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Research Paper

Conditional Weighted Residuals (CWRES): A Model Diagnostic for the FOCE Method

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Purpose. Population model analyses have shifted from using the first order (FO) to the first-order with conditional estimation (FOCE) approximation to the true model. However, the weighted residuals (WRES), a common diagnostic tool used to test for model misspecification, are calculated using the FO approximation. Utilizing WRES with the FOCE method may lead to misguided model development/evaluation. We present a new diagnostic tool, the *conditional* weighted residuals (CWRES), which are calculated based on the FOCE approximation.
Materials and Methods. CWRES are calculated as the FOCE approximated difference between an individual's data and the model prediction of that data divided by the root of the covariance of the data given the model.
Results. Using real and simulated data the CWRES distributions behave as theoretically expected under the correct model. In contrast, in certain circumstances, the WRES have distributions that greatly deviate from the expected, falsely indicating model misspecification. CWRES/WRES comparisons can also indicate if the FOCE estimation method will improve the results of an FO model fit to data.
Conclusions. Utilization of CWRES could improve model development and evaluation and give a more accurate picture of if and when a model is misspecified when using the FO or FOCE methods.

KEY WORDS: conditional estimation; model diagnostics; modeling; non-linear mixed effect models; NONMEM; pharmacometrics; statistics; weighted residuals.

INTRODUCTION

Utilization of population pharmacokinetic (PK) and pharmacodynamic (PD) models to describe clinical data is becoming increasingly important in drug development (1,2). In order to estimate the parameters of these pharmacometric models various computer programs have been developed (3–6), of which the most popular is NONMEM (Globomax, USA). When NONMEM was first introduced the only parameter estimation method available was the first-order (FO) method, based on the first-order Taylor series approximation to the population PK/PD model. Since then, improved methods of approximating the model have been developed including the first-order with conditional estimation (FOCE) method and the FOCE method with interaction (FOCEI).

The FOCE methods allow for hypothesis testing during model building (7) and generally produce less biased model parameter estimates (8,9). As a result, the NONMEM community has shifted from the FO method to the FOCE and FOCEI methods. A search on pub-med for all articles that used NONMEM for pharmacometric analysis in 2005 (search terms: NONMEM, population pharmacokinetics and population pharmacodynamics) revealed 131 studies, of which 15% used the FO method, 21% used the FOCE method, 28% used the FOCEI method, 16% used a combination of these methods and 20% did not discuss the estimation method employed.

Once a model has been fit to pharmacometric data it is crucial to evaluate the goodness of that fit. The NONMEM user's guide (10) suggests use of the weighted residuals (WRES), the weighted difference between the model prediction and the data, as one model diagnostic. Presently, use of the WRES is suggested by the United States' Food and Drug Administration (FDA) as an appropriate diagnostic for evaluating model misspecification (11). The WRES have also become a common model diagnostic in the literature. Of the 131 papers found in the above Pub-Med search, 50% specifically mentioned examining the WRES during model diagnosis, of those, 80% provided a plot of the WRES in their publication.

The WRES, however, are always calculated based on the FO approximation to the model. This is the case even if the model development process has taken place using the FOCE methods. Use of the WRES as a diagnostic when performing modeling using the FOCE methods leads to the possibility of misguided model development and diagnosis, or, at the very least, less informed model development.

In this work we present a new diagnostic tool, the conditional weighted residuals (CWRES), which are calculated in a similar manner to the WRES but based on the

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FOCE approximation. The CWRES have the advantage of being directly related to a term in the objective function used in the FOCE method of model fitting, thus giving more detailed information about the fit of a model to data using this method.

In the following sections we first present a motivating example demonstrating the possibility of misguided model development using the WRES as a diagnostic while performing FOCE analysis. In this same situation we demonstrate that use of the CWRES would not result in such an error. Next we detail how both the WRES and the CWRES are calculated. The CWRES are then explored in a more systematic simulation study. Then the possibility of using the differences between WRES and CWRES distributions as an indicator of the differences in parameter estimates between the FO and FOCE methods is investigated. Finally, we examine the CWRES in a real data example where the WRES indicate some model misspecification but the model has otherwise good fit characteristics.

BACKGROUND

Motivating Example: Misguided Model Development Using the WRES

We simulate data for 200 individuals with 25 samples per individual using a sigmoidal Emax model with exponential between-subject variability (BSV), additive residual variability (RV) and a Hill coefficient of 4.5 (i.e. a very non-linear model). For more information on this model see the "MATERIALS AND METHODS" section of this paper.

Using this model and the data simulated from this model we then re-estimate the model parameters using the FOCE method in NONMEM. For this one simulation the difference between the estimated and true parameter values is less than 10% for all parameters in the model, indicating that the FOCE method does not have a problem with the fit of model to data.

Next we examine the WRES from this model fit to data. The left graph of Fig. 1 shows the WRES as a function of the independent variable (plasma concentration in this simulation). Statistically, if the linearized model adequately describes the data the WRES should be normally distributed with mean zero and variance one (see "Calculating the WRES" section for more detail). This is clearly not the case at plasma concentrations between 0 and 75, indicating model misspecification (even though we know we are using the right model!).

Using the same simulated data, we next estimate new model parameters using a misspecified model. Misspecification is introduced by removing the hill-coefficient, reducing the model to a basic Emax model. As seen in the right graph of Fig. 1, the WRES indicate that this misspecified model fits the data better than the correct model.

As stated above, the WRES are always calculated using the FO approximation to the model even when the FOCE estimation method is used. Given that the model we are simulating from in this example is highly non-linear (hill-coefficient of 4.5); the FO approximation to the model is not likely to be as accurate as the FOCE model approximation. In this situation the WRES may indicate problems with model fit (FO problems), when, in fact there are no problems with an FOCE fit to data. The CWRES, on the other hand,

