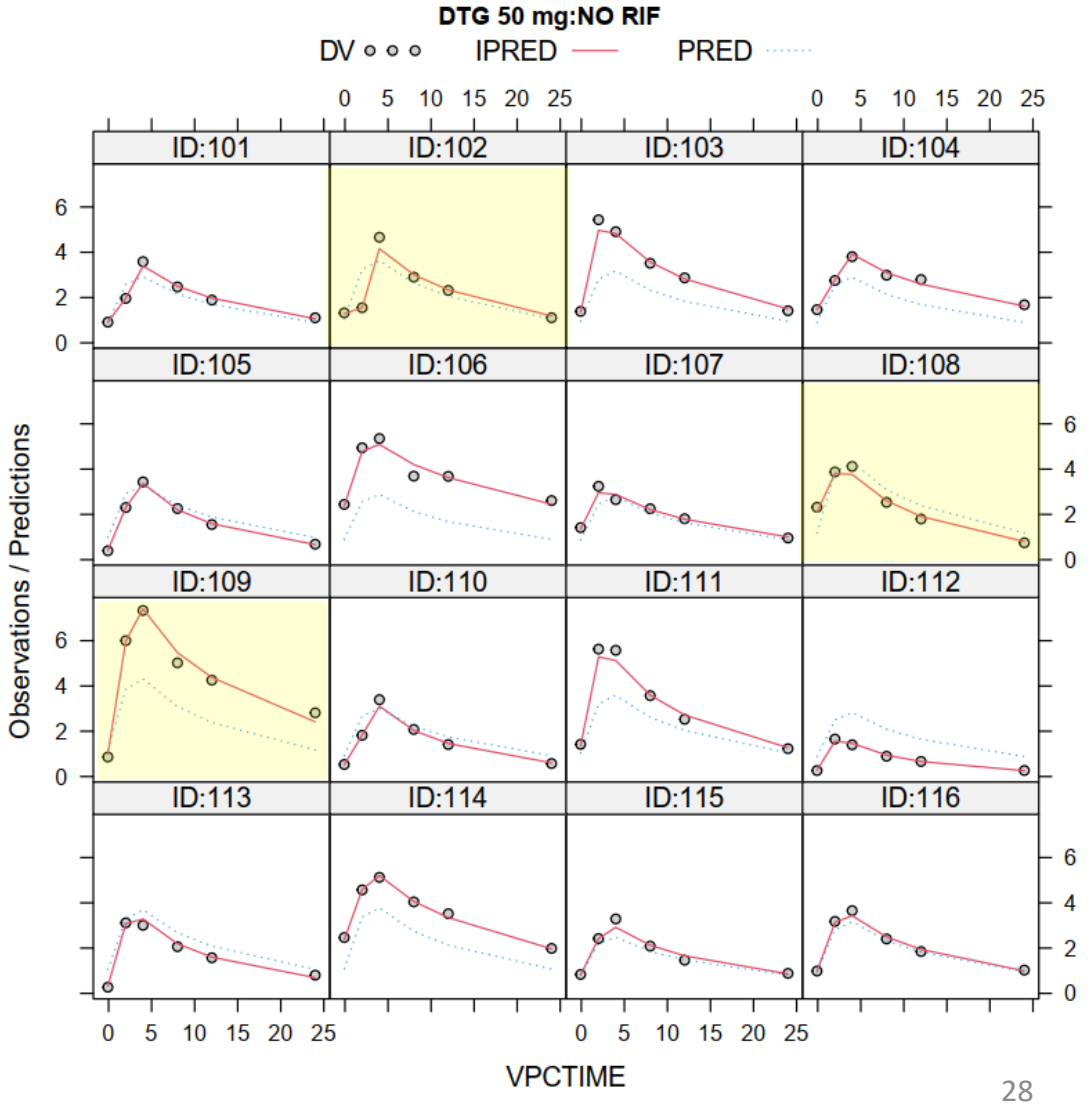
Despite all the extra parameters, the precision of estimates (done with SIR) is the same or better

