EVALUATING A PRIORI AND A POSTERIORI DOSE ADJUSTMENTS IN SILICO: THE CASE OF PHARMACOGENETICS AND TDM

Abstract

INTRODUCTION: High variability in drug exposure and subsequent drug response can hamper effectiveness and safety. Dose adjustments can be made a priori (e.g. pharmacogenetic testing) or a posteriori (e.g. therapeutic drug monitoring (TDM)). Although combining both would be ideal, this is not always possible due to scarcity of resources. High unexplained inter-individual variability (IIV) can be captured by TDM, while pharmacogenetics may be a better option in case of high inter-occasion variability (IOV) and residual unexplained variability (RUV). This study explores the effect of these variabilities and evaluates the cut-off points between a priori (in form of pharmacogenetics) and a posteriori (in form of TDM) based on those variabilities to inform decision making on those adjustment strategy.
METHODS: Pharmacokinetic models with pharmacogenetic covariates of drugs of which dosages are adjusted by both pharmacogenetic and TDM were retrieved from Pubmed. Simulations with those models were performed under different magnitudes of variability (IIV 0-1, IOV 0-1 and RUV 0-0.5,proportional). A priori simulation based on a covariate subpopulation average and a posterori simulation including all types of variability and the covariate value were compared with a theoretical true value including only the covariate average and IIV.
RESULTS: Five cases were included: tacrolimus, tamoxifen, efavirenz, risperidone and vincristine. The general pattern was similar for all the included models, where increase in IOV and RUV gave preference to a priori and increase in unexplained IIV gave preference to a posteriori.
CONCLUSION: The trade-off between the degree of explainable IIV for pharmacogenetics, versus IOV with RUV for TDM on the other hand has been visualized. TDM seems the optimal strategy for all cases, except vincristine. This is possibly influenced by the outcome measure being AUC. Our results can be used as a theoretical framework to inform biomarker selection for dosing adjustments on the included drugs.

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Introduction

In clinical practice, effectiveness and safety of drugs can be hampered by high interindividual variability in drug response. (1) Part of this difference in drug response can be explained by differences in pharmacokinetics, which results in variation in drug exposure after receiving the same dose. By understanding and/or measuring the variability in exposure, patients can get the dose tailored to their needs.(2) Dose adjustments can be made *a priori* (i.e. dose personalization, before the first administration) based on patient characteristics, such as weight or pharmacogenetics, or *a posteriori* (i.e. dose individualization, after one or more administrations) based on drug level measurements via therapeutic drug monitoring (TDM).(3,4)

Pharmacogenetic testing can inform dose adjustment before the start of treatment and thus can be considered an *a priori* strategy for dosing, which hinges on the concept that inter-individual variability (IIV) in patients can be (partially) explained by differences in genetic coding (i.e. explained inter-individual variability). (5,6) By testing for differences in the genetic coding of metabolic, the exposure of a patient can be (partially) predicted.(7) Over the last two decades a growing interest in pharmacogenetics can be seen, reflected in the number of consortia formed to develop clinical guidelines regarding dose adjustments for genetic variations. (8,9) Although such variations explain part of the differences in drug exposure between patients, the predictive capacity can be limited due to large remaining unexplained inter-individual variability or due to the fact that it often captures only one pharmacokinetic parameter (often related to clearance with metabolic enzyme variations). One example is the use of different doses for patients with CYP2D6 mutations for tamoxifen allowing for more patients reaching target endoxifen concentrations. (10)

TDM represents an *a posteriori* strategy, used to measure levels of a drug in the blood after the dose with the intention to adjust the dose if necessary. A blood sample is usually taken directly before a new dose at steady state conditions for maintenance treatment, i.e. C_{trough}, or multiple samples after dose administration when the area under the curve (AUC) should be measured. (11) TDM is only useful when there are multiple dosing occasions to adjust. (12) Unlike *a priori* based dosing strategies, TDM is able to capture the complete inter-individual variability in drug exposure. However, the measurements' relationship to individual pharmacokinetic parameters can become clouded by the presence of inter-occasion variability (IOV), i.e. the random variability between different dosing occasions, and residual unexplained variability (RUV) related to variability in the bioanalysis, within-occasion variability and potential model misspecification (figure 1, from Sassen et al. (2,11,13,14)

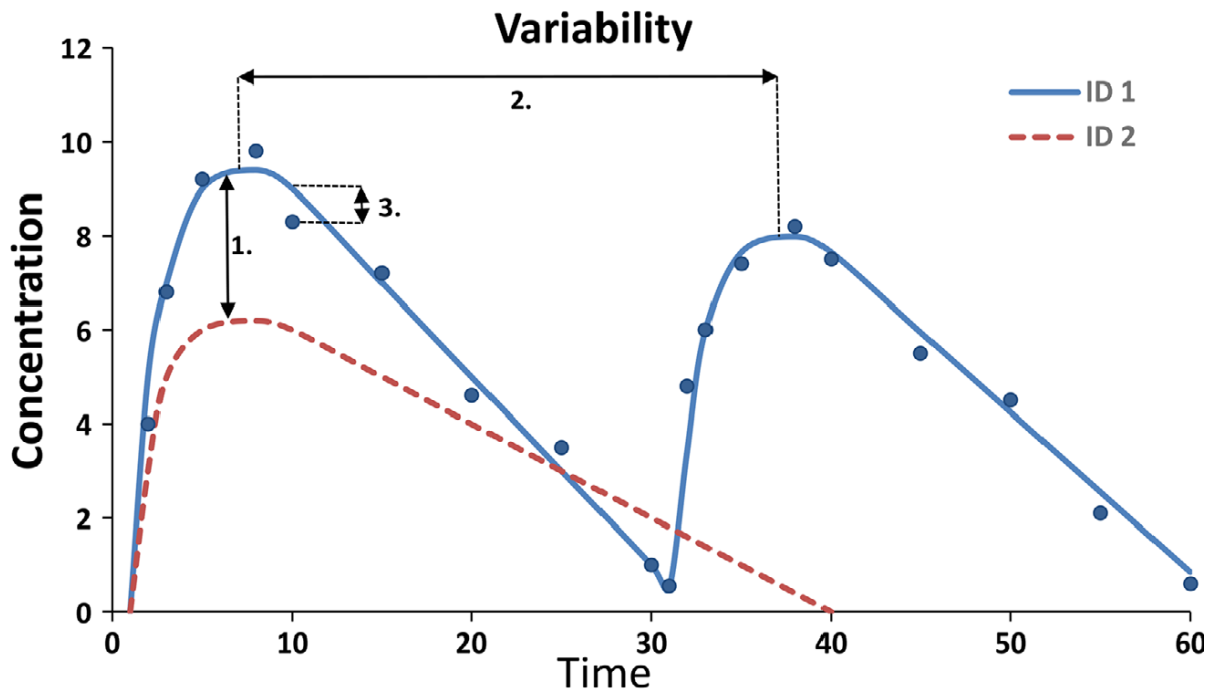


Figure 1 - three types of variability. Concentration-time curves depicting the three forms of variability. ID1 has two concentration-time curves from two subsequent dose administrations (solid line); ID2 has a single concentration-time cure after a single administration. 1. Between-subject variability (BSV), differences (e.g., in peak concentration) between the two patients; 2. Interoccasion variability (IOV), difference between dose administration time points; 3. Residual variability, due to model misspecification. (From Sassen et al. 2019)

For some drugs both pharmacogenetic and TDM-based dose adjustments have been suggested for clinical implementation. Although in theory the utilization of both methods (either in sequence or conjointly) could give rise to the best possible prediction of drug exposure and optimized dose, the combination of these methods is not always possible due to scarcity of resources and practical considerations such as the time to perform a genetic test and the feasibility of its implementation. (15) For example, if routine measurement of drug exposure is already present in clinical practice, this may have an effect on the impact of pharmacogenetic testing by accounting for the present effect of that routine measurement and previously invested resources. (5) However, scientific arguments should ultimately also play a large role in this decision. Given the fact that the magnitudes of explained, unexplained IIV, IOV and RUV influence the preference for an *a priori* based dose adjustment, versus an *a posteriori* one, it is conceivable that there is an ultimate trade-off between these measures at which preference should go to one strategy over the other.

Little empirical evidence is available comparing the two and using the magnitude of variability has not been done yet. Most trials focus on evaluation of one strategy compared to fixed dosing and there are not many comparisons available between pharmacogenetics and TDM. (1,12) Population pharmacokinetic (PK) models represent mathematical structures that capture the time course of drug concentration (16) The statistical component of PK models captures the degree of variability in patients and the companion covariate component describes sources of variability between patients, e.g. pharmacogenetic variations. Various PK models have been published that describe both variability between patients, as well as the relative contribution of pharmacogenetic differences to this variability. Such models can be exploited to simulate *in silico* clinical trials evaluating both pharmacogenetic and TDM dose interventions (16), which would not be limited by many of the practical, financial and ethical boundaries of real-life clinical trials. (17,18)

The current study provides one of the first efforts to quantitatively determine the circumstances under which *a priori* dose adjustments would be favored over *a posteriori* ones based on the

magnitude of the three types of variability. Using several relevant drug cases, where both pharmacogenetic and TDM guided dosing has been suggested as a relevant example, corresponding PK models were derived from the literature to simulate scenarios under which an *a priori* dosing strategy would be favored over an *a posteriori*. To this end, different combinations of unexplained inter-individual variability, intra-occasional variability and residual unexplained variability were assessed. Based on the results, recommendations on individual dose adjustments of the included cases can be made and give clinicians insight in the effect of variability on dose adjustments.

Methods

2. Methods

Compounds where both pharmacogenetic testing and TDM are used for personalizing dosage were selected to test the favored strategy under different circumstances. To this end, published models were retrieved via a literature search and assessed for suitability for our simulations. Model-based simulations using either a pharmacogenetic- or TDM-based strategy were performed to predict drug exposure in virtual patients, the results were repeatedly assessed for their proximity to the theoretical true value in different combinations of the variabilities.

2.1 Literature search and model selection

For the literature search term pharmacogenetic, e.g. *a priori* markers of potential interest were gathered for more focused search for suitable models. Only SNPs with a clinically relevant influence on pharmacokinetics, defined as dose adjustment for at least one phenotype, were gathered via guidelines of the Dutch Pharmacogenetic Working Group & the Clinical Pharmacogenetics Implementation Consortium. The following enzymes were included: ABCG2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, DPD, MTHFR, NUDT15, SLCO1B1 (OATP1B1), TPMT and UGT1A1.

Models that included these predefined pharmacogenetic covariates were searched for with PubMed in September 2021 to identify suitable cases. Initial screening of title and abstract was performed via Rayyan QCRI by NR and an independent sample for validation was done by MC. Doubtful cases were discussed by both to reach consensus on inclusion or exclusion. Inclusion criteria were: pharmacokinetic model available, presence of a statistically significant effect of pharmacogenetic covariate and models based on patient samples. Exclusion criteria were: in vitro models, animal models, foreign language, physiology based pharmacokinetic models, only pediatric population, models older than 2010, drugs not utilized in Dutch and Swedish clinic. Subsequently, the cases were assessed for their dosing strategy options.

Only models of drugs where both pharmacogenetic-dosing and TDM were used in the clinic were evaluated for suitability. Models based on less than 30 patients, very complex pharmacokinetics and complex formulations were excluded. If multiple models were available, models were selected based on highest sample size and samples per patient. If that did not offer an decisive answer, the models were assessed by both NR and MC to select one model. These models are discussed in ‘Results 3.1.2’.

2.2 Virtual patients and simulations

The included models and corresponding parameter estimates from the publication were translated in *mrgsolve* (version 0.11.2) for simulation in R (version 4.1.1.). (19,20) A virtual population of 1000 patients was created. For simplicity covariates other than pharmacogenetic components were fixed to a single value (e.g. weight and comedication). For this, continuous variables were fixed at median value, whereas the reference value (i.e. most used value) was used for categorical variables. The dosing regimen was simulated according to the regimen specified in the originial model publication. In the situation that amultiple doses were described, the median dose was taken. BSA was needed for the 5-FU and vincristine model, this was taken from the literature.(21) The distribution of CYP

covariates was obtained from the corresponding model, if possible or from the literature if not reported to ensure a plausible population.

First, a single model-based simulation was performed using the original published parameter values. The variabilities were calculated from the reported CV%. (22) Under normal circumstances, OMEGA represents the population variance with a mean of 0. During the first simulation round, however, IIV and IOV were simulated using a fixed effect component (i.e. THETA) representing the variability value of the original value, multiplied by a random effect component (i.e. OMEGA,) which set to a value of 1 in order to sample Z-values (i.e. number of standard deviations from the mean) from the population distribution (Eq. 1):

Eq. 1 $\theta i = \theta * \exp(\eta_i * \eta_{ij})$

Where θi represents the individual pharmacokinetic parameter value, θ represents the population value, θ(IIV) represents the original variance value from the publication and η(IIV) represents the Z-score.

Individual Z-values were subsequently exported and used in consecutive simulations, where the individual z-values were used to calculate individual SD van the mean when different fixed effect values where altered in magnitude. Individual values of the parameter of interest (clearance in most cases) were also exported to allow for scaling correction relative to the change in random effect changes during the second simulation round (Eq. 2).