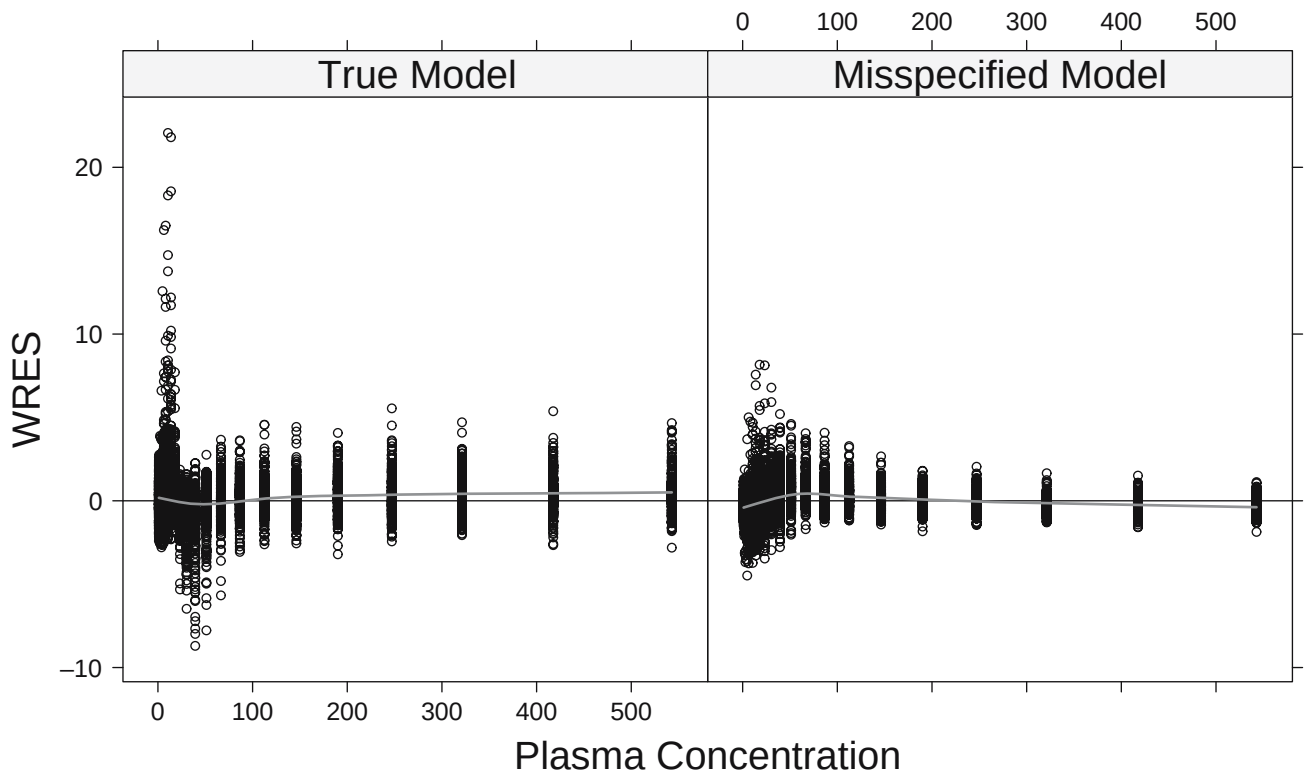

Fig. 1. The WRES for the true and misspecified model discussed in the motivating example. In this example the WRES indicate that the misspecified model is the better model.

are calculated using the FOCE approximation to the model and in such a situation could be expected to give a better diagnostic to the FOCE fit to data.

To test this hypothesis the CWRES for both the true and misspecified model fits to the data in the above example are computed (details on calculating the CWRES are presented in "The FOCE Objective Function" and "Conditionally Weighted Residuals (CWRES)" sections). Figure 2 shows plots of CWRES *versus* plasma concentration for the FOCE fits of both the true and misspecified models to the simulated data. The CWRES for the true model are clearly more normally distributed than for the misspecified model, indicating (in contrast to the WRES) that the correctly specified model is a better model to describe the given data.

The Population Model and Parameter Estimation

We define our model for the vector of measurements $\vec{y}_i$ for the ith individual in a population as:

$$\vec{y}_i = f(\vec{x}_i, \vec{\theta}, \vec{\eta}_i) + h(\vec{x}_i, \vec{\theta}, \vec{\eta}_i, \vec{\varepsilon}_i) \tag{1}$$

here $\vec{x}_i$ is the vector of independent variables for an individual's model (time, concentration in plasma, covariate values etc.), $\vec{\theta}$ is the vector of population fixed effects, $\vec{\eta}_i$ is the vector of individual realizations of the between-subject variability terms in the model and $\vec{\varepsilon}_i$ is the vector of realizations of the residual error variability terms in the model. $\vec{\eta}$ and $\vec{\varepsilon}$ are both vectors of random variables that are assumed to be normally distributed with mean zero and variance Ω and $\mathbf{\Sigma}$ respectively. In the following discussion we simplify the notation in Eq. 1 by removing $\vec{x}_i$ from future equations.

For both the FO and FOCE methods in NONMEM, the model parameter values ($\vec{\theta}, \Omega, \mathbf{\Sigma}$) that best fit a set of data are determined by minimizing minus two times the logarithm of the extended least squares objective function (OF). In its general form (and with constants removed) we have:

$$\mathrm{OF} = \sum_{i=1}^{m} \left[\log |\mathbf{Cov}(\vec{y}_i)| + \frac{(\vec{y}_i - E(\vec{y}_i))^2}{\mathbf{Cov}(\vec{y}_i)} \right] \tag{2}$$

where $\mathbf{Cov}(\vec{y}_i)$ is the covariance matrix of the data given the model, $E(\vec{y}_i)$ is the expectation of the data given the model and m is the number of individuals in the dataset.

Because Eq. 1 can be non-linear in both $\vec{\eta}_i$ and $\vec{\varepsilon}_i$ it is impossible to directly calculate $\mathbf{Cov}(\vec{y}_i)$ and $E(\vec{y}_i)$ in Eq. 2. As such, different varieties of linearizations to the model can be carried out to make these calculations possible (12).

The FO Objective Function

The simplest method of model linearization is the first order (FO) method, where the model is linearized about the mean of the random parameters in the model (zero) using the Taylor series approximation. Assuming no interaction between $\vec{\eta}_i$ and $\vec{\varepsilon}_i$ we have

$$\vec{y}_i \approx f(\vec{\theta}, \vec{\eta}_i = 0) + \frac{df(\vec{\theta}, \vec{\eta}_i = 0)}{d\vec{\eta}_i} \cdot \vec{\eta}_i + \frac{dh(\vec{\theta}, \vec{\eta}_i = 0, \vec{\varepsilon}_i = 0)}{d\vec{\varepsilon}_i} \cdot \vec{\varepsilon}_i \tag{3}$$

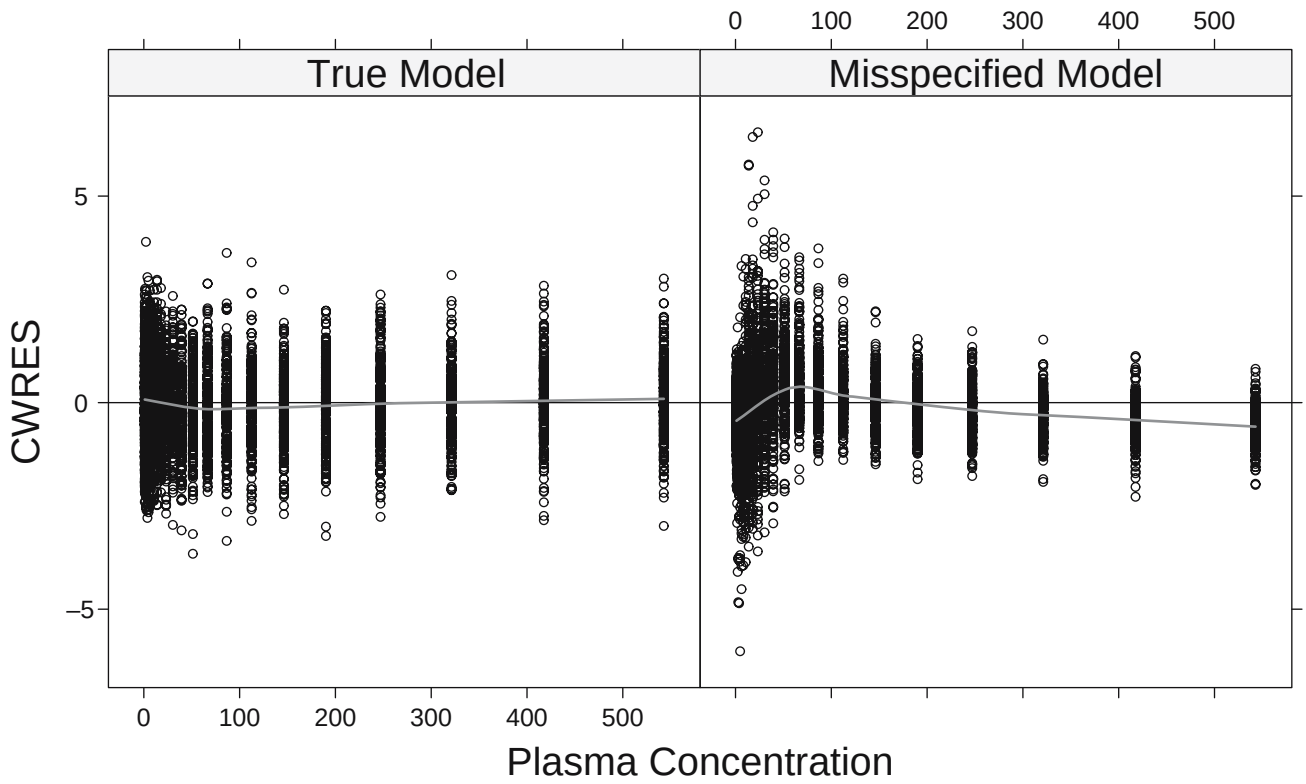

Fig. 2. The CWRES for the true and misspecified model discussed in the motivating example. The CWRES indicate that the true model better fits the simulated data in contrast to the WRES shown in Fig. 1.

where $\frac{df(\vec{\theta},\vec{\eta}_i=0)}{d\vec{\eta}_i}$ indicates the derivative of f with respect to $\vec{\eta}_i$ evaluated at $\vec{\eta}_i = 0$ and $\frac{dh(\vec{\theta},\vec{\eta}_i=0,\vec{\varepsilon}_i=0)}{d\vec{\varepsilon}_i}$ indicates the derivative of h with respect to $\vec{\varepsilon}_i$ evaluated at $\vec{\eta}_i = 0$ and $\vec{\varepsilon}_i = 0$.