Model comparison – Individual plots

BSV-only

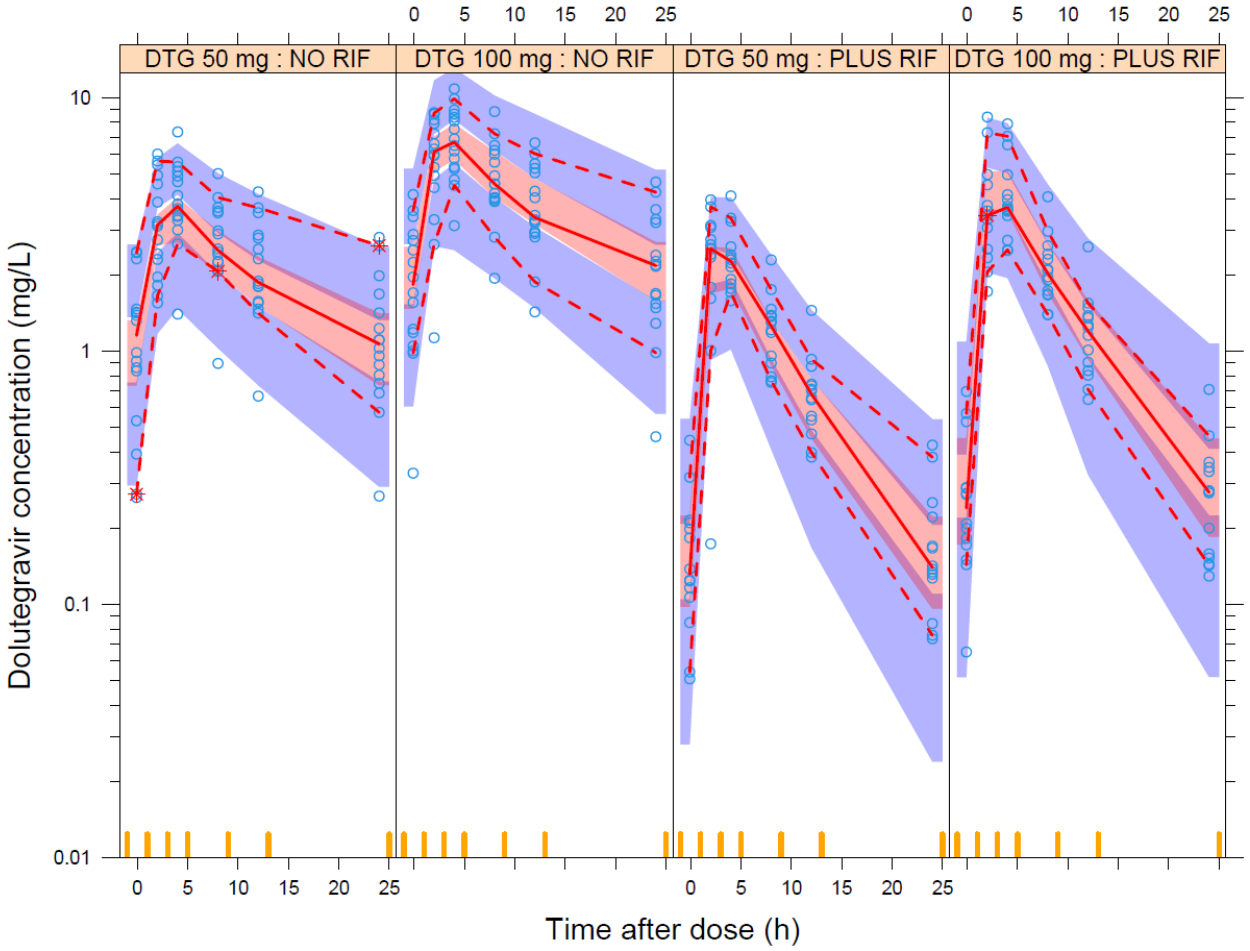


BSV+BVV+BOV

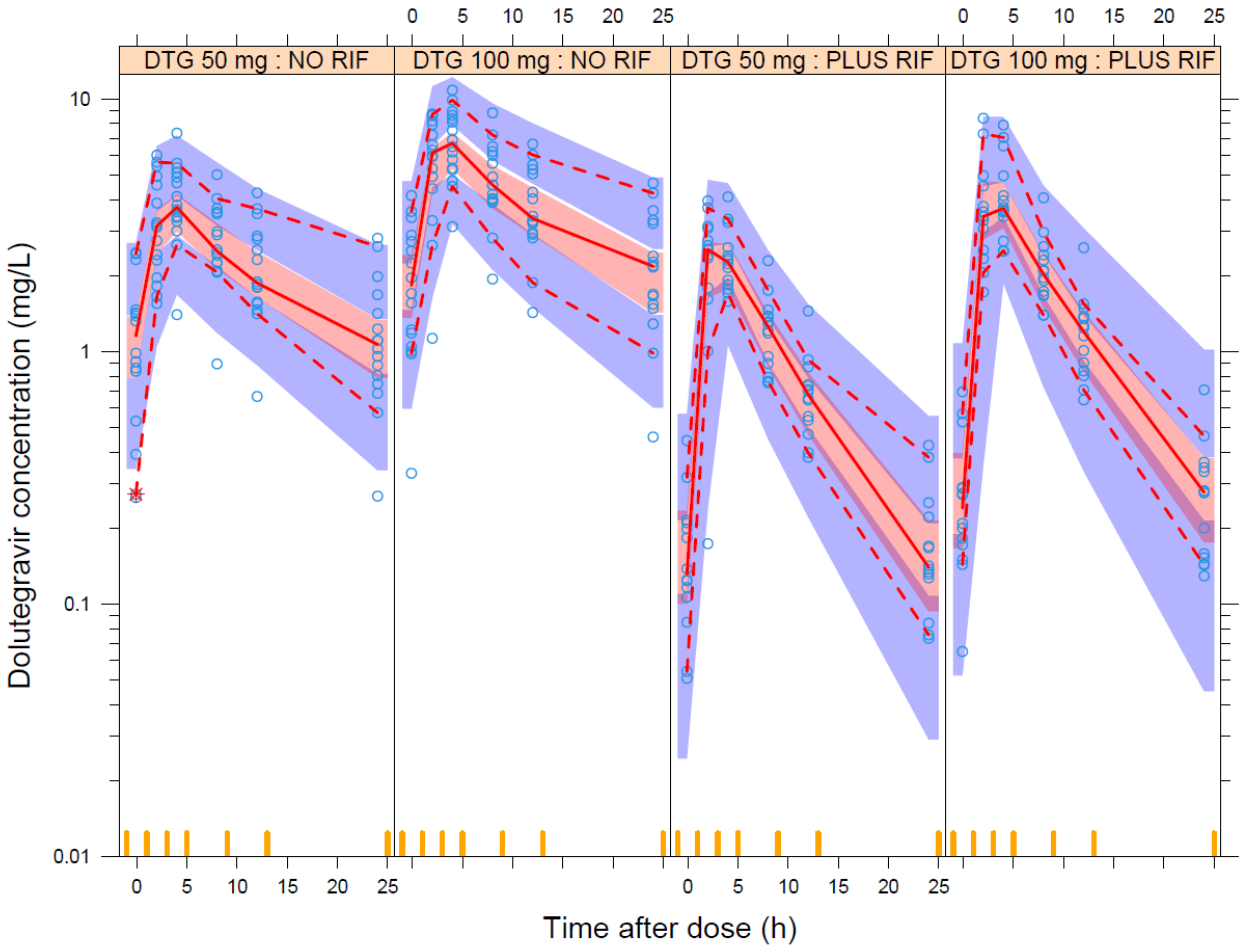


Model comparison - VPC

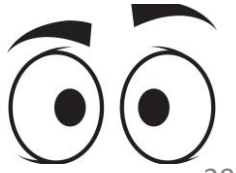
BSV-only



BSV+BVV+BOV

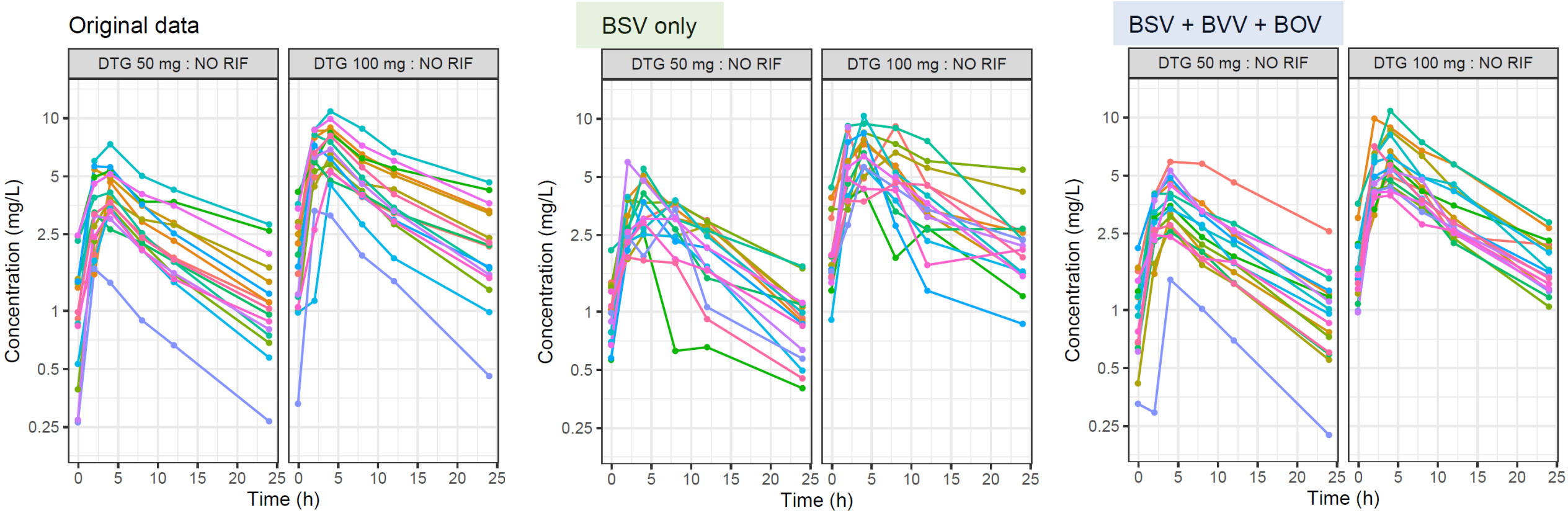


Despite all the improvements in the fit, **the VPCs look VERY similar**. It is difficult to spot any difference!



The VPC suggests that overall level of variability when simulating with either model is the same…

Is there NO difference? Let's simulate!



Let's use **BSV-only** model or the **BSV+BVV+BOV** model to re-simulate the study…

- With the **BSV-only** model, most of it is **EPS-variability**, i.e., RUV
- With the **BSV+BVV+BOV** model, there is more **ETA-variability**, while the RUV is limited.

The way the variability is organised MATTERS!
Using these models for simulation will produce very different scenarios
(e.g. optimal sampling schedule, power size calculations, etc.)

