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OBJECTIVE

Despite being an old drug, currently there is not good predictive model for phenobarbital (PBT) in clinical practice. Therefore, the main goal of this work was to develop an updated population pharmacokinetics (PK) model to identify and quantify the influence of demographic, clinical and treatment factors on the clearance (CL) of PBT in Children, Adolescents and Young Adults Patients.

METHODS

- ✓ Serum concentrations of PBT were taken from patients included in the TDM program over the last 20 years.
- ✓ Previous inclusion/exclusion criteria was applied.
- ✓ PK analysis was performed with NONMEM.
- ✓ Proportional error models were assumed to describe interindividual and residual variabilities.
- ✓ The analysed covariates were described in table 1.
- ✓ The predictive capacity was evaluated using a Bootstrap technique.

TDM Program in the University Hospital of Salamanca, Spain

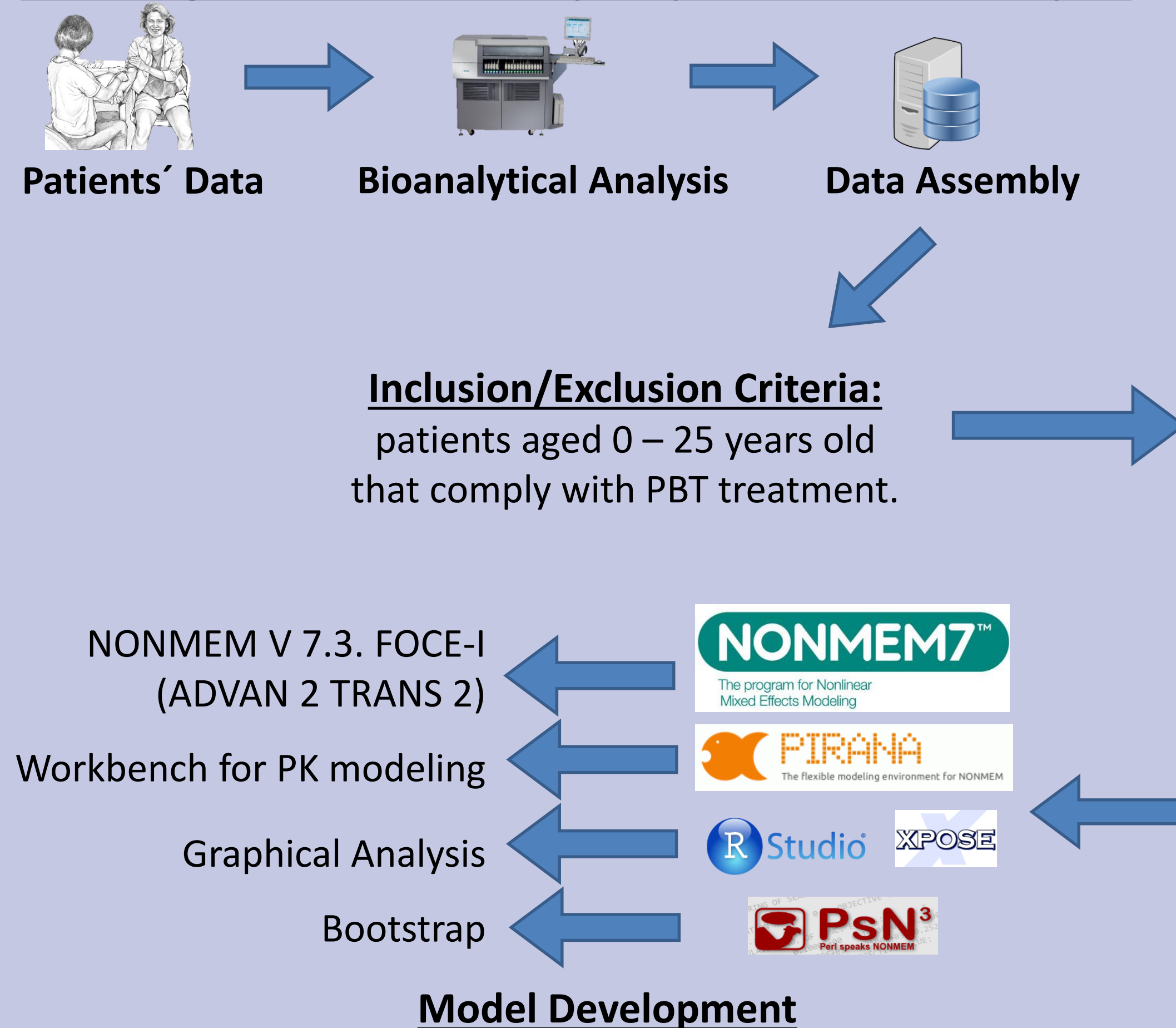


TABLE 1. Demographic and Clinical Characteristics of the Patients Included in the Study.