During the second simulation round, the magnitude of the θ_{IIV} (the interindividual variability that was adjustable) of the parameters of interest (i.e. clearance mostly and residual error) were changed per model, while the remaining parameters retained their original values and variability. In addition, the fixed effect value of the PK parameter of interest was scaled to the original individual parameter value (from simulation round 1) in order to ensure that the individual value remained identical, whilst only the relative contribution of between the random effect versus the fixed effect (i.e. the pharmacogenetic covariate effect) differed over the simulation rounds. (Eq. 2):

Eq. 2 $\text{Covariate factor}_{SIM2} = (CL_{SIM1} / CL_{SIM2}) * \text{Covariate factor}_{SIM1}$

Where CL represents the clearance from either the first simulation round (SIM1) or the second simulation round (SIM2).

During this second simulation round, simulations were performed multiple times. In each seperate simulation different combinations of magnitude for θ_{IIV} (the interindividual variability that was adjustable) were evaluated. Variability was only changed for one parameter per model, while the original variability was kept for all other parameters. During such simulations three separate endpoints relating to the exposure were outputted (figure 1) : (i) theoretical true value (Eq. 3 and 4), (ii) *a priori* predicted value (Eq. 5 and 6) and (iii) *a posteriori* predicted value that would be based on measurements (Eq. 6 and 7). The endpoint was either Ctrough or AUC, dependent on the used endpoint used in the corresponding publication. The theoretical true value included all IIV, but without IOV and RUV. The a priori value included the pharmacogenetic covariate explaining the IIV of the genetic marker, but without the remaining IIV, IOV and RUV. The a posteriori value included all three types of variability. The proportional error models was applied according to Eq. 9 and was used for all, except vincristine. The additive model was applied according to Eq. 10. For every model IIV, IOV & RUV were simulated repeatedly in different combinations of magnitudes with the imported η, ε and parameter of interest from the initial simulation. Combinations ranging from 0 – 1 in steps of 0.1 for IIV & IOV and 0 - 0.5 in steps of 0.05 for RUV, which resulted in 1331 simulations per model. For the additive error model, A range between 0% and 50% of the mean theoretical true concentration was set in eleven steps via a scaling factor.

True simulation

Eq. 3 Pharmacokinetic parameter value - $\theta i = \theta * \exp(\eta i) * COVgenotype$

Eq. 4 IPRED – $C_{ss}(t) = \text{Amount in compartment} / Vd$

Prior simulation

Eq. 5 Pharmacokinetic parameter value - $\theta i = \theta * COVgenotype$

Eq. 6 IPRED - $C_{ss}(t) = \text{Amount in compartment} / Vd$

Posteriori simulation

Eq. 7 Pharmacokinetic parameter value – $\theta i = \theta * \exp(\eta i + \eta ij) * COVgenotype$

Eq. 8 If proportional error model - IPRED – $C_{ss}(t) = \text{Amount in compartment} / Vd * (1 * \varepsilon)$

Eq. 9 If additive error model - IPRED – $C_{ss}(t) = \text{Amount in compartment} / Vd * (1 + \varepsilon * SF)$

Where IPRED represents the individual predicted plasma concentration, θi represents the individual pharmacokinetic parameter value, COVgenotype represent the covariate value for the different genotypes, θ represents the population value, ηi represents the random effect for IIV, ηij represents the random effect for IOV, Css represents the concentrations at steady state, Vd represents the volume of distribution and ε the value of the residual error, SF represents the scaling factor.

The summary metric of interest was either C_{trough} or AUC was exported after every simulation. C_{trough} was calculated when steady-state conditions were reached by calculating the plasma concentration predictions at time point before the next dose. AUC was approximated by equations 8 for first order elimination, due to difficulties with simulation of the *a priori* value and true value simultaneously with the posterior. For the posterior simulation the AUC was calculated by trapezoidal method using three time points.

Eq. 10 AUC= Dose / Clearance

Bioavailability is left out of equation 10 as only IV bolus was the route of administration for the drugs where AUC was simulated and therefore assumed 100%. Where AUC represents the area under the curve.

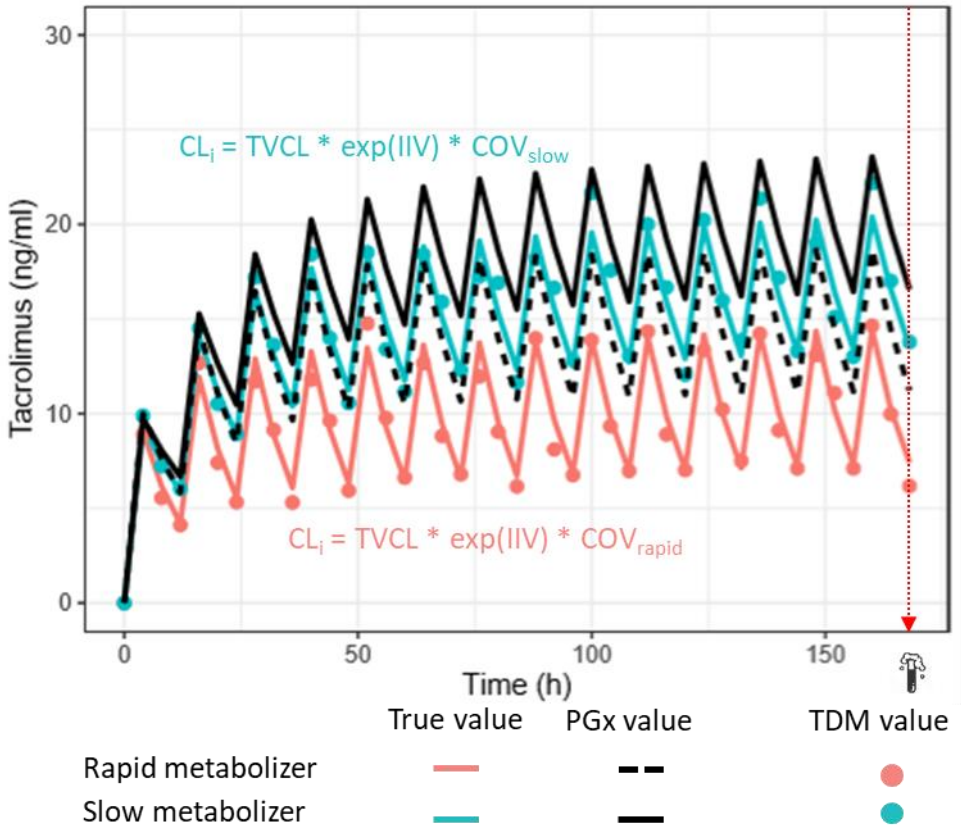


Figure 2 – schematic representation of the concept to simulate the different scenarios using tacrolimus as an example. True value includes covariate effect and IIV, PGx value includes covariate effect only and TDM value include covariate effect, IIV, IOV and RUV Cli = individual cleance, TVCL = typical value of clearance, IIV = inerindividual variability, IOV = interoccasion variability, RUV = residual unexplained variability, COVslow/rapid = the factor of the covariate of pharmacogenetic polpolymorphism, PGx = pharmacogenetics, TDM = therapeutic drug monitoring.

2.3 Graphical and numerical evaluation

To compare pharmacogenetic-based dosing (as *a priori*) with TDM-based dosing (as *a posteriori*), the predicted endpoint value of relevance based on each dosing strategy was compared to the 'true' exposure value. The biomarker that was relatively closest to the true exposure value was then considered superior, since each simulation utilized 1000 seperate individuals the % of patients favouring the a priori biomarker versus the a posteriori biomarker was summarized under all the simulated circumstances. To gain insight in the interaction between the three variabilities, a 3D plot was constructed for every model with R package plot3D (Version 1.4 where the y-axis represents residual unexplained variability , the x-axis interindividual variability and z-axis interoccasion variability. (23) Two plots were constructed for every model using R package *ggplot2* (Version 3.3.5). (24) These were 2D plots generated to summarize the information in a more condensed manner. Herein, the relationship between only two variables (e.g. IIV-IOV or IIV-RUV) are depicted, and the output represents the average of the omitted variable (e.g. IOV or RUV). For every combination of two of the variables, there were eleven simulations using eleven different values for the omitted variability. The outcomes of those simulations were averaged for every combination of the two plotted variabilities.

Results

3.1 Models in the literature

3.1.1 Literature results

Out of the 586 identified articles, 78 were selected based on the predefined selection criteria (figure 2). Of those articles, 38 were excluded for absence of use of either one or both dosing strategies in the clinic and 27 were excluded because of other models available for that drug. A total of five articles were selected from the literature search, in addition to two unpublished models recently developed at our research group. A summary on the included cases and models are discussed below.

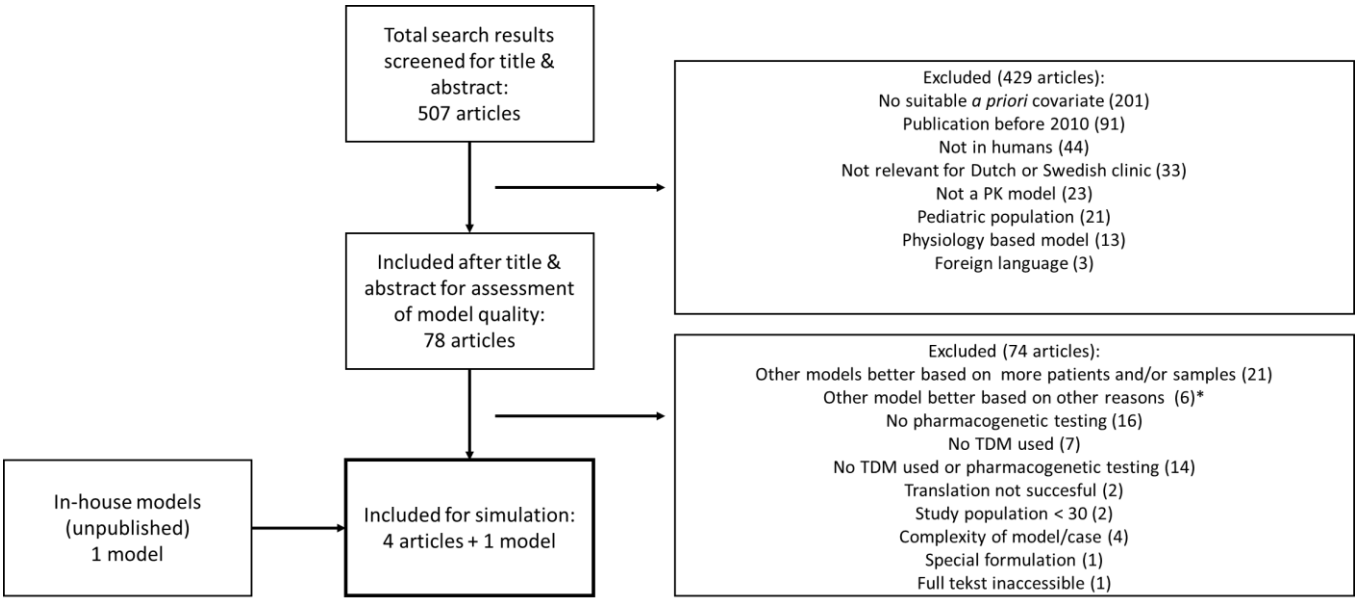


*Figure 3 - flowchart of selection process of the models. *other reasons discussed in the summary under 3.1.2.*

3.1.2 Included models

The details of the models included and the input used for this study can be found in table 1.

Tacrolimus

Tacrolimus is an immunosuppressive used to prevent rejection after solid organ transplantation. (25) Tacrolimus dosing is based on maintaining drug concentration within a therapeutic window to obtain beneficial immunosuppression whilst maintaining adequate safety, although differences are observed in which target range is used. (26) (25) Additionally, CYP3A5*1 carriers have an increased clearance of tacrolimus compared to wild-type (3A5*3), requiring an 1,5-2,5 times increased dose to achieve target concentration with less dose adjustments. (1,9)

The 2-compartment model reported in Andrews et al. (27) was used for its rich sampling (i.e. more samples per patient per occasion), sampling in whole blood, number of patients (4527 samples from 337 patients) and investigated potential covariates. The Størset et al. (28) model was not included due to the absence of a dataset for external validation and whole blood levels that were calculated on literature values. The model of Andreu et al. was not included due to the smaller group for the model validation and the aggregation of CYP3A5 and CYP3A4 in one phenotype. (29)

Tamoxifen

Tamoxifen is an oral estrogen-receptor blocker used for estrogen-receptor positive breast cancer and is converted to the active metabolite endoxifen. (30) Due to the relationship between endoxifen concentration and risk of recurrence, a plasma concentration of > 5.97 ng/ml has been proposed. (31) Dose adjustments based on TDM have been suggested to achieve this goal (30). Additionally, given the reduced endoxifen concentration of CYP2D6 intermediate metabolizers and poor metabolizers as compared to wildtype, an increase in tamoxifen dose to twice the usual dose has been recommended for patients with polymorphisms. (9) Although controversy remains, clinical use of both strategies is present.

Efavirenz

Efavirenz is a non-nucleoside reverse transcriptase, used as part of the highly active antiretroviral therapy for HIV patients. (32) Due to the relationship between efavirenz concentration and treatment outcome, a target concentration between 1.0 – 4.0 mg/L is proposed to reduce therapeutic failure and neural toxicity. (33–35). Additionally, given the influence of CYP2B6 polymorphisms (namely CYP2B6*6 carriers) of efavirenz clearance, dose reduction in patients with slow metabolizing polymorphisms are being used. (9,33)

The model of Habtewold (36) was the only with full concentration-time profile at steady state in some patients and was able to estimate more parameters than other models, that fixed parameters on literature values. Dickinson et al. (37) did not have rich sampling. Mukonzo et al. (33) had more dosing occasions, but only one mid-dose sample per occasion were taken.