BOV for TDM/MIPD

Received: 7 July 2018 | Revised: 15 January 2019 | Accepted: 4 February 2019
DOI: 10.1111/bcp.13901

ORIGINAL ARTICLE

Handling interoccasion variability in model-based dose individualization using therapeutic drug monitoring data

João A. Abrantes | Siv Jönsson | Mats O. Karlsson | Elisabet I. Nielsen

TDM – Therapeutic Drug Monitoring
MIPD - Model-informed Precision Dosing

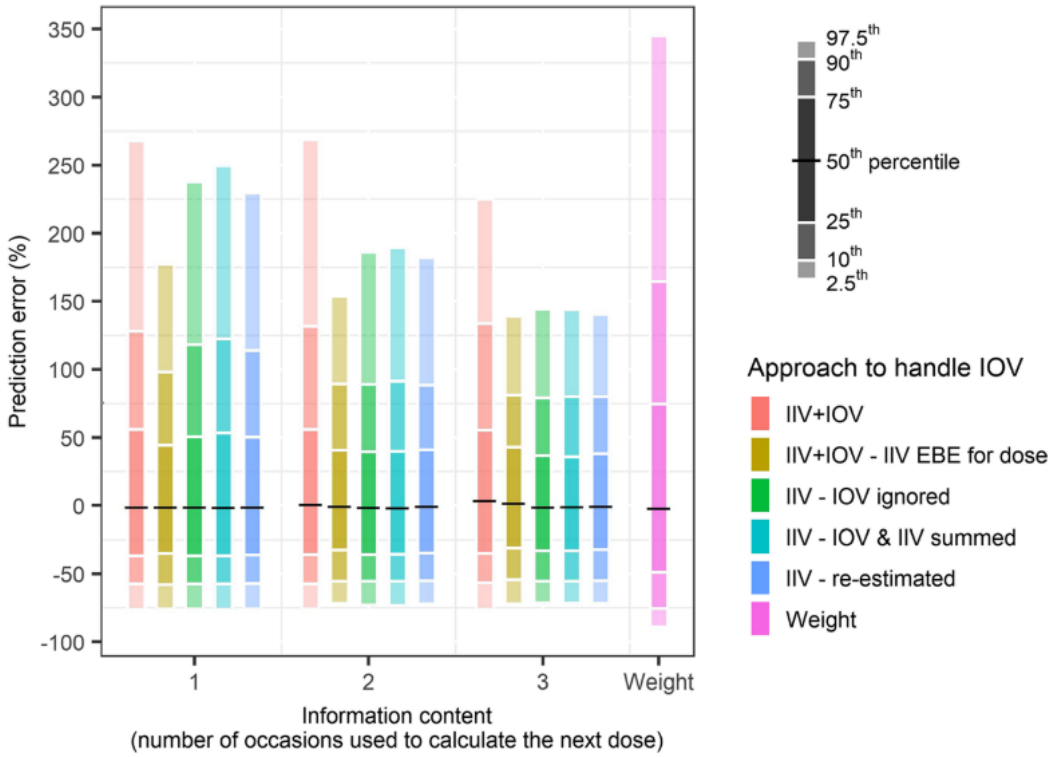
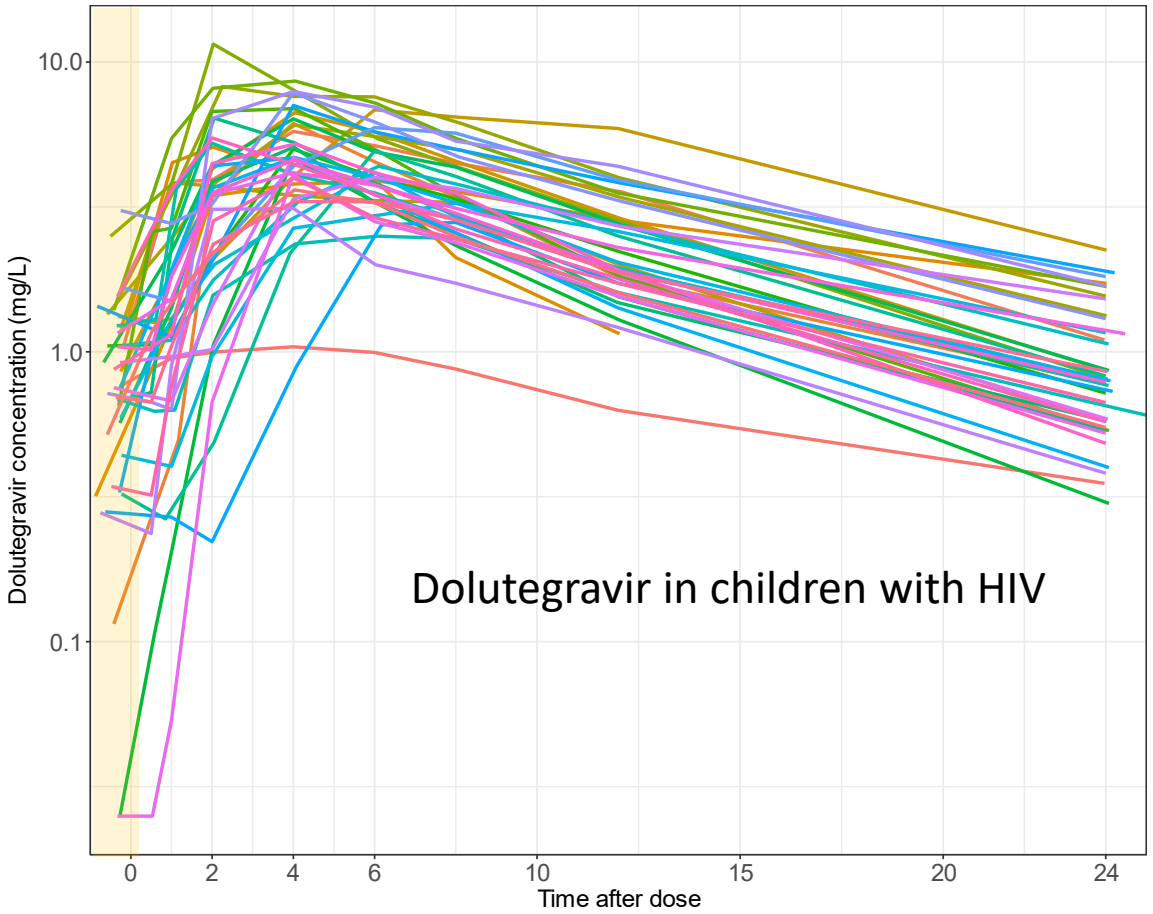