DEMOGRAPHIC	
Number of samples/patients	304/118
Gender (SEX) (male/female)	73/45
Age, median (range) (years)	20 (0.08 – 25)
Body Weight (WGT), median (range) (kg)	55 (3.9 – 110)
CLINICAL	
Doses (tablet)	
Each 24 h, median (range), 112 patients	100 (22 – 252)
Each 12 h, median (range), 6 patients	60 (20 – 200)
Concentration, median (range) (mg/L)	23.0 (3.2 – 48.7)
COMEDICATION (samples/patients)	
carbamazepine (CBZ)	112/16
clonazepam (CLO)	26/4
phenytoin (PHT)	160/19
lamotrigine (LTG)	20/3
valproic acid (VLP)	69/9
Another Common Comedication (ACC)	73/10

RESULTS

- ✓ The covariates with significant influence on CL/F_{PBT} were: WGT and concomitant treatment with CBZ, PHT, VLP and ACC.
- ✓ ACC was excluded in the backward elimination process ($p < 0.01$). The covariate CBZ was also eliminated in the final model because of the low clinical significance ($< 15\%$). See table 2.

TABLE 2. Summary of Covariates Analyses.

Covariates on the CL/F_{PBT}	Forward Inclusion Method		Backward Elimination Method		Inclusion on the Final Model
	ΔOFV^a	P Value	ΔOFV^b	P Value	
WGT*	217.608	< 0.05	270.864	< 0.01	YES
AGE*	199.444	< 0.05	----	----	NO
SEX	0.431	NS	----	----	NO
COMEDICATION					
CBZ	12.068	< 0.05	9.619	< 0.01	NO ^d
CLO	1.141	NS	----	----	NO
PHT	21.378	< 0.05	37.532	< 0.01	YES
LTG	0.277	NS	----	----	NO
VLP	78.372	< 0.05	82.497	< 0.01	YES
ACC	10.254	< 0.05	5.176	NS	NO ^c

* Correlated variables, $R = 0.84$

^a Reduction in the objective function value (OFV) between consecutive models.

^b Increase in the OFV between consecutive models.

^c ACC was excluded in the backward elimination process ($p < 0.01$).

^d CBZ was also eliminated in the final model because of the low clinical significance ($< 15\%$). NS, non-significant.

- ✓ The Goodness of fit in final model is better than basic model, see figure 1.
- ✓ Inclusion covariates WGT, PHT and VLP in the final model explained interindividual variability of CL/F_{PBT} (ETA1), see figure 2.