Risperidone

Risperidone is a second-generation antipsychotic, used in the treatment of schizophrenia amonst other psychiatric disorders. (38) It is metabolized into 9OH-risperidone, later marketed as paliperidone. (39) Poor metabolizers of CYP2D6 are recommended a lower dose to reduce the chance of neurological side effects, as risperidone has a higher blood-brain barrier passage than its metabolite. (40) The exposure-response relation is moderately substantiated. Some evidence is available for improvement of schizophrenia and reduced neurological side-effects. (41) Both strategies are reactively performed to explain lack of effect or unexpected side effects. (42)

The 2-compartment model of Vandenberghe et al. (43) was included. One model with richer sampling was available however, the samples of Vandenberghe were more representative for clinical practice in terms of dosing and phenotypes and were taken under steady-state conditions. Although Yoo et al. had rich samples of the patients, they only received one dose for bioequivalence studies and no poor metabolizers were included. (44)

Vincristine

A few studies in children suggested an effect of CYP3A5*1 carriers (expressors) compared to CYP3A5*3 (non-expressors and most common in Caucasian population) with a reduced risk and severity on peripheral neuropathy for expressors. (45) However, contradictory results are available. Exposure-response analysis provide indications for an exposure-response relationship with progression-free survival and side-effects (anemia and peripheral neuropathy). (46)

The 2-compartment model was available inhouse and is not yet published. (47) First order elimination was included in the model. Although developed for a pediatric population, it was included. It is one of the few models that have allometric scaling using weight instead of body surface area and adds a case where C_{trough} cannot be used as outcome measure, but AUC can.

Table 1 – Characteristics of included models.

Drug name	Model characteristics	Number of patients (number of samples)	Patient characteristics	Variability	Genetic covariate and factor	Dose	Time of sampling	Simulated endpoint	Ref.
Tacrolimus	Starting dose model 2-COMP First order elimination	337 (4527)	CYP3A4*22: no Age: 56 years BSA: 1.93 m2 Weight: 70 kg	IIV CL: 0.144; Vc: 0.256; Vp: 0.253; Q: 0.49 IOV CL: 0.021 RUV (prop.) Tac.: 0.059 (of LC-MS method)	CL: 1 L/h (CYP3A5*1*1) CL: 1.62 L/h (CYP3A5*1*3)	2 times a day 0.1 mg/kg	168 hours	C_{trough}	(28)
Tamoxifen	2-COMP First order elimination	468 (1935)	SSRI: no Rifampicin: no Age: 64	IIV CL_{tam}: 0.148; CL_{end}: 0.201 IOV CL_{tam}: 0.022; CL_{end}: 0.029 RUV (prop.) Tam: 0.026; End: 0.027	CL: 0.533 (CYP2D6 UM) CL: -0.211 (CYP2D6 NM) CL: -0.510 (CYP2D6 IM) CL: -0.722 (CYP2D6 PM)	1 time a day 20 mg	2160 hours	C_{trough}	(49)
Efavirenz	4-COMP First order elimination	313 (1185)	-	IIV CL_{EFV}: 0.142; $CL_{9OH\text{-}EFV}$: 0.310; Vc_{EFV}: 0.892; $Vmax_{EFV}$: 0.223; $Km_{9OH\text{-}EFV}$: 0.641 IOV - RUV (prop.) $EFV_{Central}$: 0.116; 9OH-$EFV_{Central}$: 0.423; $EFV_{Peripheral}$: 0.229; 9OH-$EFV_{Peripheral}$: 0.313	CL: 18 (CYP2B6*1*1) CL: 14 (CYP2B6*1*6) CL: 8.6 (CYP2B6*6*6)	1 time a day 800 mg	288 hours	C_{trough}	(37)

Risperidone	2-COMP First order elimination	150 (178)	CYP2D6 inhibitor: no	IIV CL_{risp} : 0.155 CL_{pali} : 0.097 FR : 1.00 IOV - RUV (prop.) Risp: 0.168 Pali: 0.137	FR: 2.6 (CYP2D6 NM/UM) FR: -0.85 (CYP2D6 IM) FR: -2.6 (CYP2D6 PM)	1 time a day 4 mg	168 hours	C_{trough}	(41)
Vincristine	2-COMP First order elimination	35 (425) – pediatric population	BSA: 1.83 m2	IIV CL: 0.315 Vc: 0.478 IOV CL: 0.352 RUV (add.) Vin: 0.137	CL: CYP3A5 wt CL: CYP3A5 mut	1.5 mg/m2, maximum 2 mg	0-24 hours	AUC (three samples at time = 0, 0.6 and 24 hours)	(47) Unpublished

COMP = amount of compartments, CYPXXX = Cytochrome P450, subtype XXX, BSA = body surface area, IIV = inter-individual variability, IOV = inter-occasional variability, RUV = residual unexplained variability, prop. = proportional error model, add. = additive error model, CL = clearance, Vc = volume of distribution of central compartment, Vp = volume of distribution of peripheral compartment, Q = intercompartmental clearance, Vmax = maximum rate achieved by system, Km = Michaelis constant, PM = poor metabolizer, IM = intermediate metabolizer, NM = normal metabolizer, UM = ultrarapid metabolizer, wt = wildtype, mut = mutation, FR = fraction value, tac = tacrolimus, tam = tamoxifen, end = endoxifen, EFV = efavirenz, 9OH-EFV = 9-hydroxy-efavirenz, risp = risperidone, pali = paliperidone, vinc = vincristine

3.2 *Effect of variability*

Figure 4 shows the included cases with either IOV or RUV plotted against the IIV with every combination representing the average of the percentages at different values of the omitted variable. In general, we observe similar effects of alterations in variability. An increase in the unexplained IIV from 0 - 1 results in a lower percentage of the *a priori* simulations being closer to the true value than *a posterori.* Contrarily, increasing the IOV and the RUV results in the opposite. An increase in IOV from 0 - 1 results in a higher percentage of the *a priori* simulations being closer to the true value than *a posteriori.* The same holds true for RUV, although this variability ranges from 0 – 0.5. Due to this, a steeper increase is seen for RUV and it cannot be compared directly to the IOV pattern.

Although these general principles hold for all the models, the steepness of the change for proximity to the true value differs per model. Most notably is the differences between the models that are measured at C_{trough} compared to models of which an AUC is sampled. A higher share of individuals where the *a priori* value was simulated closer to the true value was seen for the AUC calculated simulation. This model was also less sensitive to changes in the IOV and RUV, indicated by the relatively straight line parallel to the y-axis. Differences are also seen within models of the same group of outcome measure.

Also within the cases that were simulated for C_{trough} differences in intensity are observed. Under different magnitudes of IOV compared to IIV, efavirenz shows the biggest differences under extreme magnitudes. Followed by risperidone, tamoxifen and tacrolimus in that order. The same pattern is seen for RUV compared to IIV.

Pharmacogenetic versus TDM

Table 2 shows the models with their original values. It can be seen that the models simulated with C_{trough} show a percentage lower than the 50% cut-off of patients which have an *a priori* simulation better approximating the true value than the *a posteriori* simulation. Contrarily, the AUC dependent simulations show a percentage of *a priori* favoring individuals above the 50% cut-off. Based on the original variabilities in the published models, the C_{trough} simulations favor TDM guided dosing and the AUC simulation with favor pharmacogenetic-guided dosing. The distance to the cutoff plane (figure 5) is also of relevance. The majority of C_{trough} have approximately 10% of the *a priori* simulations being closer to the true value, except for efavirenz at 40.5%. Efavirenz original combinations of variability lie close to the cut-off plane of 50%. The original values of risperidone are far away from the cut-off plane in green (50%). For the other two cases, tacrolimus and tamoxifen, the original values could approach the cut-off plane if the IOV would be increased. Less effect is seen from an increase in RUV. The AUC dependent simulation, vincristine, has 78.0% of the *a priori* simulations being closer to the true value. The original combination of variability lies around the 75% plane, which is almost the only one of the three planes visible in that plot. Only some extreme combinations lie around the cut-off plane (50%).

Table 2 – percentage of a priori individuals closest to the true value based on original variabilities from published model

Case/drug	**Individuals *a priori* simulation closest to true value (%)**	IIV (ω)	IOV (ω)	RUV (σ)
Tacrolimus	10.6	0.144 (CL)	0.021 (CL)	0.059 (Prop)
Tamoxifen	12.7	0.201 (CL_{end})	0.029 (CL_{end})	0.027 (Prop, end)
Risperidone	8.50	1.000 (FR)	0.000	0.168 (Prop, risp)
Efavirenz	40.5	0.142 (CL_{EFV})	0.000	0.116 (Prop, $EFV_{Central}$)
Vincristine	78.0	0.315 (CL)	0.352 (CL)	0.137 (Add)

A value of 0.000 means that it was not reported in the publication of the model; IIV = inter-individual variability, IOV = inter-occasional variability, RUV = residual unexplained variability, prop. = proportional error model, add. = additive error model, CL = clearance, Vmax = maximum rate achieved by system, FR = fraction value, end = endoxifen, EFV = efavirenz, risp = risperidone

Discussion

To the best of our knowledge, this is the first study to systematically evaluate how differences in sources of pharmacokinetic variability give rise to favoring an *a priori* dosing strategy versus *a posteriori*. The different 'drug cases' evaluated enabled the evaluation of different model structures and subsequent pharmacokinetic characteristics to evaluate how these influence the benefit of an *a priori* versus *a posteriori* dosing strategy. The general pattern was similar for all the included models, where increase in IOV and RUV gave preference to a priori and increase in unexplained IIV gave preference to a posteriori. It was found that, based on the variability reported, TDM-guided dosing would be favored for drugs where C_{trough} can be measured, while pharmacogenetic-guided dosing was favored for the case where AUC needs to be measured.

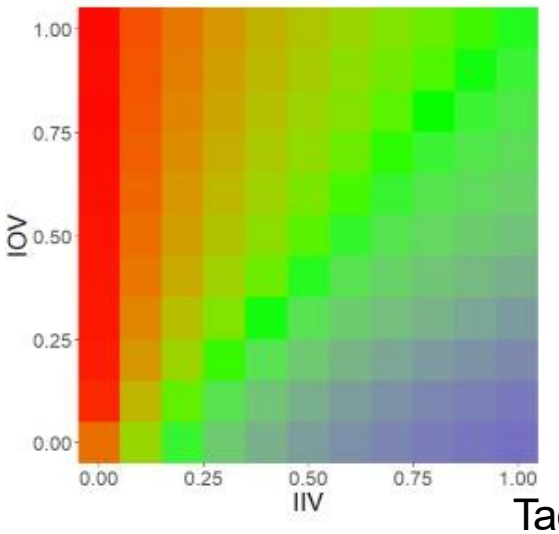
By using multiple models from examples subject to discussion on pharmacogenetics and TDM, the results are relevant to clinical practice. Models from different therapeutic areas have been included, increasing the generalizability of the results. Clinicians can get better understanding of the effects of IIV, IOV and RUV for these choices. Furthermore, the approach can be extended to other *a priori* and *a posteriori* dosing strategies influenced by IIV, IOV and RUV.

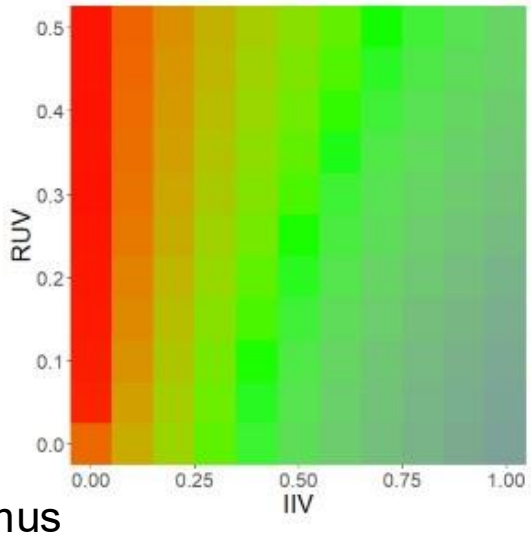
The differences observed between the models could be due to the remaining IIV over the other parameters. In this study the IIV over one parameter, usually clearance, was altered. The remaining IIV was left untouched and was thus not taken into account in the *a priori* simulations and therefore still had an effect on the outcome. This is supported by the fact that even in the hypothetical situation that all IIV could be explained, the *a posteriori* strategy sometimes still is favored over the *a priori*. The observed differences between simulations where the AUC was calculated compared to those where we simulated C_{trough} could arise from the calculation of the AUC for the *a posteriori*. We used three occasions, to imitate TDM measurements, to calculate this while using the same formula for the true simulations and the *a priori*. Suboptimal choice of both time and number of the occasions, could steer the simulations into the direction favoring *a priori* simulations.