FIGURE 2 Percentiles of the prediction error for the alternative model-based therapeutic drug monitoring approaches when forecasting the dose leading to a coagulation factor VIII activity of 0.01 IU/mL at 48 hours postdose, using information from 1, 2 or 3 occasions, or weight-based dosing. EBEs: empirical Bayes estimates; IIV: interindividual variability; IOV: interoccasion variability

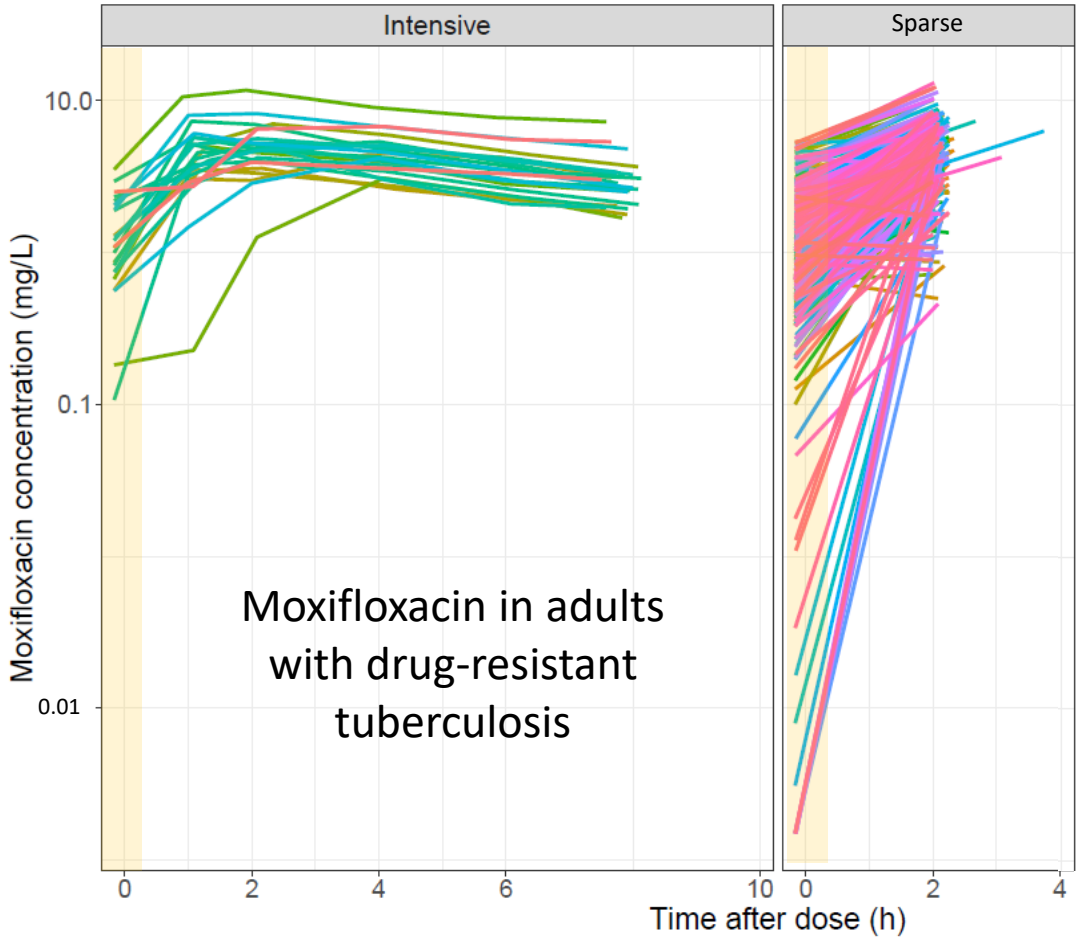
Abrantes et al., 2019, http://doi.wiley.com/10.1111/bcp.13901


DINOSAUR
ADVISORY
LESS BORING CONTENT

Not all occasions are the same…



Waalewijn, et al., Article under review in JPIDS



Resendiz-Galvan et al., unpublished work

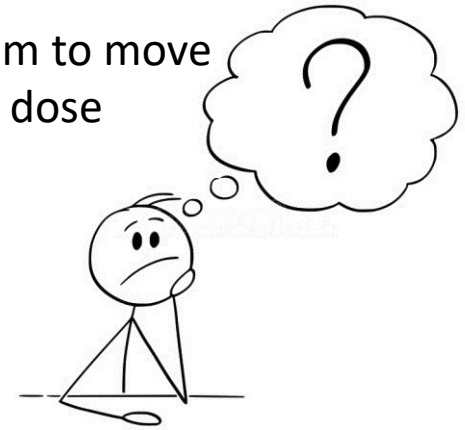
Somehow, PK/PD is **SO MUCH MORE** variable when none observes the patients taking their treatment…

How handle this extra uncertainty/variability?