Using this approximation, the expectation and covariance of the model in Eq. 1 are:

$$E_{\mathrm{FO}}\left(\vec{y}_i\right) = f\left(\vec{\theta}, \vec{\eta}_i = 0\right)$$
$$\mathbf{Cov}_{\mathrm{FO}}\left(\vec{y}_i\right) = \frac{df\left(\vec{\theta},\vec{\eta}_i=0\right)}{d\vec{\eta}_i}\cdot\Omega\cdot\frac{df\left(\vec{\theta},\vec{\eta}_i=0\right)'}{d\vec{\eta}_i} + diag\left(\frac{dh\left(\vec{\theta},\vec{\eta}_i=0,\vec{\varepsilon}_i=0\right)}{d\vec{\varepsilon}_i}\cdot\sum\cdot\frac{dh\left(\vec{\theta},\vec{\eta}_i=0,\vec{\varepsilon}_i=0\right)'}{d\vec{\varepsilon}_i}\right) \quad (4)$$

where $f(.)'$ indicates the transpose of f and $diag(\mathbf{x})$ indicates the diagonal elements of the matrix $\mathbf{x}$. Note that the second term in the covariance equation is diagonal due to a further assumption of independence between individual random measurement errors in our model (in NONMEM, the term is actually block diagonal if the L2 data item is used (10)). The FO objective function can then be written as

$$\mathrm{OF}_{\mathrm{FO}} = \sum_{i=1}^{m}\left[\log\left|\mathbf{Cov}_{\mathrm{FO}}(\vec{y}_i)\right| + \frac{(\vec{y}_i - E_{\mathrm{FO}}(\vec{y}_i))^2}{\mathbf{Cov}_{\mathrm{FO}}(\vec{y}_i)}\right] \quad (5)$$

The FOCE Objective Function

The FOCE method uses a more advanced method of model linearization conditioning the linearization of the model around each individual's empirical Bayes (post-hoc) estimates of the between-subject variability random effects $\widehat{\eta}_{\mathrm{PH},i}$:

$$\vec{y}_i \approx f\left(\vec{\theta}, \vec{\eta}_i = \widehat{\eta}_{\mathrm{PH},i}\right) + \frac{df\left(\vec{\theta},\vec{\eta}_i=\widehat{\eta}_{\mathrm{PH},i}\right)}{d\vec{\eta}_i}\cdot\vec{\eta}_i - \frac{df\left(\vec{\theta},\vec{\eta}_i=\widehat{\eta}_{\mathrm{PH},i}\right)}{d\vec{\eta}_i}\cdot\widehat{\eta}_{\mathrm{PH},i} + \frac{dh\left(\vec{\theta},\vec{\eta}_i=0,\vec{\varepsilon}_i=0\right)}{d\vec{\varepsilon}_i}\cdot\vec{\varepsilon}_i \quad (6)$$

Linearization is still performed about the mean of the residual error terms ($\vec{\varepsilon}_i = 0$) and done assuming no interaction between the population random effects and the individual random effects (the h term is not linearized about $\vec{\eta}_i$). For more information about the third term in this linearization please see Lindstrom and Bates (13). The expectation and covariance of the model can then be computed as:

$$E_{\mathrm{FOCE}}\left(\vec{y}_i\right) = f\left(\vec{\theta},\vec{\eta}_i = \widehat{\eta}_{\mathrm{PH},i}\right) - \frac{\mathrm{d}f\left(\vec{\theta},\vec{\eta}_i = \widehat{\eta}_{\mathrm{PH},i}\right)}{\mathrm{d}\vec{\eta}_i}\cdot\widehat{\eta}_{\mathrm{PH},i}$$
$$\mathbf{Cov}_{\mathrm{FOCE}}\left(\vec{y}_i\right) = \frac{\mathrm{d}f\left(\vec{\theta},\vec{\eta}_i = \widehat{\eta}_{\mathrm{PH},i}\right)}{\mathrm{d}\vec{\eta}_i}\cdot\Omega\cdot\frac{\mathrm{d}f\left(\vec{\theta},\vec{\eta}_i = \widehat{\eta}_{PH,i}\right)'}{\mathrm{d}\vec{\eta}} + diag\left(\frac{\mathrm{d}h\left(\vec{\theta},\vec{\eta}_i = 0,\vec{\varepsilon}_i = 0\right)}{\mathrm{d}\vec{\varepsilon}_i}\cdot\Sigma_i\cdot\frac{\mathrm{d}h\left(\vec{\theta},\vec{\eta}_i = 0,\vec{\varepsilon}_i = 0\right)'}{\mathrm{d}\vec{\varepsilon}_i}\right) \quad (7)$$

The FOCE objective function can then be written as:

$$\mathrm{OF}_{\mathrm{FOCE}} = \sum_{i=1}^{m}\left[\log\left|\mathbf{Cov}_{\mathrm{FOCE}}\left(\vec{y}_i\right)\right| + \frac{\left(\vec{y}_i - E_{\mathrm{FOCE}}\left(\vec{y}_i\right)\right)^2}{\mathbf{Cov}_{\mathrm{FOCE}}\left(\vec{y}_i\right)}\right] \quad (8)$$

Calculating the WRES

Given a model that describes the data, the square root of the second term in Eq. 2 should be normally distributed with a mean of zero and a variance of one (data minus the expectation of that data divided, or normalized, by the standard deviation of that data):

$$\frac{\vec{y}_i - E\left(\vec{y}_i\right)}{\sqrt{\mathbf{Cov}\left(\vec{y}_i\right)}} \in N(0,1) \quad (9)$$

Consequently, these values can be used as a diagnostic to see if a model adequately describes the data. Note that, in the above equation, we have not specified the way in which the expectation and covariance on the model are calculated (e.g. using the FO or FOCE approximations).

In NONMEM the values in Eq. 9 are computed using the FO approximation to the model shown in Eq. 4, these values are known as the weighted residuals (WRES)

$$\mathrm{WRES} = \frac{\vec{y}_i - E_{\mathrm{FO}}\left(\vec{y}_i\right)}{\sqrt{\mathbf{Cov}_{\mathrm{FO}}\left(\vec{y}_i\right)}} \quad (10)$$

The WRES should be $N(0,1)$ as long as the model adequately describes the data and the model linearization is adequate to describe the model. Most importantly, we note again that in the NONMEM program the WRES are *always* calculated using the FO approximation to the model, *even when using the FOCE approximation*. This means that, when using the FOCE method, the WRES are not the square root of the second term of the $\mathrm{OF}_{\mathrm{FOCE}}$, and are consequently of less diagnostic value. (SAS and NMLE in S-Plus similarly utilize the FO approximation to calculate the WRES, however they use a simplified version of the calculation in Eq. 10, for a comparison see (14)).