Braal et al. (48) showed that TDM is a viable strategy for patients using tamoxifen to increase the proportion of patients with endoxifen levels above the lower limit. Despite a relatively low IOV (16%), some patients went below the limit on different occasions. CYP2D6 was mentioned to be a strong predictor. It is also shown that CYP2D6-guided dosing improved patients reaching the target concentration. Nonetheless, poor metabolizers often still did not reach the target concentration. (49) Binkhorst et al. (30) argued TDM to be the better strategy. It should be noted that the effect of CYP2D6 and TDM on clinical outcome has been controversial. (50)

Risperidone can be individualized best by TDM according to de Leon, but genotyping can be useful to identify poor metabolizers. (51,52) TDM is superior because it captures all the other variability in this case. It was unclear how CYP2D6 genotype would be able to optimize risperidone, but that remains the

Efavirenz





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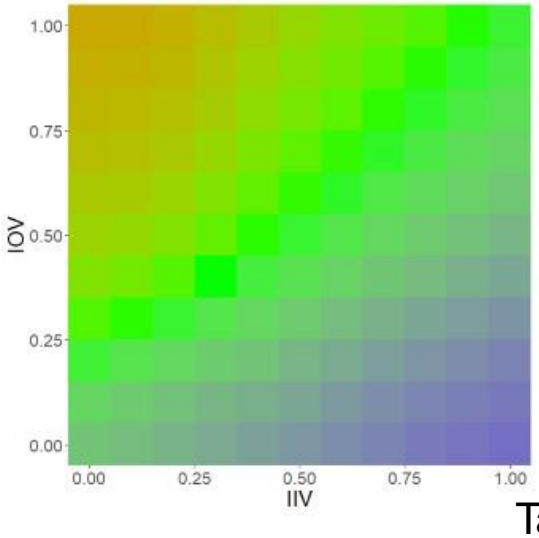
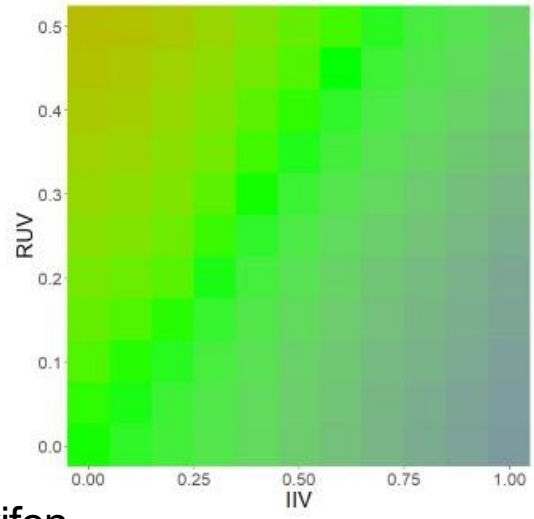
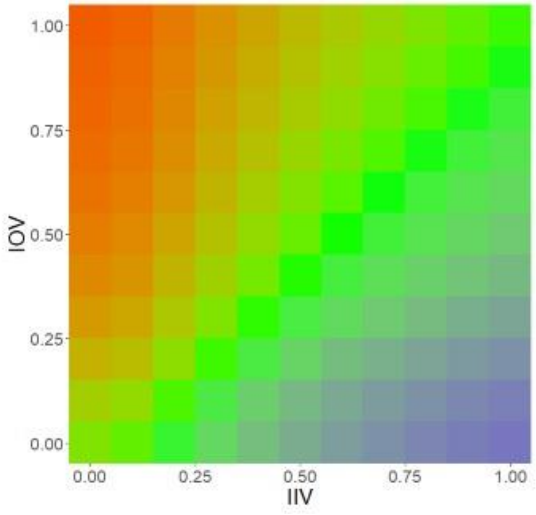
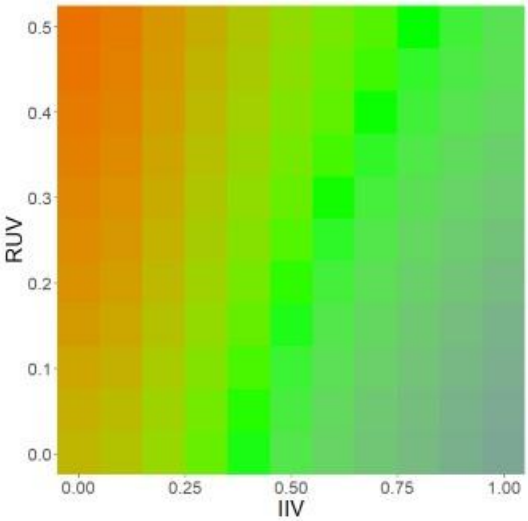


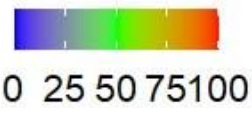


Tamoxifen





Percentage of virtual patients of which *a priori* simulations are closest to the theoretical true value



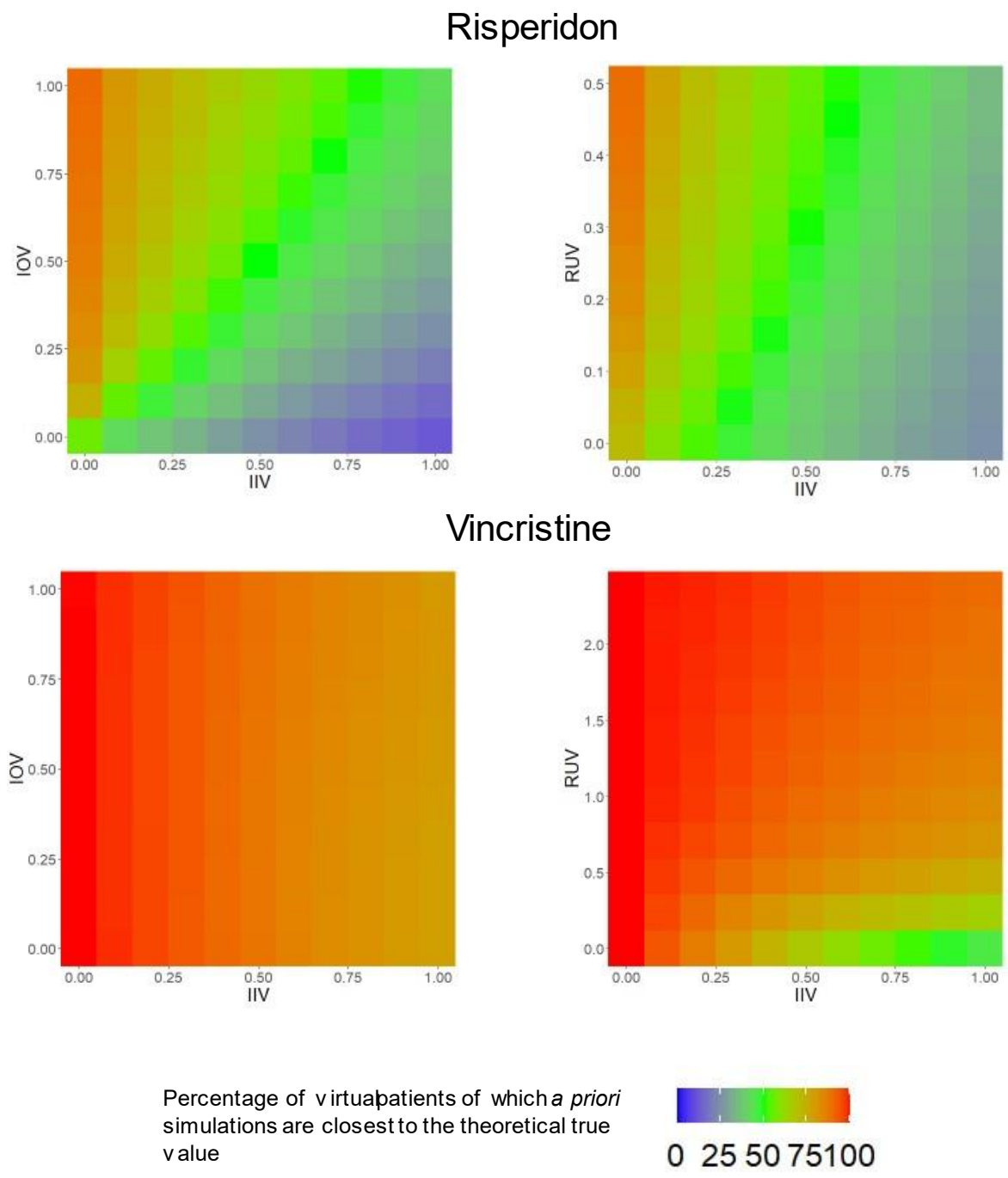


Figure 4 – 2D plots of all included models. The plot show the IIV and IOV ranging from 0– 1 and the RUV ranging from 0– 0.5. For every combination of IOV and IIV in the figure, simulations are performed with eleven different RUV values. For every combination of RUV and IIV in the figure, simulations are performed with eleven different IOV values. The color of the plotted dot indiciate the proportion of the simulated patients of which the a priori endpoint was closer to the true value than the a posteriori endpoint. The mean percentage of a priori simulations being closer to the true value of the eleven simulations are plotted with every tile. Shown on the left for IOV and shown on the right for RUV. Ctrough value at steady state was the endpoint for tacrolimus, tamoxifen, risperidone and efavirenz and AUC value using 3 measurements was the endpoint for 5-fluorouracil and vincristine. The black line indicates the 50% border, i.e. the cut-off points where one strategy is favored over the other.

same for TDM. (53,54) For efavirenz, Figueroa et al. explored the added gain of pharmacogenetics to TDM already and was questioning the added value. For adjustment of the initial dose the authors deemed it valuable, but that should be confirmed in clinical practice (55). Martin investigated dose reductions using both and results suggested a better tolerance and found it to be cost-effectiveness compared to standard dosing. Either one of the two strategies might be even better use of resources.

TDM guided dosing is recommended for tacrolimus, however the time to reach target concentrations is lower for pharmacogenetic testing. (56) Still, no added benefit is shown in those studies. It appears that TDM dosing is quick enough in getting the right dose.(57)

Limited evidence is available for dose personalization and individualization of vincristine is available, although there are suggestions for CYP3A5 guided dosing. (47,48) This observation is in line with the preference for pharmacogenetic-guided dosing found in our study.

There were several limitations to this study. Firstly, the results are dependent on the models that were found and included. Altough effort was taken into careful selection, any bias or uncertainty in the models will persist into the simulations and reduce the validity of the results. The accuracy of the combination of variability in the model is essential for conclusions in this study. The risperidone model had one sample per patient, reducing accuracy of the estimations and this made the model unable to capture IOV. The IOV was also not reported in the efavirenz model. By excluding IOV it will inflate either IIV or RUV (13) with possibly misjudging the favored strategy as a consequence. Assumptions have been made on other covariates and used dose. Secondly, the presented approach is not completely representative for the clinical situation by using the proximity to the true value. Dose adjustment based on pharmacogenetic testing are based on the subgroups average while TDM dose adjustments are on the individual and therefore more precise. This would increase the number of simulated individuals favoring TDM.

This study offers a theoretical approach to aid in rational decision-making on dosing strategies. After model development, the magnitude of the variability can be a useful addition to the decision-making. By rational optimizing of the dosing strategy, patients are able to receive better treatment under circumstances where resources are scarce and effective pharmaceutical care is critical. There should be room for other considerations too. For example the severity of the consequences can play a role, as 5-FU severe side effects can occur rapidly after the first dose. TDM is not capable of aiding in that, possibly tipping the balance in favor of pharmacogenetic testing.

Extending the principle to other drugs where both dosing strategies are available could be focus of further research. For example, TPMT-testing for thiopurines and CYP2D6-testing for amitriptyline can be compared to TDM for these drugs. To be able to use the principle presented in this study, more and larger models should be developed incorporating genotypes explaining IIV.

Although this study focusses on the comparison between both dosing strategies, ideally they are combined to create a more sophisticated dose adjustment. Both strategies can work complementary to each other for optimal treatment. It would be of great interest to provide insight in the added gain of combining both strategies instead of opting for either one. This applies to pharmacokinetics, but also pharmacodynamics changes and economical outcomes. Pharmacoeconomic studies could be very relevant for policy makers to allocate the resources for dose personalization and individualization.