There is extra uncertainty/variability in some sections of the data.
We need to put a patch on it…

Should we use an **epsilon-patch**?
We let the model allow more error when fitting the pre-dose concentrations

Or should we use an **eta-patch**?
We let the model have more freedom to move the PK parameters from yesterday's dose

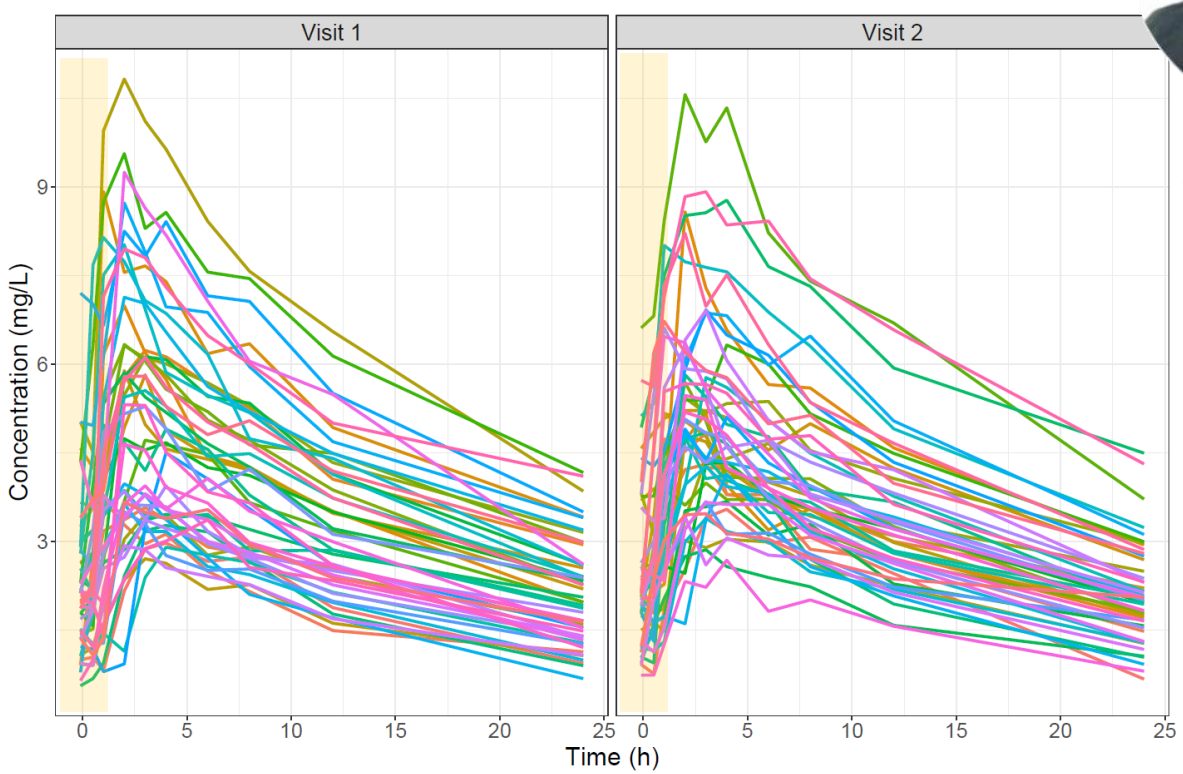


Simulation study

Sharon Sawe

Parameter	Value
CL (L/h)	0.7
Vc (L)	14
F (.)	1 FIX
Tlag fasted (h)	0.5
Food on Tlag (fold-change)	2
ka (1/h)	1.6
Q (L/h)	1
Vp (L)	4
Proportional error (.)	5%
Additive error (mg/L)	0.1
Extra BOV* (-fold change)	2.5
Extra ADD error* (mg/L)	-
Btwn **SUBJECT** Var **CL**	20%
Btwn **VISIT** Var **CL**	5%
Btwn **SUBJECT** Var **Vc**	10%
Btwn **SUBJECT** Var **F**	10%
Btwn **OCCASION** Var **F**	30%
Btwn **SUBJECT** Var **ka**	20%
Btwn **OCCASION** Var **ka**	60%
Btwn **SUBJECT** Var **Tlag**	20%
Btwn **OCCASION** Var **Tlag**	60%

50 patients – 2 Visits – Intensive sampling
Extra variability/uncertainty in pre-dose



Only BSV allowed
Only BSV allowed + **epsilon patch** (extra error for pre-doses)

Any variability (**BSV, BVV, or BOV**) allowed, if statistically significant
Any variability + **eta-patch** (extra BOV for unobserved doses)