MATERIALS AND METHODS

Conditionally Weighted Residuals (CWRES)

Given the poor performance of the FO method in many situations and the creation of the FOCE and other higher order methods to replace the FO method, it does not seem logical to use the WRES, based on the FO approximation, to evaluate models built using the FOCE method (or other higher order methods). To correct the WRES for the FOCE method, in this paper we present the CWRES. The CWRES

are computed in the same manner as the WRES but using the FOCE approximation to the model:

$$\text{CWRES} = \frac{\vec{y}_i - E_{\text{FOCE}}\left(\vec{y}_i\right)}{\sqrt{\mathbf{Cov}_{\text{FOCE}}\left(\vec{y}_i\right)}} \tag{11}$$

Like the WRES, the CWRES should be $N(0,1)$ as long as the model adequately describes the data and the model linearization is adequate to describe the model. The CWRES are the square root of the second term in the OF_{FOCE}. Using the CWRES one would expect a more specific understanding of what is happening in an FOCE model fit to data.

CWRES are computed using verbatim code in NONMEM and a post processing step implemented in either *R* (http://www.r-project.org) or MATLAB (Mathworks, USA). The *R* version of the script has been incorporated into version 4 of the software package Xpose (15) and is freely available at xpose.sourceforge.net. The MATLAB script is available by request. Automation of the CWRES computation has been developed in Perl Speaks NONMEM (16), which automatically adds the needed verbatim code to a NONMEM model, runs that model in NONMEM and then runs Xpose 4 to compute the CWRES. PsN is freely available at psn.sourceforge.net.

Tests and Graphs

Because the CWRES and WRES should both be $N(0,1)$, when the assumptions used in their calculations are correct, we can use various numerical and visual tests to compare their distributions. In this paper we compare the two distributions through visual inspection of plots of the CWRES and WRES *versus* the independent variable. Mean, variance and kurtosis of each distribution are also examined. Kurtosis is a measure of normality; a value larger than 3 indicates a distribution that is more heavy tailed than a normal distribution, while a value less than three indicates a distribution that is more peaked than a normal distribution (17).

The Motivating Example

The model used for simulation of data (the 'true' model) in the motivating example presented in "Motivating Example: Misguided Model Development Using the WRES" section was a sigmiodal Emax model with exponential between-subject variability and additive residual error:

$$\begin{aligned} \overline{Effect}_i &= 1 + \frac{E_{\max,i}\,\vec{C}_i^{\,\gamma}}{\vec{C}_i^{\,\gamma} + C_{50,i}^{\,\gamma}} + \vec{\varepsilon}_i \\ E_{\max,i} &= \theta_1 e^{\eta_{1,i}} \\ C_{50,i} &= \theta_2 e^{\eta_{2,i}} \\ \gamma &= \theta_3 \end{aligned} \tag{12}$$

where the model describes an individual's vector of effect measurements of drug X dependent on the concentration $\vec{C}_i$ of the drug in plasma. Parameter values for the model were $(\theta_1, \theta_2, \theta_3)=(100, 20, 4.5)$, $\boldsymbol{\Omega} = \begin{pmatrix} 0.5 & 0 \\ 0 & 0.5 \end{pmatrix}$ and $\boldsymbol{\Sigma} = 250$. This model and all other models described in this paper were implemented in NONMEM VIβ. The same models have also been tested in NONMEM VI and no differences were found.

Using this simulated data, parameter estimates were obtained using the FOCE method in NONMEM for both the model described above and a misspecified model where the value of the hill coefficient, γ, was fixed to a value of one, reducing the model to an Emax model. Parameter estimates were compared to the values used for simulation to assess model fit to data. For both the true and misspecified models, WRES values were obtained from the NONMEM output and CWRES values were computed as described in the "Conditionally Weighted Residuals (CWRES)" section. Visual comparison of the CWRES and WRES was then used to evaluate each diagnostic.

Effects of Model Non-linearity on CWRES and WRES

Next, we investigated the CWRES and WRES in a more systematic simulation study. Investigating the distributional properties of both the WRES and CWRES as the population model becomes more and more non-linear. Simulation and estimation (using FOCE) was performed using the same model as described in the motivating example, while varying the hill-coefficient θ_3 between the values of 1 and 4.5. Increasing the hill-coefficient increases the non-linear properties of the model. No model misspecification was used in this example.

1000 datasets were simulated for each value of θ_3 (1, 1.5, 2, 2.5, 3, 3.5, 4 and 4.5). Parameter bias and root mean standard error (RMSE) estimates were computed to assess model fit as follows (18):

$$\begin{aligned} \text{BIAS}(\theta_k) &= \frac{1}{\theta_{k,\text{TRUE}}}\left[\frac{1}{N_e}\sum_{i=1}^{N_e}\left(\hat{\theta}_{k,i} - \theta_{k,\text{TRUE}}\right)\right] \times 100\% \\ \text{RMSE}(\theta_k) &= \frac{1}{\theta_{k,\text{TRUE}}}\left[\frac{1}{N_e}\sum_{i=1}^{N_e}\left(\hat{\theta}_{k,i} - \theta_{k,\text{TRUE}}\right)^2\right]^{1/2} \times 100\% \end{aligned} \tag{13}$$

where $\hat{\theta}_{k,i}$ is the estimated kth model parameter for the ith simulation and N_e is the number of simulations (1000 in this example). For each simulation the WRES and CWRES values were then computed along with the mean, variance and kurtosis of the two distributions.

FO/FOCE Differences from CWRES/WRES Differences in FO

The potential use of the CWRES as an indicator of the differences in parameter estimates between the FO and FOCE methods was then examined. As the WRES are the square root of the second term of the OF_{FO} their calculation should give us direct insight into what is happening with an FO fit to data. Similarly, the CWRES are the square root of the second term of the OF_{FOCE} and should give us insight into what is happening with an FOCE fit to data. However, CWRES can be computed using the FO method in combination with a POSTHOC step in NONMEM. By comparing the CWRES and WRES values computed during an FO fit we may obtain information about how an FOCE fit would differ from an FO fit.

To investigate this possibility, we examined a number of models, each with several different sets of parameter values, resulting in a range of models from almost linear to highly

non-linear (the latter being where FOCE and FO are expected to give different results). For each model and each set of parameters 1000 datasets were simulated and parameter estimates were obtained using both the FO and FOCE methods in NONMEM. For each simulation the WRES and CWRES values were computed along with the mean, variance and kurtosis of the two distributions, parameter bias and RMSE for each parameter were also computed using Eq. 13. The average difference between the FO and FOCE parameter RMSE ($\overline{\text{RMSE}}_{\text{FO-FOCE}}$) values as well as the average difference of the absolute values of the FO and FOCE parameter bias ($\overline{\text{BIAS}}_{|\text{FO}|-|\text{FOCE}|}$) values were then calculated:

$$\begin{aligned}\overline{\text{BIAS}}_{|\text{FO}|-|\text{FOCE}|} &= \frac{1}{N_k}\sum_{k=1}^{N_k}\left(|\text{BIAS}_{\text{FO}}(\theta_k)| - |\text{BIAS}_{\text{FOCE}}(\theta_k)|\right)\\ \overline{\text{RMSE}}_{\text{FO-FOCE}} &= \frac{1}{N_k}\sum_{k=1}^{N_k}\left(\text{RMSE}_{\text{FO}}(\theta_k) - \text{RMSE}_{\text{FOCE}}(\theta_k)\right)\end{aligned} \tag{14}$$

where N_k is the number of model parameters (e.g. $N_k = 6$ for the model in "The Motivating Example" section). We take the absolute value of the parameter bias in the above equation because we are attempting to get a measure of total model bias, thus negative bias from one parameter should not cancel out positive bias from another parameter in the model. These values were compared to the difference between the FO calculated CWRES and WRES values; calculated as the difference between the mean of the distributional measurements (mean, variance and kurtosis) of the FO based CWRES and WRES:

$$\begin{aligned}\overline{\Delta\text{MEAN}}_{\text{FO}} &= \overline{\text{MEAN}}_{\text{WRES}} - \overline{\text{MEAN}}_{\text{CWRES}}\\ \overline{\Delta\text{VAR}}_{\text{FO}} &= \overline{\text{VAR}}_{\text{WRES}} - \overline{\text{VAR}}_{\text{CWRES}}\\ \overline{\Delta\text{KURT}}_{\text{FO}} &= \overline{\text{KURT}}_{\text{WRES}} - \overline{\text{KURT}}_{\text{CWRES}}\end{aligned} \tag{15}$$

where

$$\begin{aligned}\overline{\text{MEAN}}_{\text{(C)WRES}} &= \frac{1}{N_e}\sum_{i=1}^{N_e}\text{mean}_{\text{(C)WRES,FO},i}\\ \overline{\text{VAR}}_{\text{(C)WRES}} &= \frac{1}{N_e}\sum_{i=1}^{N_e}\text{variance}_{\text{(C)WRES,FO},i}\\ \overline{\text{KURT}}_{\text{(C)WRES}} &= \frac{1}{N_e}\sum_{i=1}^{N_e}\text{kurtosis}_{\text{(C)WRES,FO},i}\end{aligned} \tag{16}$$