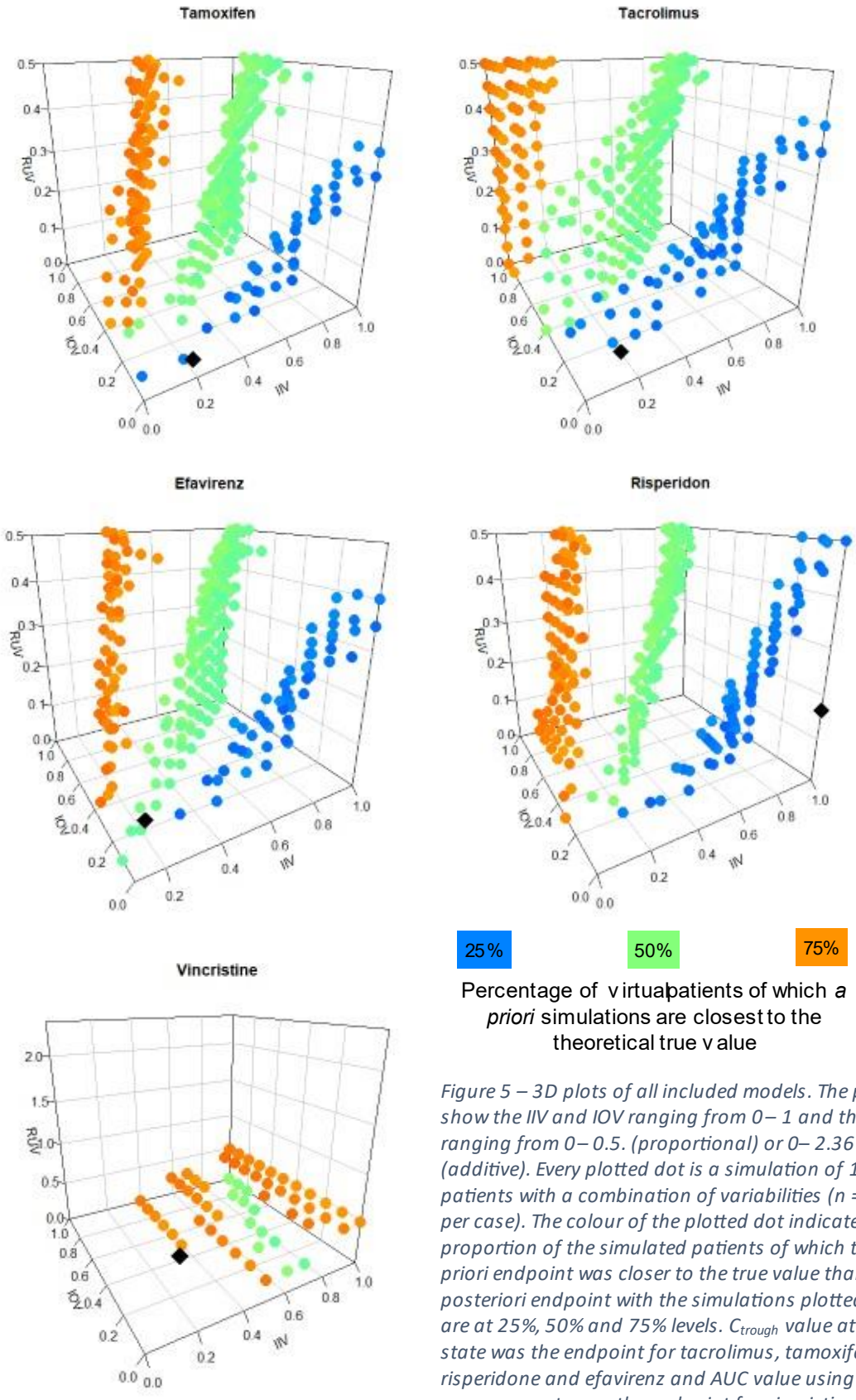


Figure 5 – 3D plots of all included models. The plot show the IIV and IOV ranging from 0– 1 and the RUV ranging from 0– 0.5. (proportional) or 0– 2.36 (additive). Every plotted dot is a simulation of 1000 patients with a combination of variabilities (n = 1331 per case). The colour of the plotted dot indicate the proportion of the simulated patients of which the a priori endpoint was closer to the true value than the a posteriori endpoint with the simulations plotted that are at 25%, 50% and 75% levels. C_{trough} value at steady state was the endpoint for tacrolimus, tamoxifen, risperidone and efavirenz and AUC value using 3 measurements was the endpoint for vincristine. The black diamond shows the original combination of variabilities retrieved from the publication of that model.

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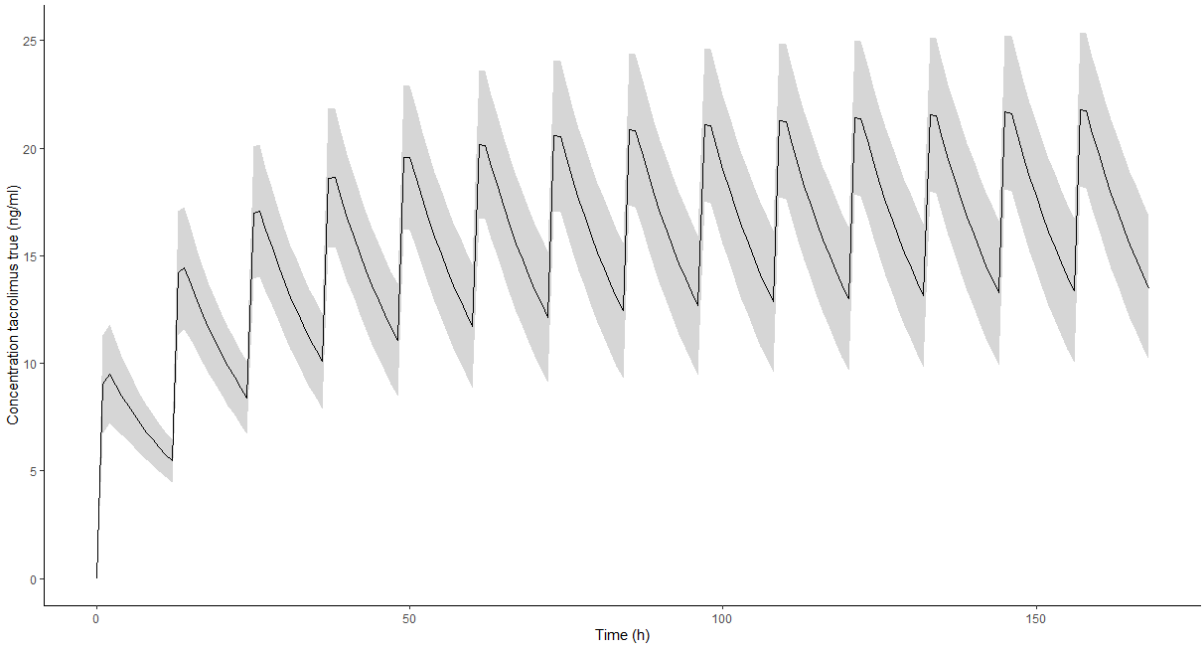
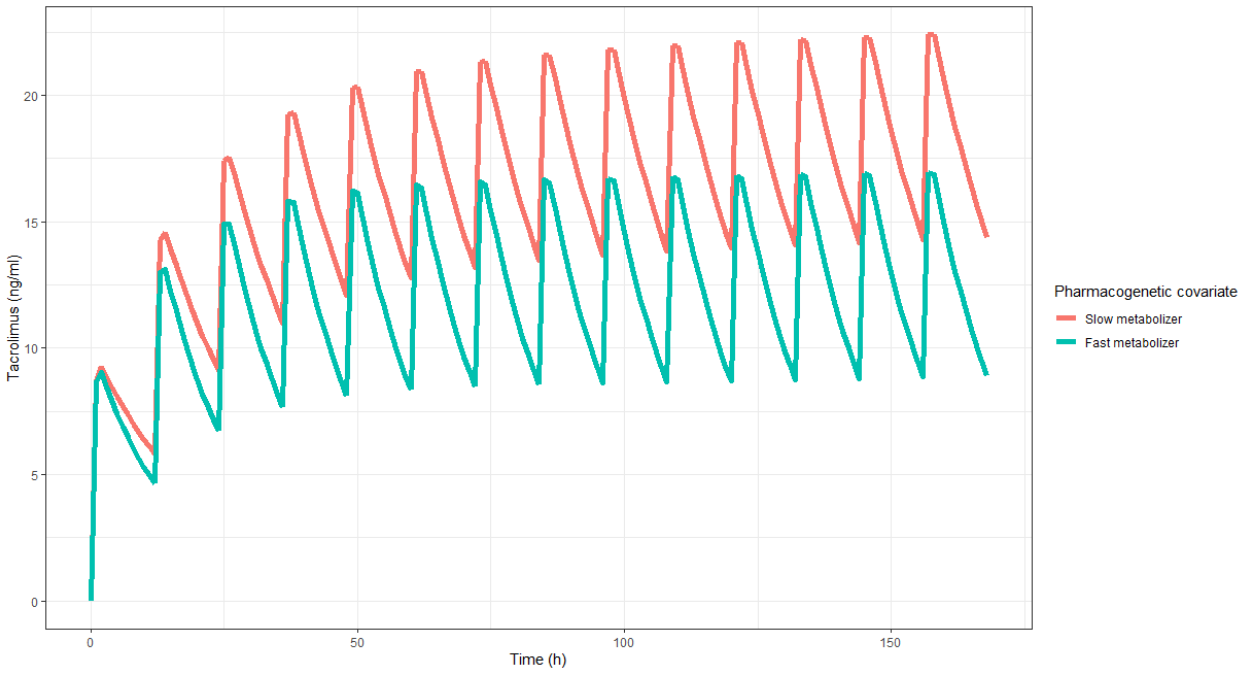
Supplementary information

S1 – For every model, the plasmaconcentration curve is shown of the theoretical true value based on all individuals and the different groups of the pharmacogenetic covariate.

Tacrolimus





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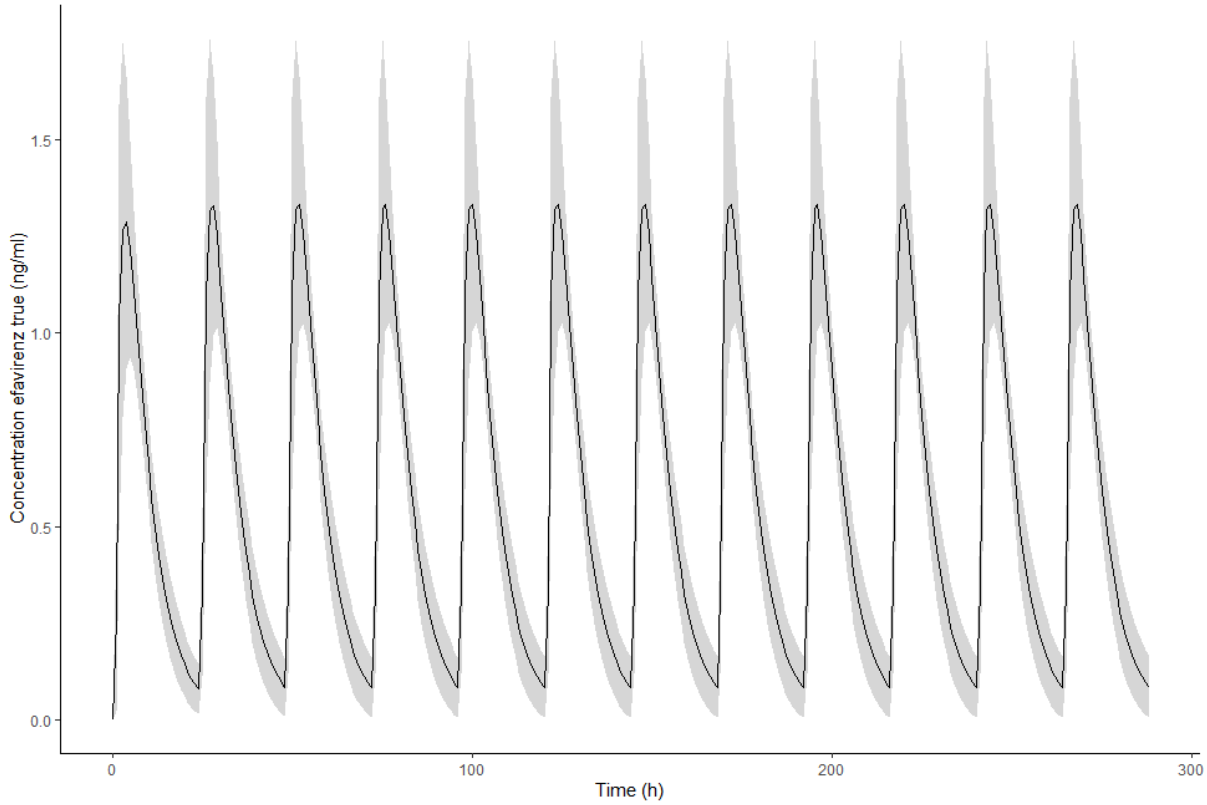
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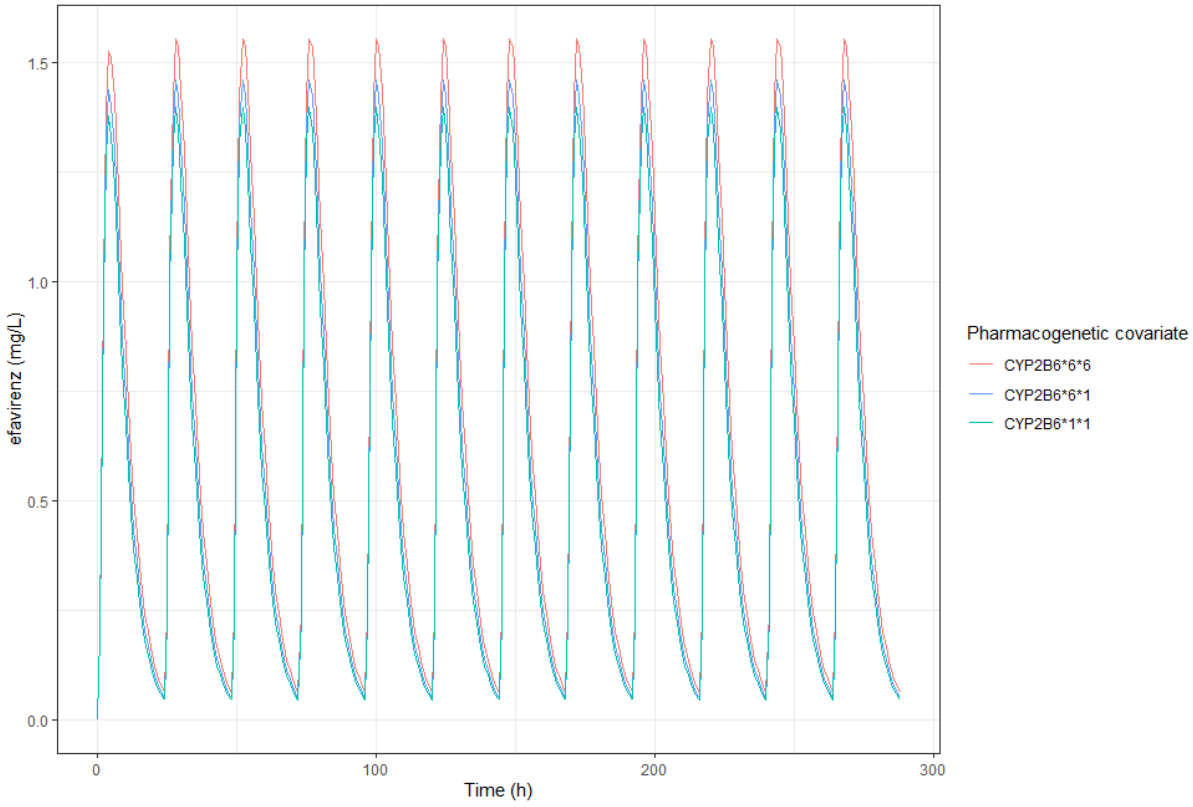
300
Time (h)