Results – Data from 1 Visit only

	Simul model	1 Visit			
		BSV only		Any variability	
dOFV		REF	-24	-36	-93
CL (L/h)	0.7	0.73	0.73	0.65	0.74
Vc (L)	14	11.9	10.9	12.2	13.0
F (.)	1 FIX	1 FIX	1 FIX	1 FIX	1 FIX
Tlag fasted (h)	0.5	0.45	0.44	0.55	0.37
Food on Tlag (fold-change)	2	-	-	-	-
ka (1/h)	1.6	0.90	0.93	1.06	0.97
Q (L/h)	1	1.9	1.8	0.9	0.6
Vp (L)	4	5.7	5.7	4.6	5.5
Proportional error (.)	5%	13%	11%	11%	10%
Additive error (mg/L)	0.1	0.17	0.16	0.13	0.10
Extra BOV* (-fold change)	2.5	-	-	-	**2.5**
Extra ADD error* (mg/L)		-	**0.21**	-	-
Btwn **SUBJECT** Var **CL**	20%	35%	34%	36%	22%
Btwn **VISIT** Var **CL**	5%	-	-	-	-
Btwn **SUBJECT** Var **Vc**	10%	17%	17%	16%	15%
Btwn **SUBJECT** Var **F**	10%	24%	24%	-	-
Btwn **OCCASION** Var **F**	30%	-	-	28%	33%
Btwn **SUBJECT** Var **ka**	20%	72%	68%	-	-
Btwn **OCCASION** Var **ka**	60%	-	-	61%	55%
Btwn **SUBJECT** Var **Tlag**	20%	83%	86%	-	-
Btwn **OCCASION** Var **Tlag**	60%	-	-	79%	69%

All models perform similarly:

With **BSV only**, the model uses BSV for both BOV and BSV.

Extra ADD for the predose improves OFV and decreases the other errors.

With **any variability** allowed, the model only identifies the more prominent level.

Extra BOV mitigates the effect of predose. Lower OFV, smaller BSV/BOVs.

Results – Data from 2 Visits

	Simul model	1 Visit				2 Visits			
		BSV only		Any variability		BSV only		Any variability	
dOFV		REF	-24	-36	-93	REF	-47	-998	-1194
CL (L/h)	0.7	0.73	0.73	0.65	0.74	0.58	0.66	0.67	0.73
Vc (L)	14	11.9	10.9	12.2	13.0	13.3	13.5	12.3	13.5
F (.)	1 FIX	1 FIX	1 FIX	1 FIX	1 FIX	1 FIX	1 FIX	1 FIX	1 FIX
Tlag fasted (h)	0.5	0.45	0.44	0.55	0.37	0.72	0.31	0.48	0.47
Food on Tlag (fold-change)	2	-	-	-	-	-	-	-	-
ka (1/h)	1.6	0.90	0.93	1.06	0.97	0.91	0.93	1.45	1.53
Q (L/h)	1	1.9	1.8	0.9	0.6	0.9	0.9	0.6	0.6
Vp (L)	4	5.7	5.7	4.6	5.5	17.4	14.2	4.3	5.0
Proportional error (.)	5%	13%	11%	11%	10%	26%	25%	7%	5%
Additive error (mg/L)	0.1	0.17	0.16	0.13	0.10	0.24	0.23	0.34	0.27
Extra BOV* (-fold change)	2.5	-	-	-	**2.5**	-	-	-	**2.1**
Extra ADD error* (mg/L)		-	**0.21**	-	-	-	**0.25**	-	-
Btwn **SUBJECT** Var **CL**	20%	35%	34%	36%	22%	30%	28%	26%	21%
Btwn **VISIT** Var **CL**	5%	-	-	-	-	-	-	21%	9%
Btwn **SUBJECT** Var **Vc**	10%	17%	17%	16%	15%	12%	12%	14%	13%
Btwn **SUBJECT** Var **F**	10%	24%	24%	-	-	19%	19%	-	-
Btwn **OCCASION** Var **F**	30%	-	-	28%	33%	-	-	36%	32%
Btwn **SUBJECT** Var **ka**	20%	72%	68%	-	-	1%	1%	-	-
Btwn **OCCASION** Var **ka**	60%	-	-	61%	55%	-	-	83%	79%
Btwn **SUBJECT** Var **Tlag**	20%	83%	86%	-	-	135%	114%	-	-
Btwn **OCCASION** Var **Tlag**	60%	-	-	79%	69%	-	-	60%	54%

With **BSV only**:

- The RUV increases dramatically
- BSV in KA no longer supported
- Bias in peripheral volume

With **any variability**:

- smaller RUV
- smaller bias

Extra BOV further improves the estimates

Some suggestions/ideas

When only 1 visit is available

Using **BSV** or **BOV** makes little difference

However, having BOV for each dose (e.g. yesterday's dose) offers some extra flexibility in the fit, similar to an epsilon-patch (extra error)

When intensive data from >1 visit is available

Using **only BSV** (ignoring BOV) severely affects the fit.
The model may not be able to identify variability in some parameters that significantly change between visits
Most of the extra data just inflates the RUV

With multiple layers of eta-variability, the model can take advantage of the additional data, more accurate estimates, lower RUV.

Extra BOV for pre-dose can mitigate the bias due to uncertainty on the dosing history…

Further tests/future work…
Testing different epsilon-patches (proportional error or inflation factor)
Repeat the simulations to investigate difference adherence patterns

Is this WSV/BOV business reeeeally that important?