The models used in this investigation included:

Model 1 A simple one parameter model:

$$\begin{aligned}\vec{y_i} &= 1/Cl_i + \vec{\varepsilon_i}\\ Cl_i &= \theta_1 e^{\eta_{1,i}}\end{aligned} \tag{17}$$

Parameter values for the model remained constant except for the variance associated with $\eta_{i,1}$ (6 separate values between 0.1 and 1) which determined how linear the model was: $\theta_1 = 1$, $\boldsymbol{\Omega} = (0.1\text{–}1)$ and $\boldsymbol{\Sigma} = 0.1$. Simulated data for this model had 100 individuals and five samples per individual.

Model 2 The same set of sigmiodal Emax models described in "The Motivating Example" section.

Model 3 A linear model with an exponential between subject variability on the intercept parameter defined for individual i as,

$$\begin{aligned}\vec{y_i} &= m_i \cdot \vec{t_i} + b_i + \vec{\varepsilon_i}\\ m_i &= \theta_1 + \eta_{i,1}\\ b_i &= \theta_2 e^{\eta_{2,i}}\end{aligned} \tag{18}$$

Parameter values for the model remained constant except for the variance associated with $\eta_{i,2}$ (6 separate values between 0.005 and 1) which determined how linear the model was: $(\theta_1, \theta_2) = (1, 10)$, $\boldsymbol{\Omega} = \begin{pmatrix} 0.05 & 1 \\ 0 & 0.005-1 \end{pmatrix}$ and $\boldsymbol{\Sigma} = 1$. Simulated data for this model had 200 individuals, ten samples per individual, with sample times evenly distributed between 1 and 100 min.

Model 4 A linear model with an exponential between subject variability on the slope parameter defined for individual i as,

$$\begin{aligned}\vec{y_i} &= m_i \cdot \vec{t_i} + b_i + \vec{\varepsilon_i}\\ m_i &= \theta_1 e^{\eta_{1,i}}\\ b_i &= \theta_2 + \eta_{i,2}\end{aligned} \tag{19}$$

Parameter values for the model remained constant except for the variance associated with $\eta_{i,1}$ (6 separate values between 0.05 and 1) which determined how linear the model was: $(\theta_1, \theta_2) = (1, 10)$, $\boldsymbol{\Omega} = \begin{pmatrix} 0.05-1 & 0 \\ 0 & 0.5 \end{pmatrix}$ and $\boldsymbol{\Sigma} = 1$. Data was simulated in the same manner as for model 3.

CWRES for Real Data

We next examined the CWRES of a model describing the PK of moxonidine first published by Karlsson *et al.* (19) and later improved with the implementation of a transit-compartment model (20). This model was selected as it exhibited good model fit characteristics but had a WRES distribution that was not $N(0,1)$. We calculated the CWRES based on the model and original data and compared the WRES and CWRES graphically. To obtain an understanding of what the WRES and CWRES should look like with this model we then simulated from this model and computed the WRES and CWRES from this simulated data.

RESULTS

Effects of Model Non-linearity on CWRES and WRES

As described in the "Effects of Model Non-linearity on CWRES and WRES" section of "MATERIALS AND METHODS", our first investigation of the properties of the WRES and CWRES was done using the FOCE method in NONMEM by simulating and estimating from the same model (i.e. no model misspecification) as this model becomes more and more non-linear. In this case the non-linearity was induced by increasing the size of the γ parameter in a sigmiodal e-max model.

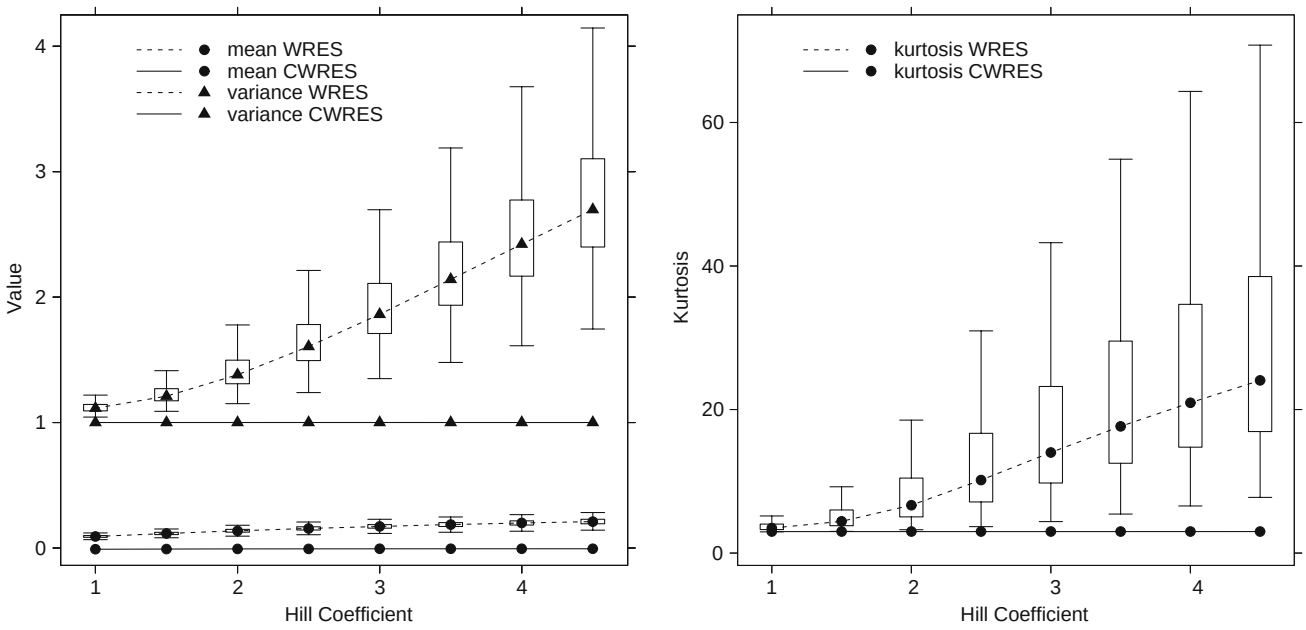

Fig. 3. When the model is correct—the mean variance and kurtosis of the CWRES and WRES for 100 simulations as model non-linearity increases. Box-plots for the CWRES curves are smaller than the size of the plot symbols representing the median value. The CWRES indicate, correctly, no model misspecification. The WRES indicate model misspecification.

In order to evaluate how well the FOCE method was doing in estimating the model parameters in this example we simulated 1,000 replicates for each of the eight different γ values investigated. From this set of parameter estimates we computed the bias and RMSE. The bias of the parameter estimates were between −1.82 and 0.634%, indicating good model fit to the data. The RMSE for the parameter estimates ranged from 1.34 to 12.8% with the estimate for ω^2_{C50} having the highest RMSE for each of the eight simulation setups (range: 10.5–12.8%). These values for the RMSE of the parameter estimates also indicate that the FOCE model fit to data was relatively good.