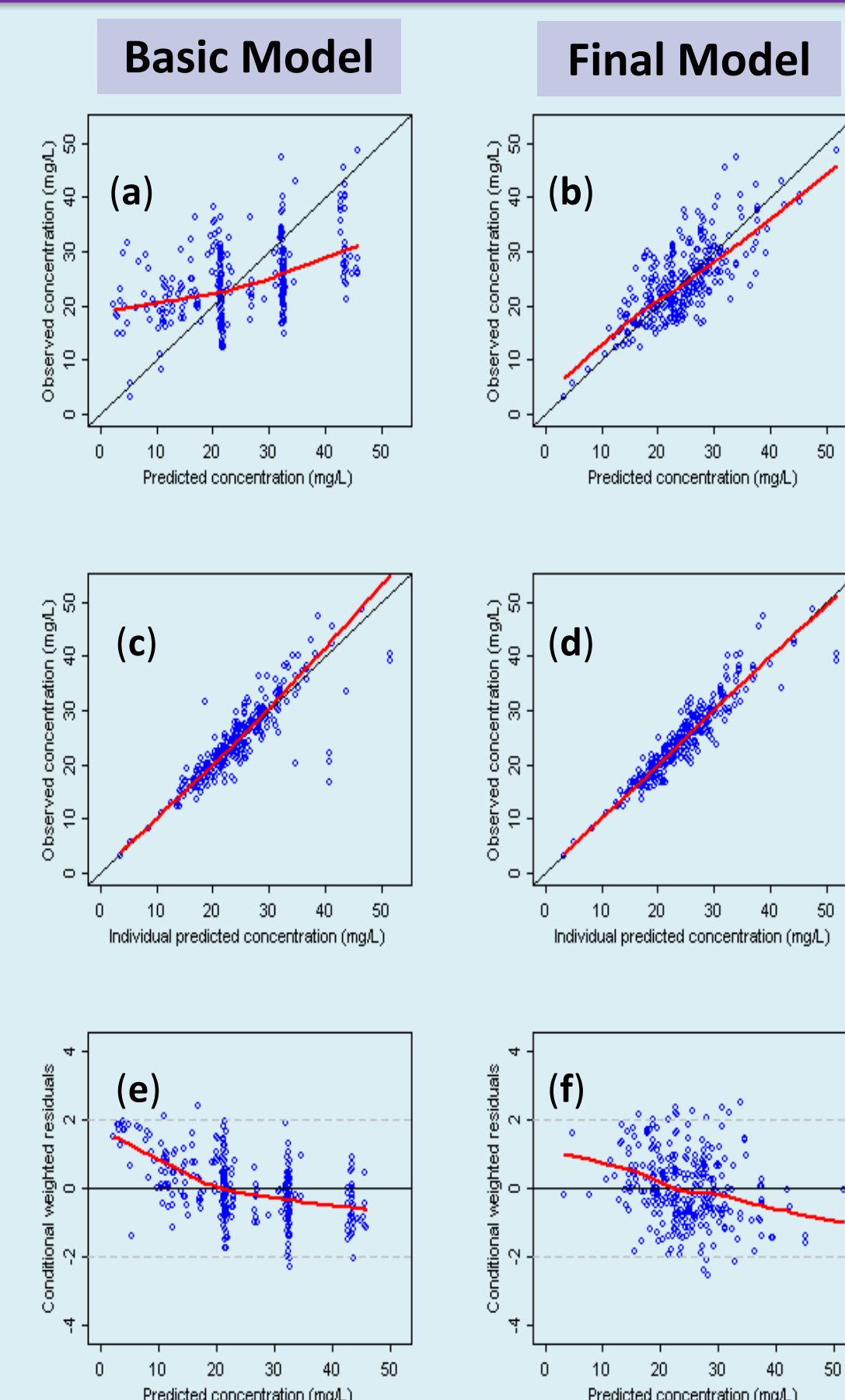


Figure 1. Goodness of Fit Plots: Basic and Final Model.

a, b: Observed concentrations vs. Populational predicted concentrations (PRED).
c, d: Observed concentrations vs. Individual predicted concentrations (IPRED).
e, f: PRED vs. Conditional weighted residuals (CWRES).
NOTE: Non significant shrinkage.