efavirenz (mg/L)
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Pharmacogenetic covariate
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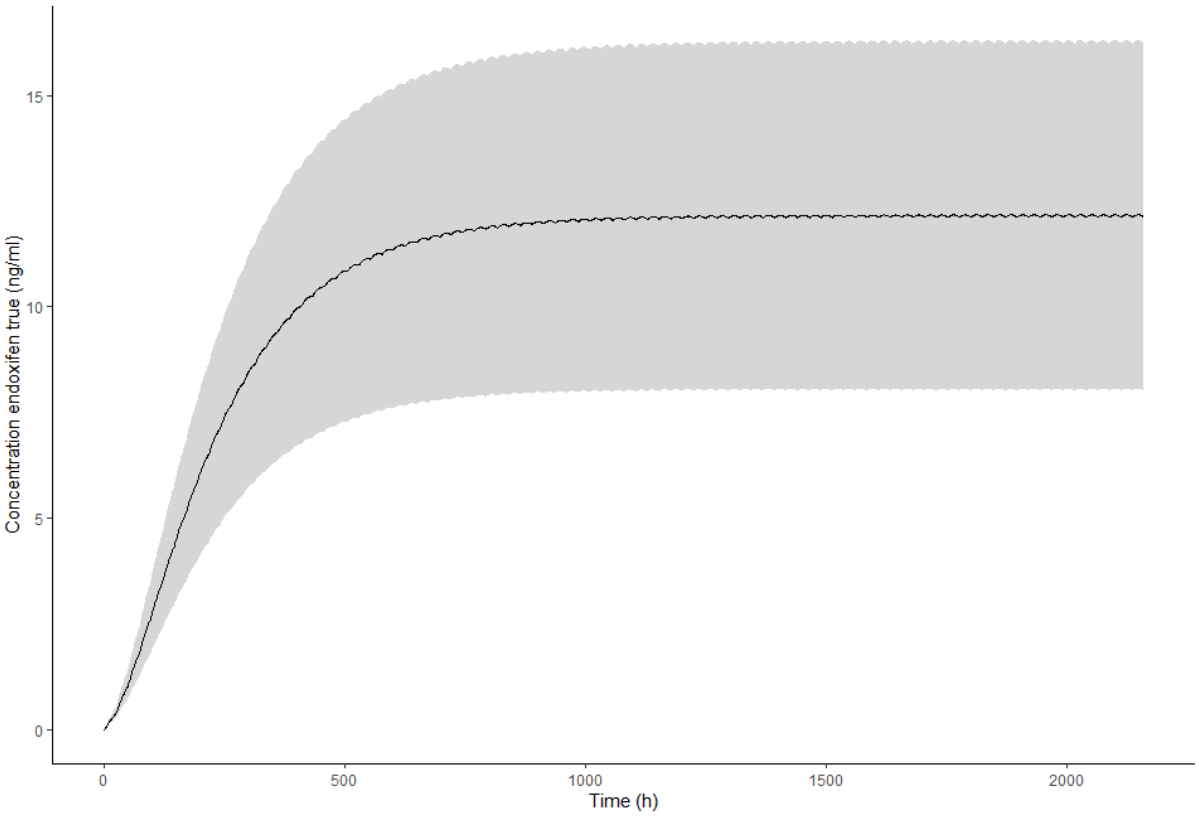
CYP2B6*1*1

Tamoxifen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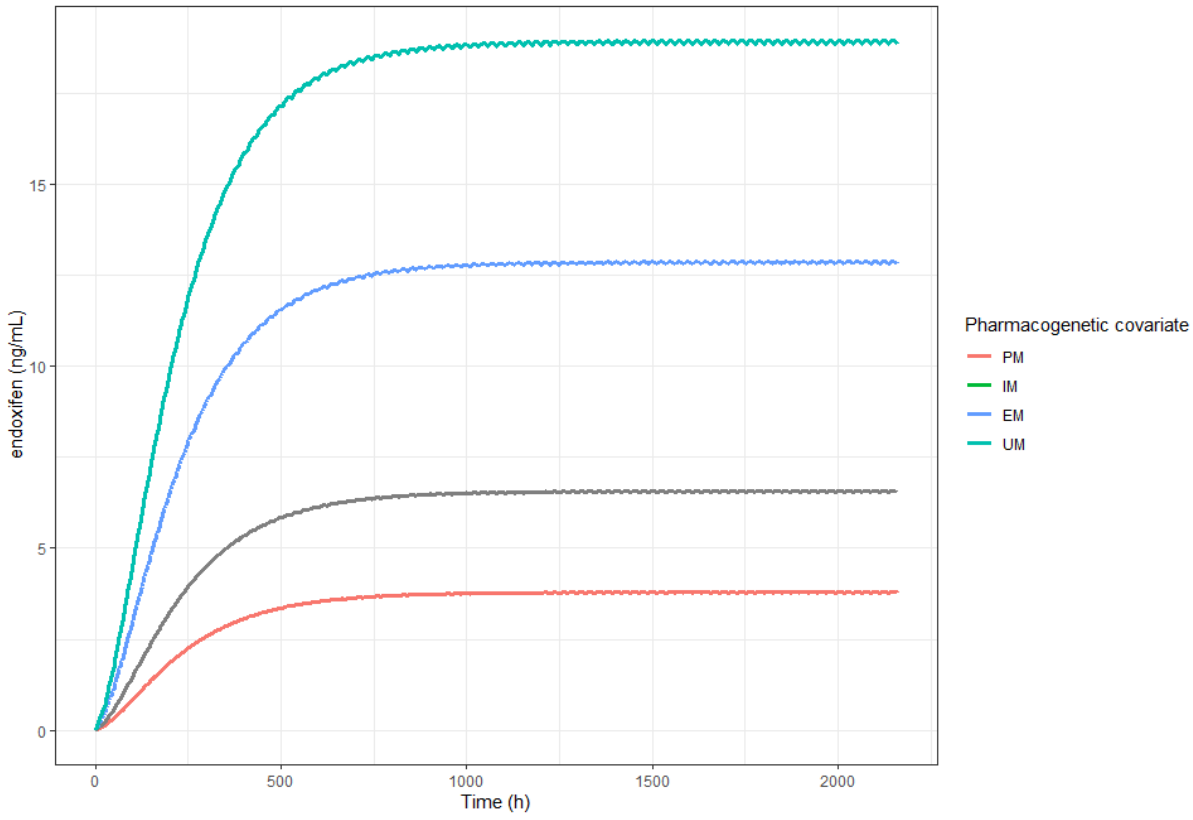
Time (h)


endoxifen (ng/mL)
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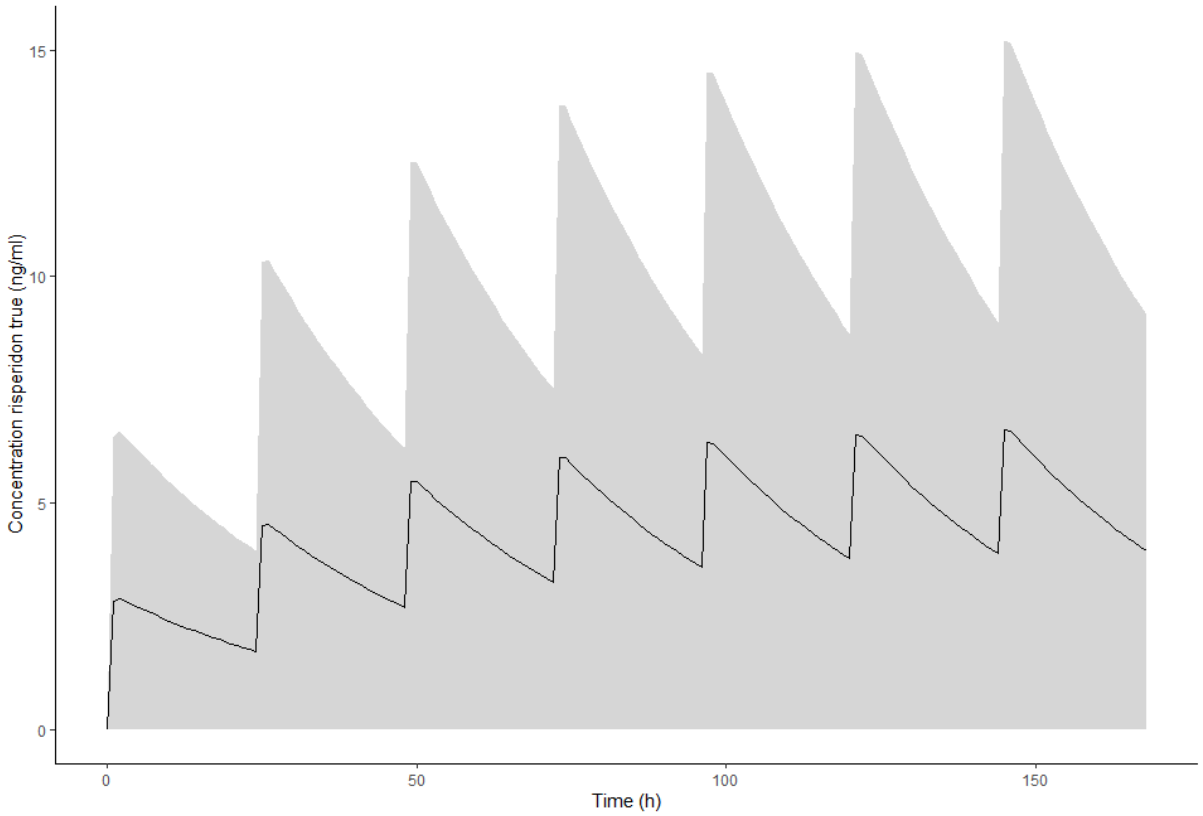
Risperidon