With the information that the FOCE method is able to adequately fit the models to the data we then investigated the properties of the CWRES and the WRES as model non-linearity increased. Because we know that the models fit the data well we would expect the CWRES and WRES to indicate a good fit (e.g. a normal distribution with mean zero and variance 1). Figure 3 shows boxplots of the 1,000 replicate calculations of the mean, variance and kurtosis of both the CWRES and WRES as the non-linearity of the model increases (as the Hill coefficient γ increases). From this figure it is clear that the CWRES, in all cases, are more normally distributed than the WRES (kurtosis values of 3). In addition, the CWRES have a mean closer to zero and a variance closer to one as theoretically expected when the model fits the data well. The WRES, on the other hand, especially at larger values of the Hill-coefficient, indicate (falsely) poor model fit characteristics.

These results show that, even if the model is correct, as model non-linearity increases WRES will begin to deteriorate. Alternatively, the CWRES seem to correctly indicate good model fit to data even in the face of relatively high model non-linearity.

FO/FOCE Differences from CWRES/WRES Differences in FO

As described in the "FO/FOCE Differences from CWRES/WRES Differences in FO" section of "MATERIALS AND METHODS" we next investigated if the differences between the WRES and CWRES computed using the FO method (using the POSTHOC step in NONMEM) could give us information about the differences in parameter estimates between the FO and FOCE methods in NONMEM. The results of this comparison for four different models with 6–8 different sets of parameter values (again used to simulate different levels of model non-linearity) are shown in Fig. 4 where the difference in parameter estimates between the two estimation methods ($\overline{\text{BIAS}}_{|\text{FO}|-|\text{FOCE}|}$ and $\overline{\text{RMSE}}_{\text{FO}-\text{FOCE}}$) are plotted *versus* the difference between WRES and CWRES using the FO method ($\Delta\overline{\text{MEAN}}_{\text{FO}}$, $\Delta\overline{\text{VAR}}_{\text{FO}}$ and $\Delta\overline{\text{KURT}}_{\text{FO}}$). Figure 4 shows that, as expected, the parameter bias and RMSE was on average smaller for the FOCE method than the FO method (because both $\overline{\text{BIAS}}_{|\text{FO}|-|\text{FOCE}|}$ and $\overline{\text{RMSE}}_{\text{FO}-\text{FOCE}}$ are positive in all six plots). The middle column of Fig. 4 shows that, in all cases, the mean variance of the FO calculated CWRES was less than or equal to the mean variance for the WRES ($\Delta\overline{\text{VAR}}_{\text{FO}}$ is always positive). The right column of Fig. 4 shows that, in all cases, the mean kurtosis of the FO calculated CWRES was less than or equal to the mean kurtosis for the WRES ($\Delta\overline{\text{KURT}}_{\text{FO}}$ is always positive). All six plots show a positive correlation in the data; as the difference between the WRES and CWRES calculated using the FO method increases, the difference between the FO and FOCE parameter estimates increases. Additionally, the plots suggest that when there is no difference between the WRES and CWRES when using the FO method then the bias and RMSE of the parameter values will not differ between the FO and FOCE methods.

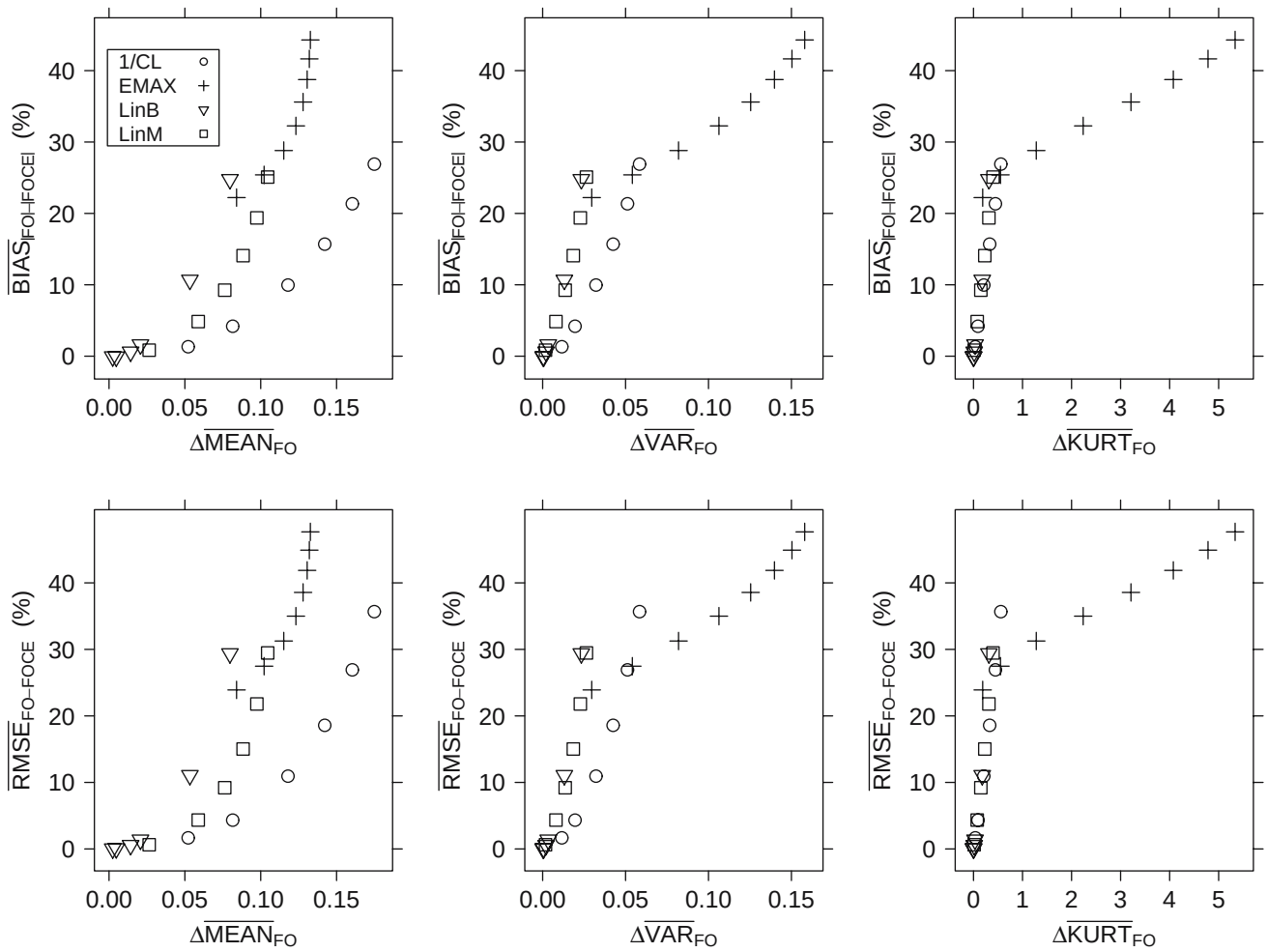

Fig. 4. The average difference in absolute bias (*top row*) and RMSE (*bottom row*) between parameters estimated by the FO and FOCE methods *vs.* the difference in the average mean (*left column*), variance (*middle column*) and kurtosis (*right column*) between the CWRES and WRES calculated during FO parameter estimation. Each point represents 1000 simulations from one of four models described in the text (LinB—model 3 , LinM—model 4). A positive correlation is evident in all plots.

Surprisingly, Fig. 4 suggests that even a small difference between the WRES and CWRES calculated with FO indicates a rather large average difference in bias or RMSE between the FO and FOCE estimation methods. For example, a change of 0.03 units in the variance between the WRES and CWRES in FO could result in between a 10 and 25% decrease in parameter bias for the FOCE method compared to the FO method (see the plot in the center column and top row). However, this study was done on only four distinct models with 6–8 different sets of parameter values. As such, we believe these results should be interpreted in a qualitative manner (i.e. as FO differences between CWRES and WRES increase so too will differences between FO and FOCE parameter estimates); an exhaustive study of many more models must be done to achieve quantitative results.