It is rather important when..

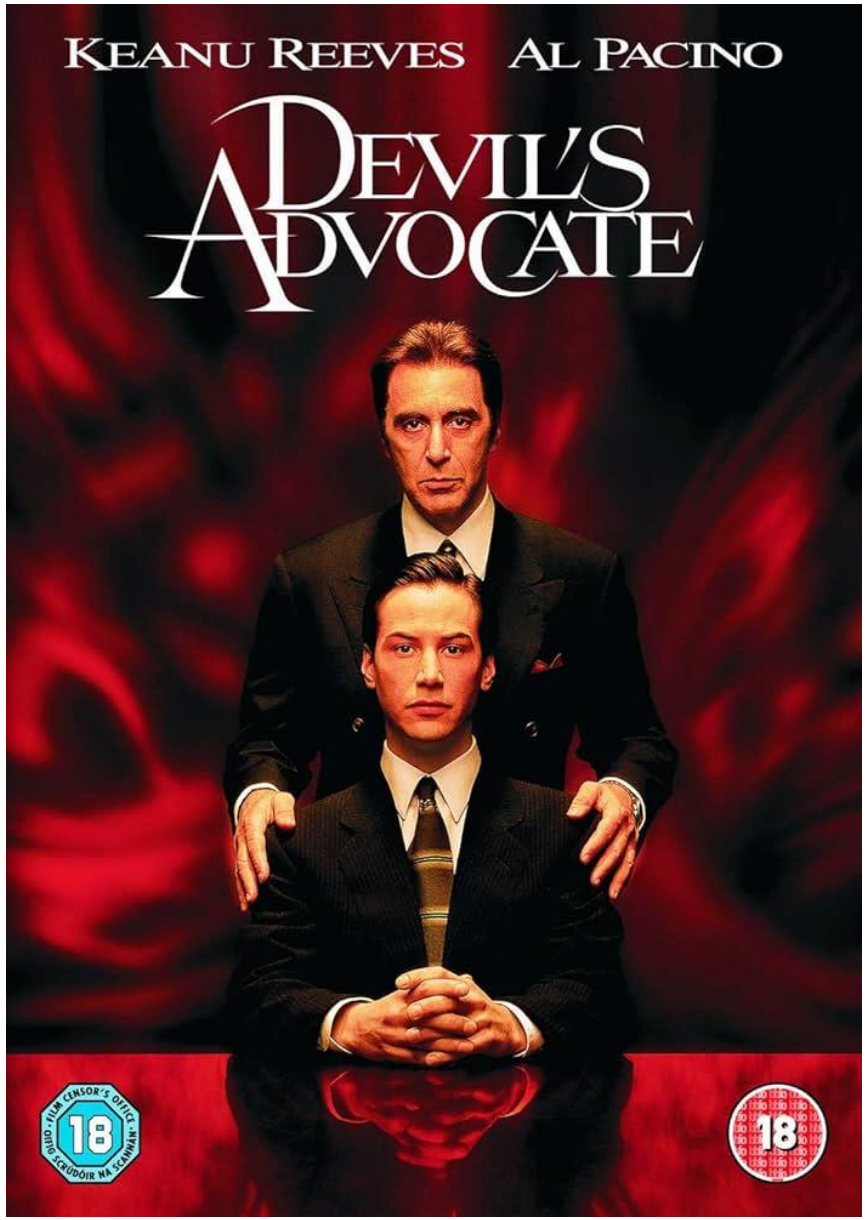
You analyse **data from multiple visits** (e.g. lots of semi-sparse sampling or mixed sparse + intensive sampling)

Your aim is to (semi-mechanistically) **characterise the PK or PD and identify covariates** (especially time varying covariates)

Your model will be used for **TDM/MIPD of drugs with significant BOV**

Your model will be used for **clinical trial simulations**, designing cross-over designs (drug-drug interactions or bio-equivalence)

Devil's advocate…



You probably don't need to worry too much about this if…

You only have **one sample collected per occasion in all individuals** (RUV and IOV cannot be distinguished)

Your aim is **just descriptive**.
If you only need overall exposure (e.g. average AUC to drive a slow PD effect over repeated doses).

Other ideas/experience from the audience? ☺

Some final thoughts

A **plausible stochastic model is essential** to reliably interpret your data and simulate realistic scenarios.

For EACH parameter, one should consider:

1. Which level of ETA-variability is expected to be prominent?
   BSV > BOV (generally disposition parameters)
   BOV > BSV (absorption parameters, baseline values in PD).

2. **What constitutes a reasonable "occasion"**?
   For absorption parameters, each dose on its own
   For disposition parameters, define a "visit" if long enough has passed

Accounting for BOV may help identify adherence issues and mitigate for poor information on dosing history.

My suggestion is to code it your dataset with OCC and VISITS from the start. Then it's easy to test BOV/BVV and disregard if not significant.

Acknowledgements

For input and discussions:
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Matt Fiddler

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My team at UCT PMX,
our supporters and donors!

Special thanks to
Allan Kengo
Sharon Sawe
Jose' Calderin-Miranda

University of Cape Town • iYunivesithi yaseKapa • Universiteit van Kaapstad

UCT Pharmacometrics

I am ready for the rotten tomatoes… ☺