Concentration risperidon true (ng/ml)
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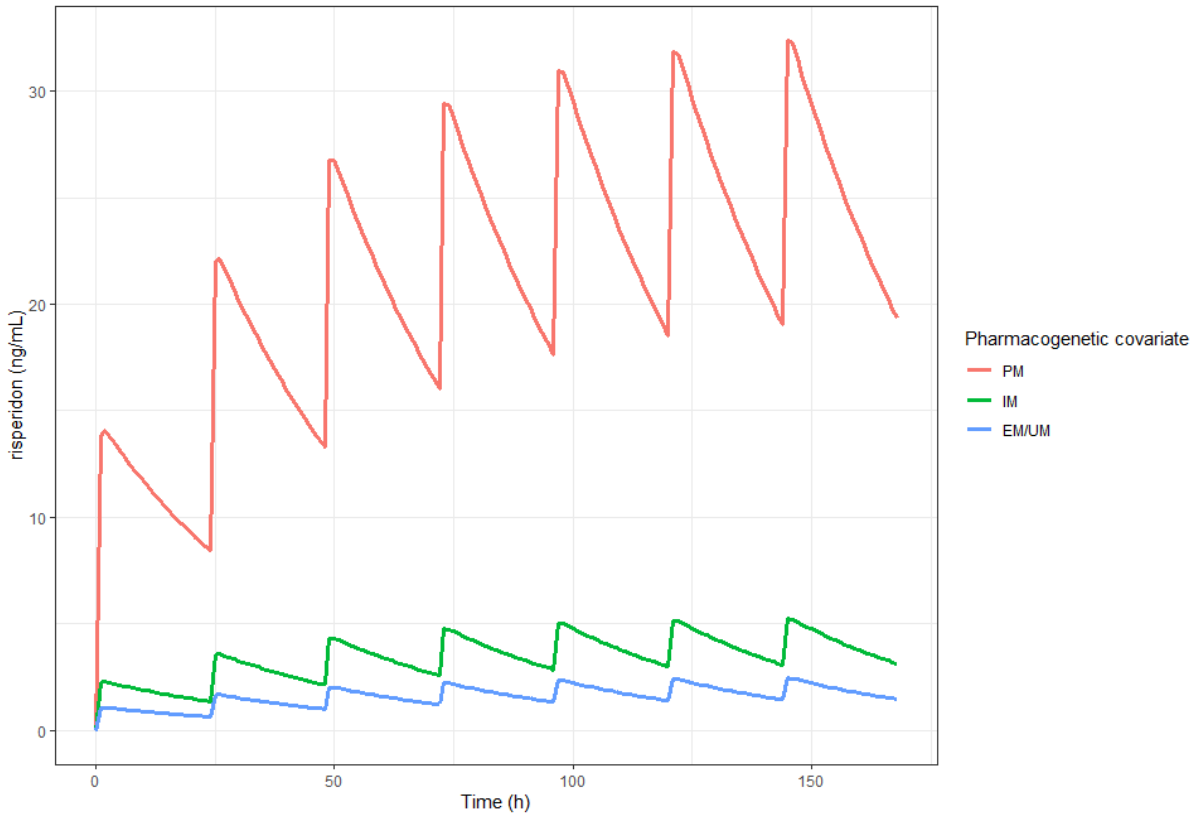
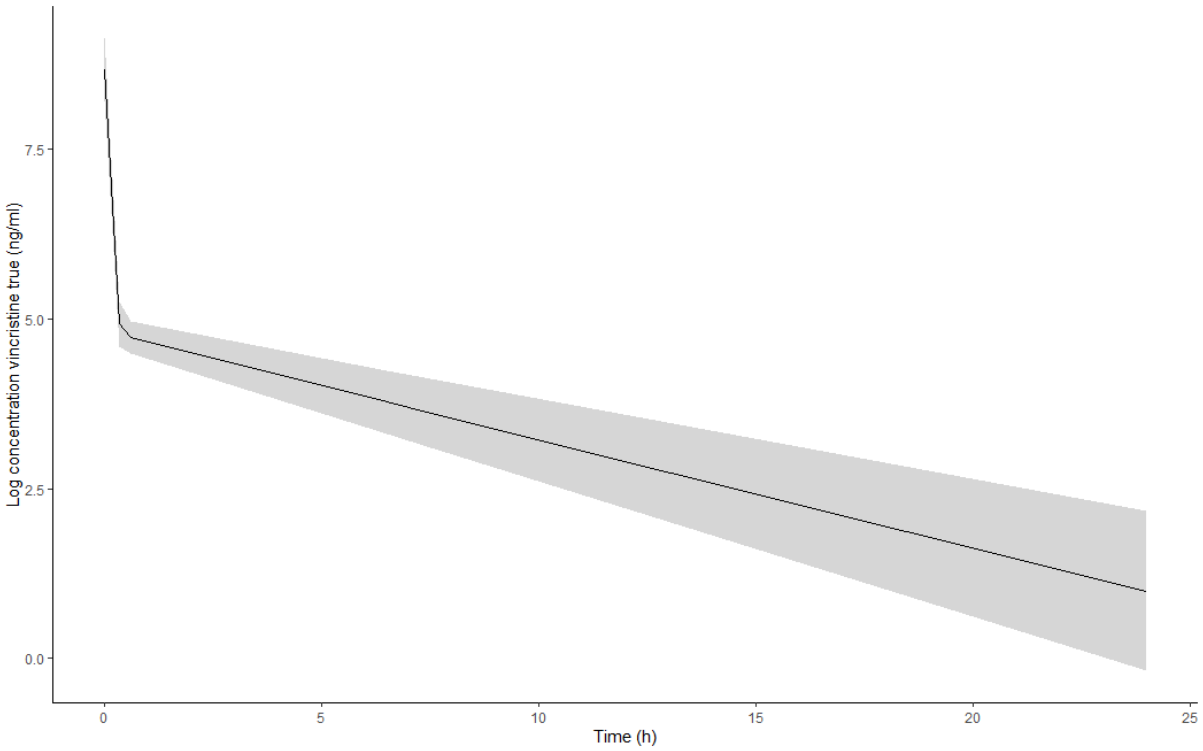
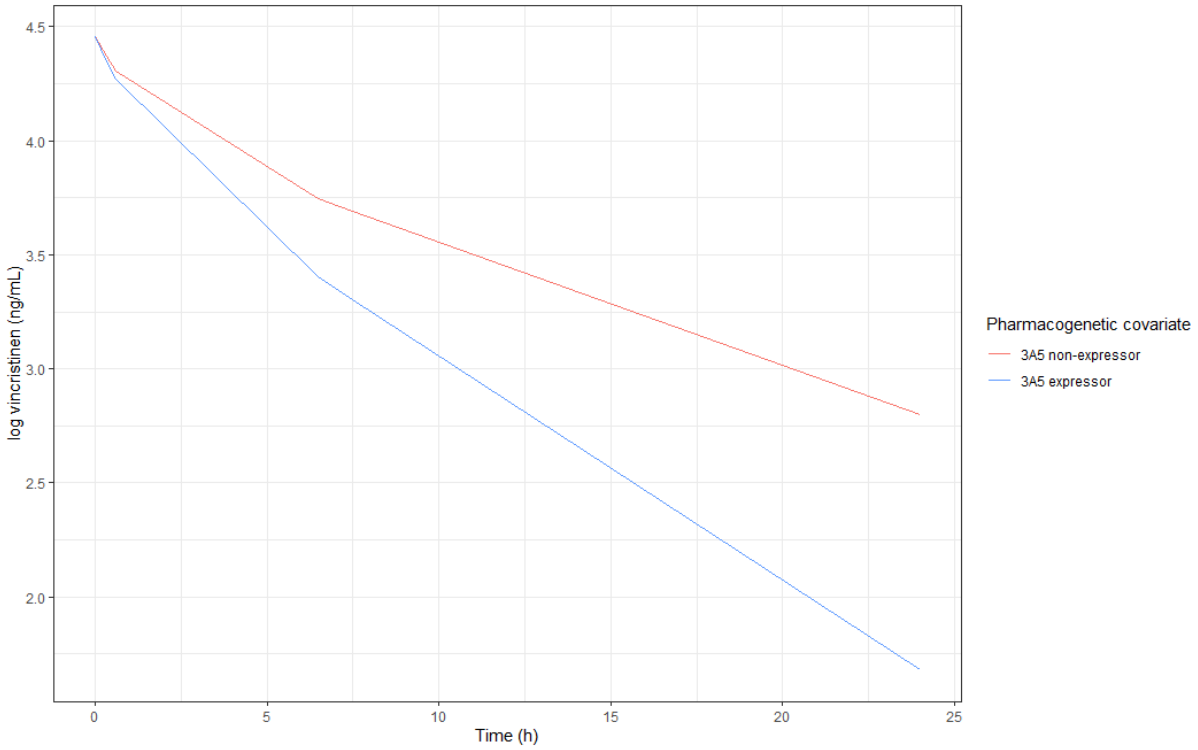
100
150
Time (h)


risperidon (ng/mL)
30
20
10
0
0
50
100
150
Time (h)
Pharmacogenetic covariate
PM
IM
EM/UM

Vincristine





S2 – example code – tamoxifen – Ctrough

```
################## Population for simulation 1 ##################
DOSET = seq(0, 2160, by=24)
#Endoxifen steady state reached can take up to 3 months (Klopp-Schulz)
TIME = rep(seq(0, 2160, by=1), times=1000)
ID = rep(seq(1, 1000, by=1), each=2161)
mrgsolve <- data.frame(ID, TIME)
mrgsolve$CMT <- 1
mrgsolve$EVID <- 0
mrgsolve$AMT <- 0

#daily dosing 20mg
mrgsolve$AMT <-  ifelse(mrgsolve$TIME %in% DOSET, 20, 0)
mrgsolve$EVID <-  ifelse(mrgsolve$TIME %in% DOSET, 1, 0)
################## Simulation 1 ##################
code <- '
$PLUGIN Rcpp
//Rifampicin & SSRI comedication not effect in the simulation
$PARAM @annotated
TVCL20    : 5.77  : CL (L/h) from tamoxifen compartment
TVCL30    : 5.10  : CL (L/h) from endoxifen compartment - fixed value from a clinical study
TVCL23    : 0.493 : Formation/intercompartmental CL (L/h) of TAM to END

TVVTAM    : 1120  : Vd of Tamoxifen (L)
TVVEND    : 400   : Vd of Endoxifen (L) - fixed value from a clinical study

TVKA      : 1.78  : Absorption constant (/h)

TVETA_CL20: 0.148 : Eta of CL20 as theta to be adjustable
TVETA_CL23: 0.201 : Eta of CL23 as theta to be
```

```
TVETA_IOV_CL20 : 0.0222 : Eta of IOV of CL20 as theta to be adjustable
TVETA_IOV_CL23 : 0.0289 : Eta of IOV of CL20 as theta to be
TVEPS_TAM : 0.0260 : EPS of Tamoxifen
TVEPS_END : 0.0267 : EPS of Endoxifen
DOSE     : 1   : Dose to be imported

$OMEGA @annotated
ETA_CL20: 1 : Eta of CL20 as theta to be adjustable
ETA_CL23: 1 : Eta of CL23 as theta to be

ETA_IOV_CL20 : 1 : Eta of IOV of CL20 as theta to be adjustable
ETA_IOV_CL23 : 1 : Eta of IOV of CL20 as theta to be

$SIGMA @block @annotated
EPS_TAM : 1        : EPS of Tamoxifen
EPS_END : 0.0169 1  : EPS of Endoxifen, including correlation with TAM

$CMT @annotated
GUT : Gut compartment for dosing
TAM_TRUE : Tamoxifen compartment
END_TRUE : Endoxifen compartment
TAM_PRIOR : Tamoxifen compartment typical individual
END_PRIOR : Endoxifen compartment typical individual
TAM_POSTERIOR : Tamoxifen compartment IPRED
END_POSTERIOR : Endoxifen compartment IPRED

$MAIN

if (NEWIND <=1) {
  double Ucyp = R::runif(0,1);
}
```

```
//AS scores of 1.5, 1, 2 and not reported assumed as reference (gNM)
if(Ucyp <= 0.85){;
double CYPCLorig = 0;
} else if(Ucyp >= 0.851 & Ucyp <= 0.930){;
  CYPCLorig = -0.510;
} else if(Ucyp >= 0.931 & Ucyp <= 0.990){;
  CYPCLorig = -0.722;
} else if(Ucyp >= 0.991 & Ucyp <= 1.000){;
  CYPCLorig = 0.533;
};

ALAG_GUT = 0.389;

double CL20_TRUE = TVCL20 * exp(ETA_CL20 * TVETA_CL20);
double CL20_PRIOR = TVCL20;
double CL20_POSTERIOR = TVCL20 * exp(ETA_CL20 * TVETA_CL20 + ETA_IOV_CL20 *
TVETA_IOV_CL20);

double CL23_TRUE_sim1 = TVCL23 * exp(ETA_CL23 * TVETA_CL23) * (1 + CYPCLorig);
double CL23_PRIOR = TVCL23 * (1 + CYPCLorig);
double CL23_POSTERIOR = TVCL23 * exp(ETA_CL23 * TVETA_CL23 + ETA_IOV_CL23 *
TVETA_IOV_CL23) * (1 + CYPCLorig);

double VTAM = TVVTAM;

double VEND = TVVEND;

double Ka = TVKA;

double K20_TRUE = CL20_TRUE / TVVTAM;
double K20_PRIOR = CL20_PRIOR / TVVTAM;
```

```
double K20_POSTERIOR = CL20_POSTERIOR / TVVTAM;

double K23_TRUE = CL23_TRUE_sim1 / TVVTAM;
double K23_PRIOR = CL23_PRIOR / TVVTAM;
double K23_POSTERIOR = CL23_POSTERIOR / TVVTAM;

double K30 = TVCL30 / TVVEND;



$ODE

dxdt_GUT = -Ka * GUT;

dxdt_TAM_TRUE = Ka * GUT - K23_TRUE * TAM_TRUE - K20_TRUE * TAM_TRUE;
dxdt_TAM_PRIOR = Ka * GUT - K23_PRIOR * TAM_PRIOR - K20_PRIOR * TAM_PRIOR;
dxdt_TAM_POSTERIOR = Ka * GUT - K23_POSTERIOR * TAM_POSTERIOR - K20_POSTERIOR *
TAM_POSTERIOR;

dxdt_END_TRUE = K23_TRUE * TAM_TRUE - K30 * END_TRUE;
dxdt_END_PRIOR = K23_PRIOR * TAM_PRIOR - K30 * END_PRIOR;
dxdt_END_POSTERIOR = K23_POSTERIOR * TAM_POSTERIOR - K30 * END_POSTERIOR;



$TABLE

double IPRED_CON_TAM = (TAM_TRUE / TVVTAM) * 1000; //True value TAM incl IIV
double IPRED_CON_END = (END_TRUE / TVVEND) * 1000; //True value END incl IIV

double IPRED_CON_PRIOR_TAM = (TAM_PRIOR / TVVTAM) * 1000; //Prior value TAM incl CYP
double IPRED_CON_PRIOR_END = (END_PRIOR / TVVEND) * 1000; //Prior value END incl CYP
```

```
double IPRED_Y_TAM = (TAM_POSTERIOR / TVVTAM) * 1000;                    //Posterior value TAM incl IOV

double Y_TAM_POSTERIOR = IPRED_Y_TAM + (IPRED_Y_TAM * EPS_TAM * TVEPS_TAM); //Posterior value TAM incl RUV

double IPRED_Y_END = (END_POSTERIOR / TVVEND) * 1000;                    //Posterior value END incl IOV

double Y_END_POSTERIOR = IPRED_Y_END + (IPRED_Y_END * EPS_END * TVEPS_END); //Posterior value END incl RUV
```

```
$CAPTURE

IPRED_CON_TAM

IPRED_CON_END

IPRED_CON_PRIOR_TAM

IPRED_CON_PRIOR_END

IPRED_Y_TAM

Y_TAM_POSTERIOR

IPRED_Y_END

Y_END_POSTERIOR


TVETA_CL20

TVETA_CL23


TVETA_IOV_CL20

TVETA_IOV_CL23


TVEPS_TAM

TVEPS_END


ETA_CL20

ETA_CL23
```

```
ETA_IOV_CL20

ETA_IOV_CL23


EPS_TAM

EPS_END


CL20_TRUE

CL23_TRUE_sim1


CYPCLorig

Ucyp


'


mod <- mcode("tamoxifen", code)


out <- mod %>%

  data_set(mrgsolve) %>%

  mrgsim(seed=12345)


# Export data from simulation 1 for subsequent simulations

DATA  <- as.data.frame(out)


################### Population and ETAs & SIGMAs for simulation round 2 ###################


exportedvalues = select(NIELS, ID, TIME, CL23_TRUE_sim1, ETA_CL23, ETA_CL20, ETA_IOV_CL20,
ETA_IOV_CL23, EPS_TAM, EPS_END, CYPCLorig, Ucyp)

exportedvalues = filter(exportedvalues, TIME==2160) ### needs to be a Ctrough at steady state!!

exportedvalues = select(exportedvalues, ID, CL23_TRUE_sim1, ETA_CL23, ETA_CL20, ETA_IOV_CL20,
ETA_IOV_CL23, EPS_TAM, EPS_END, CYPCLorig, Ucyp)

exportedvalues = unique(exportedvalues)
```

```
merged_datasets = left_join(mrgsolve, exportedvalues, by='ID')

################## Simulation round 2 ##################

code2 <- '
$PLUGIN Rcpp

//Rifampicin & SSRI comedication not included in the simulation

$PARAM @annotated
TVCL20   : 5.77  : CL (L/h) from tamoxifen compartment
TVCL30   : 5.10  : CL (L/h) from endoxifen compartment - fixed value from a clinical study
TVCL23   : 0.493 : Formation/intercompartmental CL (L/h) of TAM to END

TVVTAM   : 1120  : Vd of Tamoxifen (L)
TVVEND   : 400   : Vd of Endoxifen (L) - fixed value from a clinical study

TVKA     : 1.78  : Absorption constant (/h)

TVETA_CL20: 0.148 : Eta of CL20 as theta to be adjustable
TVETA_CL23: 0.201 : Eta of CL23 as theta to be

TVETA_IOV_CL20 : 0.0222 : Eta of IOV of CL20 as theta to be adjustable
TVETA_IOV_CL23 : 0.0289 : Eta of IOV of CL20 as theta to be

TVEPS_TAM : 0.0260 : EPS of Tamoxifen
TVEPS_END : 0.0267 : EPS of Endoxifen

DOSE      : 1 : Dose

ETA_CL20  : 1   : Exported ETA of TAM clearance from original simulation
```