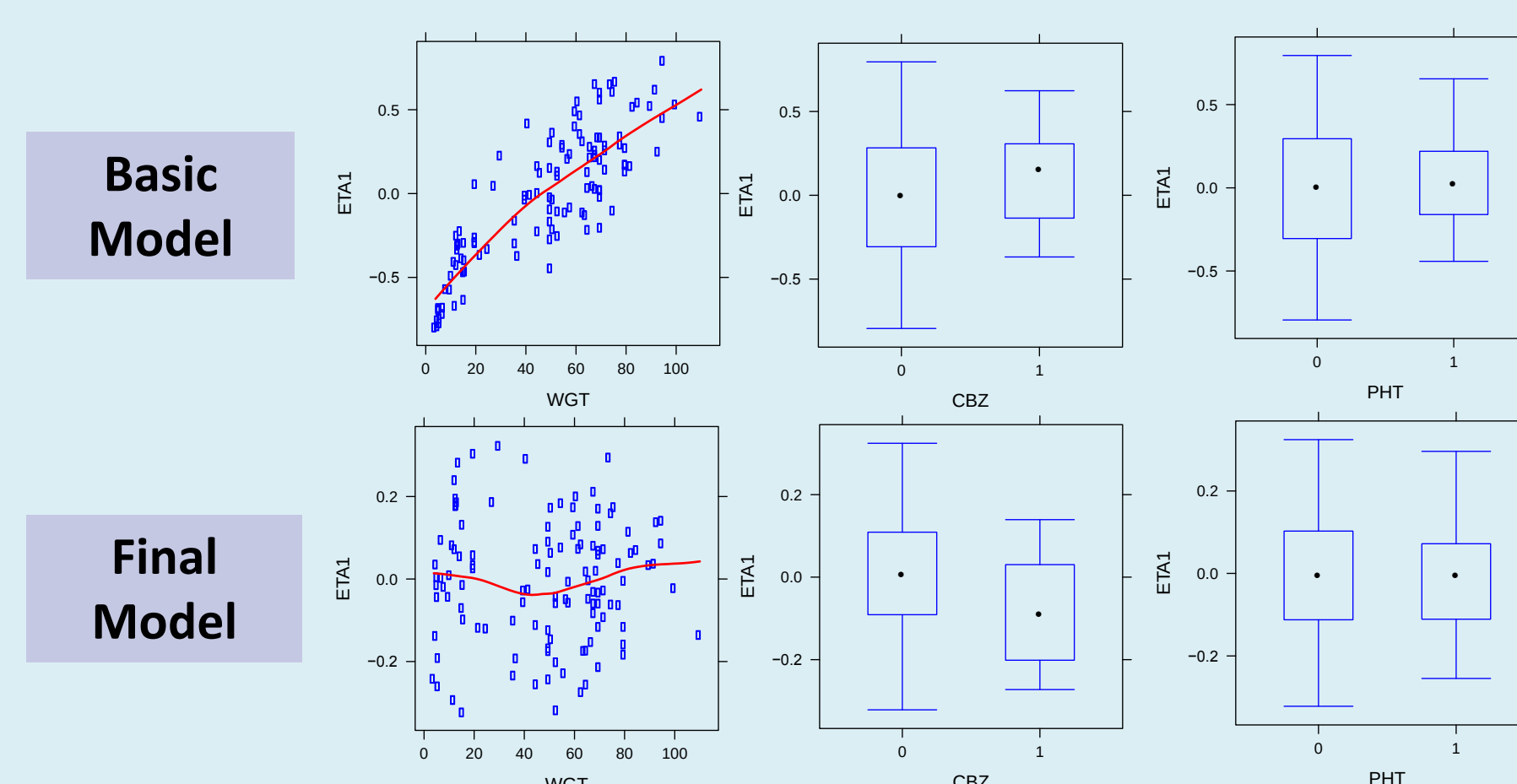


Figure 2. ETA1 vs Covariates: Basic and Final Model.

- ✓ The percentages of interindividual and residual variabilities explained by the final model are shown in table 3.

TABLE 3. Comparison of Interindividual and Residual Variabilities for Basic and Final Models

	Basic Model	Final Model	Absolute Difference	Relative Difference
ω^2	0.167 (= 41 %)	0.026 (= 16 %)	25 %	84 %
σ^2	0.021 (= 14 %)	0.012 (= 11 %)	3 %	43 %

ω^2 , interindividual variability. σ^2 , residual variability.

- ✓ The results obtained in the Bootstrap analysis show acceptable performance of the proposed model. See table 4.

TABLE 4. The Final Parameter Estimates from NONMEM and the Bootstrap Analysis.

Parameter	NONMEM		Bootstrap Analysis	
	Estimate	RSE (%)	Mean	95 % CI
K_a (h^{-1})	1.33**	----	----	----
V/F (L/kg)	0.9**	----	----	----
CL (L/h)	0.256	2.4	0.255	0.243 – 0.268
WGT*	0.582	3.9	0.579	0.530 – 0.624
PHT*	0.839	3.3	0.842	0.780 – 0.903
VLP*	0.667	5.2	0.670	0.602 – 0.737
ω^2	0.026	15.1	0.026	0.019 – 0.034
σ^2	0.012	12.4	0.012	0.009 – 0.015

1000 Bootstrap runs. RSE (%), percentage of relative standard error. CI, confidence interval. * Effect of the covariates on the CL of PBT. ** Fixed respectively [1-3].

FINAL MODEL:

$$CL/F_{PBT} (L/h) = 0.26 \cdot ((WGT/70)^{0.58}) \cdot (0.84 \cdot PHT) \cdot (0.67 \cdot VLP)$$

$\omega^2_{CL/F} = 0.026$ (CV=16 %; shrinkage=9 %)

$\sigma^2 = 0.012$ (CV=11 %; shrinkage=17 %)

The standard estimation errors were $\leq 15\%$ for all parameters.

CONCLUSION

The developed population pharmacokinetic model for PBT in children, adolescents and young adults patients includes WGT and the concomitant administration of PHT and VLP on CL/F_{PBT} . The inclusion of these covariates reduced interindividual and residual variabilities for 84 % y 43 %, respectively. This model appears to be adequate for clinical application in TDM. However, we consider necessary to carry out an external validation to confirm the results shown in this study.

REFERENCES

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