CWRES for Real Data

Next we investigated the properties of the CWRES and WRES in a model that was developed from moxonidine PK data as described in the "CWRES for Real Data" section of "MATERIALS AND METHODS". In this model all other diagnostic measures indicated that the model fit the data well, but the WRES indicated a model misspecification in the absorption phase of the data between 0 and 2 h after dosing. The WRES for this model are shown on the right-hand side of Fig. 5a. When this model was presented at the PAGE conference in 2004, it was suggested that the poor properties of the WRES in the absorption phase of the model was a result of small numerical difficulties NONMEM had with the transit compartment model. However, when the CWRES are calculated for this model (shown on the left-hand side of Fig. 5a) there is much less deviation from normal and they do not indicate model misspecification. We interpret these results to mean that the WRES indicate that the transit compartment model used to model the absorption phase of the data would perform poorly using the FO method while the CWRES indicate that the model performs adequately using the FOCE method.

To be more certain that our interpretation of the CWRES and WRES plots presented in Fig. 5a was correct, we simulated data from the final model to see if we could recreate the same plots from simulated data. By simulating we remove the confounding factor of model misspecification from our plots and we see what these two plots should look like if our model was exactly correct. Figure 5b shows both the CWRES

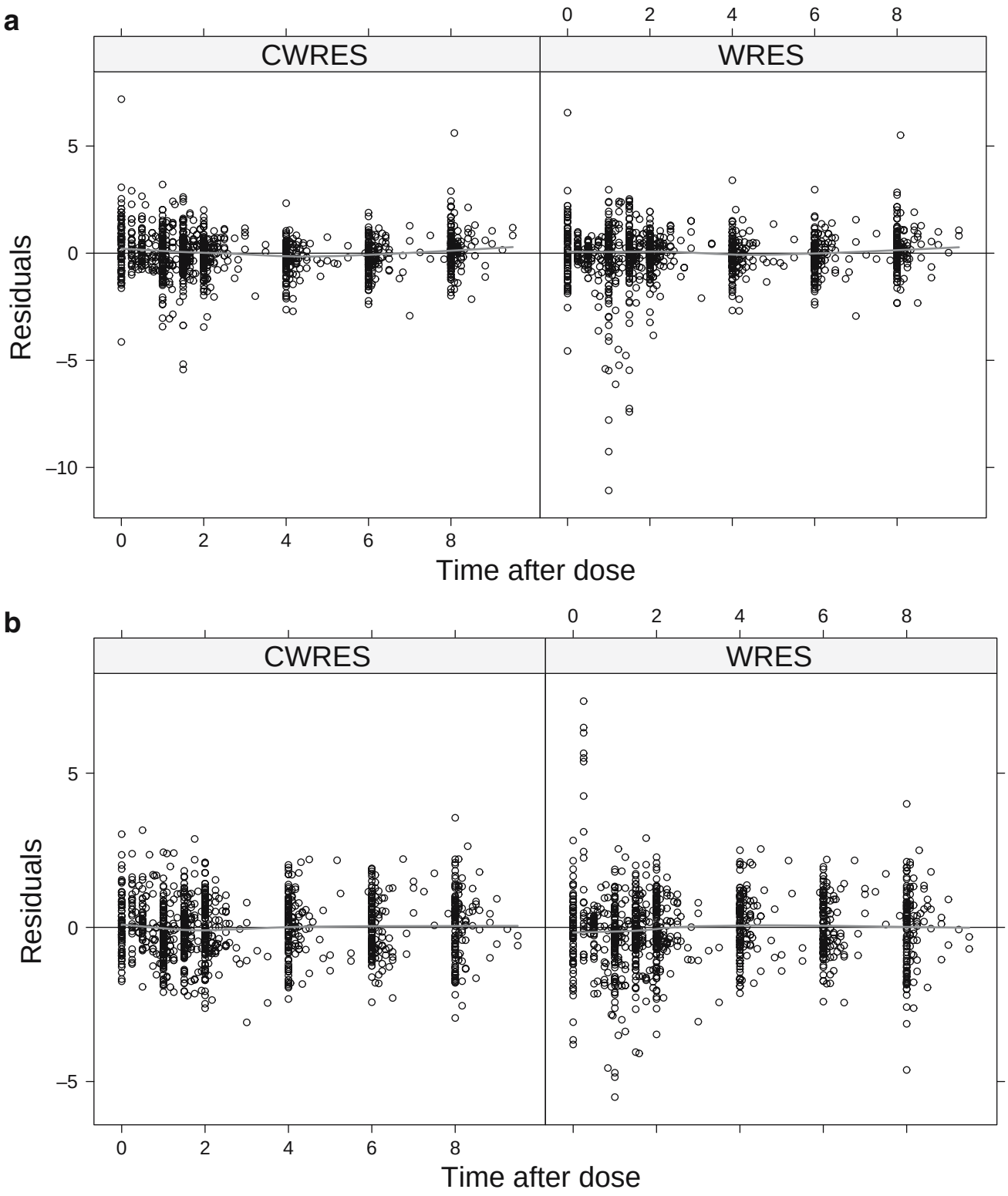

Fig. 5. **a** The WRES and CWRES using real data and the PK model for moxonidine. The CWRES indicate much less model misspecification, in line with other model diagnostics performed on this model. **b** The WRES and CWRES using data simulated from the PK model for moxonidine. Both plots have similar trends compared to the real data.

and WRES calculated from simulated data. We see that the plots have similar patterns to the real data plots of Fig. 5a, with the WRES indicating model misspecification between 0 and 2 h after dosing (even when we know that there is no misspecification) while the CWRES do not indicate model misspecification. These simulation results bolster our interpretation of the plots of the real data CWRES and WRES. We can now say with much more certainty that the WRES in Fig. 5a do not indicate model misspecification and that the CWRES indicate that the model fits well to the data.

CONCLUSIONS

In this article we have presented a new model diagnostic called the conditional weighted residuals. The CWRES are calculated in a similar manner to the well known weighted residuals but are calculated using the FOCE approximation to the population model as opposed to the FO approximation used by the WRES. Because of the different approximations used in the calculations, the CWRES are directly related to one term in the FOCE objective function as calculated by NONMEM, while the WRES are directly related to the analogous term in the FO objective function. As such, we can expect the CWRES to give us relevant diagnostic information about the fit of a population model to a set of data using the FOCE estimation method. Alternatively, we can expect the WRES to give similar diagnostic information when using the FO estimation method.

As has been demonstrated in a wide variety of cases, the FO method is often inadequate in fitting pharmacometric data to population models, resulting in highly inflated critical values for hypothesis testing and biased parameter estimates. These poor properties are a consequence of the first order linearization to the model used in the method and therefore new methods with less extreme linearizations (such as the FOCE and Laplace methods) have been developed. In this work, with four simple models we have shown that, on average, the bias and RMSE in the parameter estimates using the FOCE method were always better than when using the FO method (see Fig. 4).

Because the WRES are directly related to a term in the FO objective function, we can reasonably assume that when the FO method breaks down, so too will the WRES calculations. That is, when models are relatively non-linear, then the FO method will fail and so too will the WRES calculation. If, in general, modelers are using the FOCE method, but looking at the WRES, then in cases where the FO method breaks down but the FOCE method performs adequately we can expect the WRES to be a poor diagnostic to describe how a model fits the data. In this work we have investigated this property of the WRES with a sigmiodal e-max model, using different values of the hill-coefficient γ to vary the non-linearity of the model. We found that even though the FOCE method adequately estimated model parameters the WRES had a distribution that deviated from the theoretically expected distribution (Gaussian, mean zero, variance one), in nearly all cases investigated, even with little non-linearity in the model, indicating poor model fit properties. Further, in one extreme example, with data simulated from a highly non-linear model ($\gamma = 4.5$) we found that the WRES were more normally distributed when a misspecified model was used to fit the data (γ fixed to one). This indicates that by using the WRES as a model diagnostic when using the FOCE estimation method, misspecified models could be selected in the model building process. Because of this result, we suggest substituting CWRES for all WRES type diagnostics used when estimating model parameters using the FOCE method.