ETA_CL23 : 1 : Exported ETA of END formation from original simulation

ETA_IOV_CL20 : 1 : Exported ETA of TAM clearance from original simulation

ETA_IOV_CL23 : 1 : Exported ETA of END formation from original simulation

EPS_TAM : 1 : Exported ETA of TAM clearance from original simulation

EPS_END : 1 : Exported EPS of END formation from original simulation

CL23_TRUE_sim1 : 1 : Exported true value of CL from original simulation

CYPCLorig : 1 : Exported factor for CYP covariate

Ucyp : 1 : Exported RNG for CYP covariate value determination

#OMEGAs and SIGMAs are imported

$OMEGA @annotated

//ETA_CL20: 1 : Eta of CL20

//ETA_CL23: 1 : Eta of CL23

//ETA_IOV_CL20 : 1 : Eta of IOV of CL20

//ETA_IOV_CL23 : 1 : Eta of IOV of CL20

$SIGMA @block @annotated

//EPS_TAM : 1 : EPS of Tamoxifen

//EPS_END : 0.0169 1 : EPS of Endoxifen, including correlation with TAM

$CMT @annotated

GUT : Gut compartment for dosing

TAM_TRUE : Tamoxifen compartment

END_TRUE : Endoxifen compartment

```
TAM_PRIOR : Tamoxifen compartment typical individual

END_PRIOR : Endoxifen compartment typical individual

TAM_POSTERIOR : Tamoxifen compartment IPRED

END_POSTERIOR : Endoxifen compartment IPRED


$MAIN


double CLprev = TVCL23 * exp(ETA_CL23 * TVETA_CL23) * (1 + CYPCLorig);

double COV_CL = CL23_TRUE_sim1 / CLprev;


if(Ucyp <= 0.85){;

double CYPCL = (1 + 0) * COV_CL;

} else if((Ucyp >= 0.851) & (Ucyp <= 0.930)){;

  CYPCL = (1 + -0.510) * COV_CL;

} else if((Ucyp >= 0.931) & (Ucyp <= 0.990)){;

  CYPCL = (1 + -0.722) * COV_CL;

} else if((Ucyp >= 0.991) & (Ucyp <= 1.000)){;

  CYPCL = (1 + 0.533) * COV_CL;

};


ALAG_GUT = 0.389;


double CL20_TRUE = TVCL20 * exp(ETA_CL20 * TVETA_CL20);

double CL20_PRIOR = TVCL20;

double CL20_POSTERIOR = TVCL20 * exp(ETA_CL20 * TVETA_CL20 + ETA_IOV_CL20 *
TVETA_IOV_CL20);


double CL23_TRUE = TVCL23 * exp(ETA_CL23 * TVETA_CL23) * CYPCL;

double CL23_PRIOR = TVCL23 * CYPCL;

double CL23_POSTERIOR = TVCL23 * exp(ETA_CL23 * TVETA_CL23 + ETA_IOV_CL23 *
TVETA_IOV_CL23) * CYPCL;
```

```
double VTAM = TVVTAM;

double VEND = TVVEND;

double Ka = TVKA;

double K20_TRUE = CL20_TRUE / TVVTAM;
double K20_PRIOR = CL20_PRIOR / TVVTAM;
double K20_POSTERIOR = CL20_POSTERIOR / TVVTAM;

double K23_TRUE = CL23_TRUE / TVVTAM;
double K23_PRIOR = CL23_PRIOR / TVVTAM;
double K23_POSTERIOR = CL23_POSTERIOR / TVVTAM;

double K30 = TVCL30 / TVVEND;



$ODE

dxdt_GUT = -Ka * GUT;

dxdt_TAM_TRUE = Ka * GUT - K23_TRUE * TAM_TRUE - K20_TRUE * TAM_TRUE;
dxdt_TAM_PRIOR = Ka * GUT - K23_PRIOR * TAM_PRIOR - K20_PRIOR * TAM_PRIOR;
dxdt_TAM_POSTERIOR = Ka * GUT - K23_POSTERIOR * TAM_POSTERIOR - K20_POSTERIOR *
TAM_POSTERIOR;

dxdt_END_TRUE = K23_TRUE * TAM_TRUE - K30 * END_TRUE;
dxdt_END_PRIOR = K23_PRIOR * TAM_PRIOR - K30 * END_PRIOR;
dxdt_END_POSTERIOR = K23_POSTERIOR * TAM_POSTERIOR - K30 * END_POSTERIOR;
```

```
$TABLE

double IPRED_CON_TAM = (TAM_TRUE / TVVTAM) * 1000; //True value TAM incl IIV

double IPRED_TRUE = (END_TRUE / TVVEND) * 1000; //True value END incl IIV

double IPRED_CON_PRIOR_TAM = (TAM_PRIOR / TVVTAM) * 1000; //Prior value TAM incl CYP

double IPRED_PRIOR = (END_PRIOR / TVVEND) * 1000; //Prior value END incl CYP

double IPRED_Y_TAM = (TAM_POSTERIOR / TVVTAM) * 1000;                    //Posterior value TAM incl
IOV

double Y_TAM_POSTERIOR = IPRED_Y_TAM + (IPRED_Y_TAM * EPS_TAM * TVEPS_TAM); //Posterior
value TAM incl RUV

double IPRED_Y_END = (END_POSTERIOR / TVVEND) * 1000;                    //Posterior value END incl
IOV

double IPRED_POSTERIOR = IPRED_Y_END + (IPRED_Y_END * EPS_END * TVEPS_END); //Posterior
value END incl RUV

//Formation from TAM is influenced by 2D6 so CL23, END RUV captured because most active
compound (>200x TAM)

double IIV = TVETA_CL23;

double IOV = TVETA_IOV_CL23;

double RUV = EPS_END;

$CAPTURE

IPRED_CON_TAM

IPRED_TRUE

IPRED_CON_PRIOR_TAM

IPRED_PRIOR

IPRED_Y_TAM

Y_TAM_POSTERIOR
```

```
IPRED_Y_END
IPRED_POSTERIOR

IIV
IOV
RUV

CYPCLorig
CYPCL
Ucyp

'

mod2 <- mcode("tamoxifen", code2)
#######################   Dataset for adjustment of variability ############################
datasetloop = merged_datasets
### 1331 combinations of variability
IIVsel = rep(seq(0, 1, by=0.1), times=121)   # n x n x n
IOVsel = rep(rep(seq(0, 1, by=0.1), each=11), times=11)
RUVsel = rep(seq(0, 0.5, by=0.05), each=121)
dataframe <- data.frame(IIVsel, IOVsel, RUVsel)

####################   Function for automated simulations round 2 ########################
looptacrolimus <- function(n){
  nSeeds <- ceiling(10000*rnorm(n))
  # IIVvalue = 0
  # IOVvalue = 0
  # RUVvalue = 0
  dataset=datasetloop
  # dataset$TVETA_CL = IIVvalue
```

```
 # dataset$TVETA_IOV = IOVvalue
 # dataset$TVEPS = RUVvalue
 dataframe=dataframe
 rownr=1
 i = 1
 while (i <= n) {
  noseed = print(nSeeds[i])
  set.seed(noseed)
  rand_no = floor(runif(1, min=0, max=99999))
  out <- mod2 %>%
   data_set(dataset) %>%
   mrgsim(seed=12345)   # HIER MOET JE NUMMER VERVANGEN MET noseed
  NIELS_SIM2 <- as.data.frame(out)#save as data frame for ggplot plotting

  output = filter(NIELS_SIM2, TIME==2160)
  output$PRIOR = output$IPRED_PRIOR/output$IPRED_TRUE # Looking at relative difference, not
sure if necesserely better
  output$POSTERIOR = output$IPRED_POSTERIOR/output$IPRED_TRUE
  output$PRIOR_DIF = sqrt((output$PRIOR-1)^2)
  output$POSTERIOR_DIF = sqrt((output$POSTERIOR-1)^2)
  output$SCORE <-  ifelse(output$PRIOR_DIF > output$POSTERIOR_DIF, 1, 0)

  data = output %>% filter(SCORE==0) %>% summarise(percentage_prior=((n()/1000)*100))
  IIVx=mean(output$IIV)
  IOVx=mean(output$IOV)
  RUVx=mean(output$RUV)
  data <- data.frame(data, IIVx, IOVx, RUVx)

  if(i==1){
   data2 = data
  } else {
```

```
  data2 = bind_rows(data, data2)
 }

 if(i==1){
  output2 = output
 } else {
  output2 = bind_rows(output, output2)
 }

 IIVvalue=data$IIV
 IOVvalue=data$IOV
 RUVvalue=data$RUV

 # if(IIVvalue<1){
 #   IIVvalue = IIVvalue + 0.5
 # } else {
 #   IIVvalue = 0
 # }

 dataframe2=dataframe %>% slice(rownr)

 dataset$TVETA_CL23 <- dataframe2$IIVsel
 dataset$TVETA_IOV_CL23 <- dataframe2$IOVsel
 dataset$TVEPS_END <- dataframe2$RUVsel

 i = i + 1
 rownr=rownr+1
}

print(data2)
# print(i)
```

```
  # print(IIVx)
  # print(IOVx)
  # print(RUVx)
  # return(data2)
  # print(dataframe2)
  # print(dataset)
  # print(output2)
}
loopamount = nrow(dataframe)
dataframeNIELS=looptacrolimus(loopamount)
```

S3 – code AUC calculation (only new elements compared to previous example)

```
NCAtime = c(0, 0.6, 24)

code <- '

$PLUGIN Rcpp mrgx
$GLOBAL
#### defining function for AUC calculation ###
using namespace Rcpp;
NumericVector NCAtime;

bool within(Rcpp::NumericVector x, double val) {
int n = x.size();
for (int i = 0; i < n; ++i) {
if (x[i] == val) {
return true;
}
}
return false;
}
$TABLE
if (within(NCAtime, TIME)) {
if (NEWIND <=1) {
  double MEAS = 0;
  double CP2 = 0;
  double AUCper = 0;
}
 MEAS = MEAS+1;
if (TIME == 0) {          //UITLEG4 als tijd 0 is dan initieert die dit, om concentratie baseline vast te
stellen
```

```
  double AUClastNCA=0;
  double CP1 = Y_CON_POSTERIOR;
  double TIME1 = self.time;
}

if(EVID == 0) {          //UITLEG6 voorzichtig zijn dat je EVID matcht met die van je table

 CP2 = Y_CON_POSTERIOR;    // je difinieert hier concentratie 1 en 2 telkens waarmee de auc tussen twee tijdsputen wordt bepaald
 double TIME2 = self.time;

 AUCper = (CP1 + CP2)*(TIME2 - TIME1)/2;
 if (CP2 < CP1) {
  AUCper = (CP2 - CP1)/(log(CP2) - log(CP1))*(TIME2 - TIME1);
 }

 TIME1 = self.time;
 double CPold = CP1;
 CP1 = Y_CON_POSTERIOR;        // hier update je concentratie 1 naar het nieuwe tijdspunt voor de volgende ronde
 AUClastNCA = AUClastNCA + AUCper;   //UITLEG6 trapezoidaal hier waarbij je de AUCs summarized
}
}

double AUC_POSTERIOR = AUClastNCA;
‘
```