Even if the FO method is used in model development (recall that, in 2005, 15% of the models in the literature have estimated parameters using the FO method) the CWRES can be a useful diagnostic. Because the CWRES are directly related to a term in the FOCE objective function, but they can be calculated using the FO method (using the POST-HOC step in NONMEM), differences between the WRES and CWRES calculated using the FO method can give information about the differences in parameter estimates between the FO and FOCE methods. In this work we have shown that, for a select few models, as FO differences between CWRES and WRES increase so too will differences between FO and FOCE parameter estimates. However, in order to understand and quantify the magnitude of this correlation, tests should be made over a much wider rage of different models and types of data. In our experience, the two main reasons for using FO are, first, that some models can not be made to run using the FOCE or FOCEI methods (due to, e.g. stability issues in the methods) and, second, that run times for these methods are prohibitive. As such, using the CWRES in conjunction with the FO method could give modelers more information about the relative confidence they should have in their model parameters.

It is important to note that the CWRES are based on the FOCE approximation to the model and do not incorporate the interaction terms present in the FOCEI objective function. The computation of weighted residuals for the FOCEI method is more complex mathematical problem and work is ongoing to calculate a CWRES with interaction. However, on a practical note, when using the FOCEI method, the FOCE method is a much closer neighbor compared to the FO method. As such, we would still recommend using the CWRES instead of the WRES when model fitting with the FOCEI method.

In our view, the CWRES should be used with the FO, FOCE and FOCEI methods for the reasons stated above. However, implementing the code needed in NONMEM and then computing the CWRES in a secondary step can be a daunting task. To make this calculation easier we have automated the process using Pearl Speaks NONMEM (PsN) and Xpose 4. In addition, in Xpose 4 we have developed a range of easily created diagnostic plots using the CWRES. Both PsN and Xpose 4 are freely available on the internet (xpose.sourceforge.net and psn.sourceforge.net).

Finally, in a less theoretical setting (and taking our own advice), we have computed the CWRES for several models with real, rather than simulated, data (20–22) (only one presented in this article). All of these models had good model fit characteristics aside from WRES distributions that were not N(0,1) and indicated model misspecification. In all cases, the CWRES showed markedly better distributions and did not indicate model misspecification. We interpret these results to mean that, for these models, the problem was with the WRES and not misspecification of the models. Simulations from the final models and subsequent calculations of WRES and CWRES confirmed the poor properties of the WRES for these models (even with data simulated from the model the WRES were poor).

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REFERENCES

1. L. Zhang, V. Sinha, S. T. Forgue, S. Callies, L. Ni, R. Peck, and S. R. Allerheiligen. Model-based drug development: the road to quantitative pharmacology. *J. Pharmacokinet Pharmacodyn* **33**:369–393 (2006).
2. L. Aarons, M. O. Karlsson, F. Mentre, F. Rombout, J. L. Steimer, and A. Peervan. Role of modelling and simulation in Phase I drug development. *Eur. J. Pharm. Sci.* **13**:115–122 (2001).
3. J. C. Pinheiro, M. J. Lindstrom. Model building for nonlinear mixed effects models, (1994).
4. A. T. Galecki, R. D. Wolfinger, O. A. Linares, M. J. Smith, and J. B. Halter. Ordinary differential equation PK/PD models using the SAS macro NLINMIX. *J. Biopharm. Stat.* **14**:483–503 (2004).
5. P. Girard and F. Mentré. A comparison of estimation methods in nonlinear mixed effects models using a blind analysis, PAGE Abstracts of the Annual Meeting of the Population Approach Group in Europe, Vol. 14, Abstr 834 [http://www.page-meeting.org/?abstract=834], Pamplona, Spain, 2005.
6. S. Beal and L. Sheiner. The NONMEM system. *Am. Stat.* **34**:118–119 (1980).
7. U. Wahlby, E. N. Jonsson, and M. O. Karlsson. Assessment of actual significance levels for covariate effects in NONMEM. *J. Pharmacokinet. Pharmacodyn.* **28**:231–252 (2001).
8. E. N. Jonsson, J. R. Wade, and M. O. Karlsson. Comparison of some practical sampling strategies for population pharmacokinetic studies. *J. Pharmacokinet. Biopharm.* **24**:245–263 (1996).
9. B. P. Booth and J. V. Gobburu. Considerations in analyzing single-trough concentrations using mixed-effects modeling. *J. Clin. Pharmacol.* **43**:1307–1315 (2003).
10. S. Beal and L. Sheiner. *NONMEM User's Guide*, University of California, San Francisco, 1992.
11. Guidance for industry on Population Pharmacokinetics; availability. Food and Drug Administration, HHS. Notice. Fed Regist. 64:6663–6664 (1999).
12. M. Davidian and D. M. Giltinan. *Nonlinear models for repeated measurement data*, Chapman & Hall, New York, 1995.
13. M. L. Lindstrom and D. M. Bates. Nonlinear mixed effects models for repeated measures data. *Biometrics.* **46**:673–687 (1990).
14. F. Mentre and S. Escolano. Prediction discrepancies for the evaluation of nonlinear mixed-effects models. *J. Pharmacokinet. Pharmacodyn.* **33**:345–367 (2006).
15. E. N. Jonsson and M. O. Karlsson. Xpose—an S-PLUS based population pharmacokinetic/pharmacodynamic model building aid for NONMEM. *Comput. Methods Programs Biomed.* **58**:51–64 (1999).
16. L. Lindbom, P. Philgren, and N. Jonsson. PsN-Toolkit—a collection of computer intensive statistical methods for non-linear mixed effect modelling using NONMEM. *Comput. Methods Programs Biomed.* **79**:241–257 (2005).
17. M. Abramowitz and I. A. Stegun. *Handbook of mathematical functions with formulas, graphs, and mathematical tables, 9th printing*, Dover, New York, 1972.
18. J. E. Bennett and J. C. Wakefield. A comparison of a Bayesian population method with two methods as implemented in commercially available software. *J. Pharmacokinet. Biopharm.* **24**:403–432 (1996).
19. M. O. Karlsson, E. N. Jonsson, C. G. Wiltse, and J. R. Wade. Assumption testing in population pharmacokinetic models: illustrated with an analysis of moxonidine data from congestive heart failure patients. *J. Pharmacokinet. Biopharm.* **26**:207–246 (1998).
20. R. Savic, D. M. Jonker, T. Kerbusch, and M. O. Karlsson. Evaluation of a transit compartment model *versus* a lag time model for describing drug absorption delay, PAGE Abstracts of the Annual Meeting of the Population Approach Group in Europe, Vol. 13, Abstr 513 [http://www.page-meeting.org/?abstract=513], Uppsala, Sweden, 2004.
21. A. Hooker, A. J. T. Tije, M. A. Carducci, H. Gelderblom, F. W. Dawkins, W. P. McGuire, J. Verweij, M. O. Karlsson, and S. D. Baker. Population pharmacokinetic modeling of total and unbound docetaxel plasma concentrations in cancer patients with poor liver function, PAGE Abstracts of the Annual Meeting of the Population Approach Group in Europe, Vol. 14, Abstr 815 [http://www.page-meeting.org/?abstract=815], Pamplona, Spain, 2005.
22. A. Quartino, M. O. Karlsson, A. Freijs, N. Jonsson, P. Nygren, J. Kristensen, E. Lindhagen, and R. Larsson. Population Based Pharmacodynamics for *In Vitro* Drug Sensitivity Assays: Prediction of Model Based Parameters of Drug Activity and Relationship to Clinical Outcome, PAGE Abstracts of the Annual Meeting of the Population Approach Group in Europe, Vol. 14, Abstr 809 [http://www.page-meeting.org/?abstract=809], Pamplona, Spain, 2005.