Population Approach Group in Europe
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Methods to Detect Non-Compliance and Minimize its Impact on Population PK Parameter Estimates

Leonid Gibiansky[1], Ekaterina Gibiansky[1], Valérie Cosson[2], Nicolas Frey[2], Franziska Schaedeli Stark[2]

[1]QuantPharm LLC, North Potomac, MD, USA

[2]F. Hoffmann-La Roche Ltd, Basel, Switzerland

Introduction

- Non-compliance is an important issue for many drugs with chronic outpatient administration;
- Concentration-time profiles of non-compliers (subjects who do not follow prescribed dosing pattern) cannot be adequately described by the model that assumes full compliance;
- Even a small fraction of non-compliant patients may significantly bias population PK parameter estimates as most estimation methods are sensitive to outliers (observations not consistent with the expected profiles or subjects with significantly different parameters);
- There are no commonly accepted and tested modeling methods to identify non-compliant patients and obtain unbiased estimates of population PK parameters.

Objectives

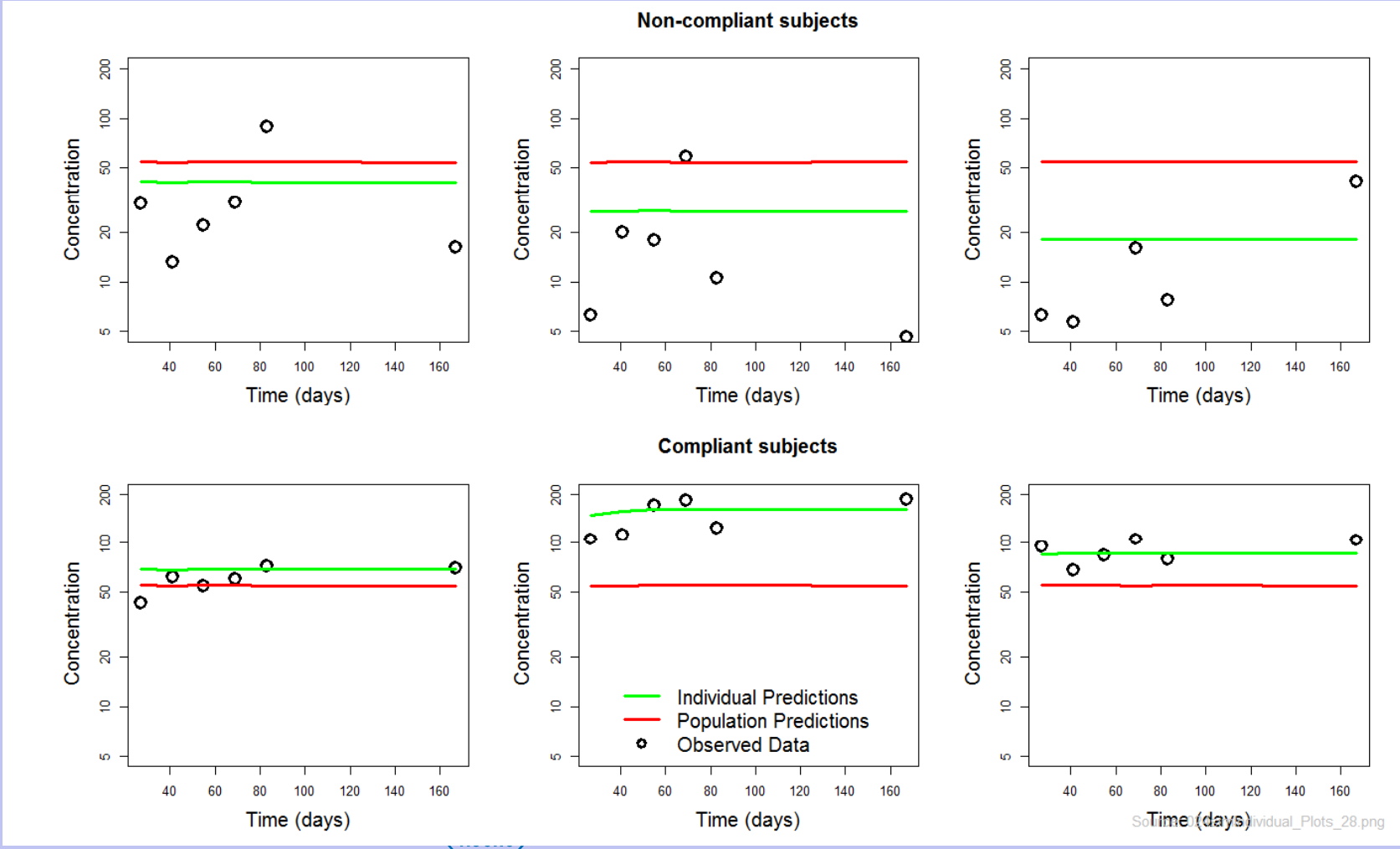
- To propose and evaluate two methods (CM1 and CM2) that would allow:
  - Detection of non-compliance and identification of non-compliant subjects using concentration-time data;
  - Unbiased estimation of population PK parameters in a population with prevalent non-compliance;

CM1: Compliance Method 1; CM2: Compliance Method 2

Illustration of the problem (sparse data)

QD oral administration; steady-state trough values; proportional residual error (CV=20%); simulated with non-compliance; estimated assuming full compliance.

Observation: non-compliers have higher residual variability



CM1 Method: Motivation

Ref. [1] proposed to detect subjects with odd observations and reduce their influence on the population PK parameter estimates by introduction of the random effect (η_ε) on the residual error. Example:

```
SD=IPRED                                  ; proportional error model
Y = IPRED+SD*EPS(1)                       ; error model without random effect
Y = IPRED+SD*EPS(1)*EXP(ETA(1))   ; error model with random effect
```

We apply the same idea to detect non-compliant patients who can be distinguished by large fluctuations of their observed concentrations that are not explained by the model that assumes full compliance and time-independent parameters.

[1] Karlsson MO, Jonsson EN, Wiltse CG, Wade JR, Assumption testing in population pharmacokinetic models: illustrated with an analysis of moxonidine data from congestive heart failure patients. J Pharmacokinet Biopharm. 1998 Apr; 26(2):207-46

CM1 Method: Proposed Procedure

- Fit the model with the random effect η_ε on the residual error;
- Identify subjects with strong non-compliance as those with high η_ε;
- Exclude non-compliant subjects from the dataset to obtain unbiased estimates of model parameters.

Three procedures for exclusion were tested:

- Exclude subjects with large residual error, e.g., $\eta_\varepsilon > 0$;
- Investigate η_ε distribution to identify subjects with high error visually;
- Exclude 10%, 20%, etc., 60% of study subjects with the highest η_ε from the data set while checking the parameter estimates and variance of η_ε.

CM1 Method: Simulated Example

Model: two-compartment linear; once-a-day (QD) administration; relatively long (2 days) half-life, and significant drug accumulation (C_{trough} accumulation ratio of about 5).

Non-compliance pattern:

- 50% of non-compliers;
- Non-compliers :
  - ✓ Missed 60% of doses (randomly);
  - ✓ Shortest drug holiday: 2 days; longest drug holiday: 6 - 18 days;
- In-patient doses (on sample days) assumed to be administered.

Subjects and samples:

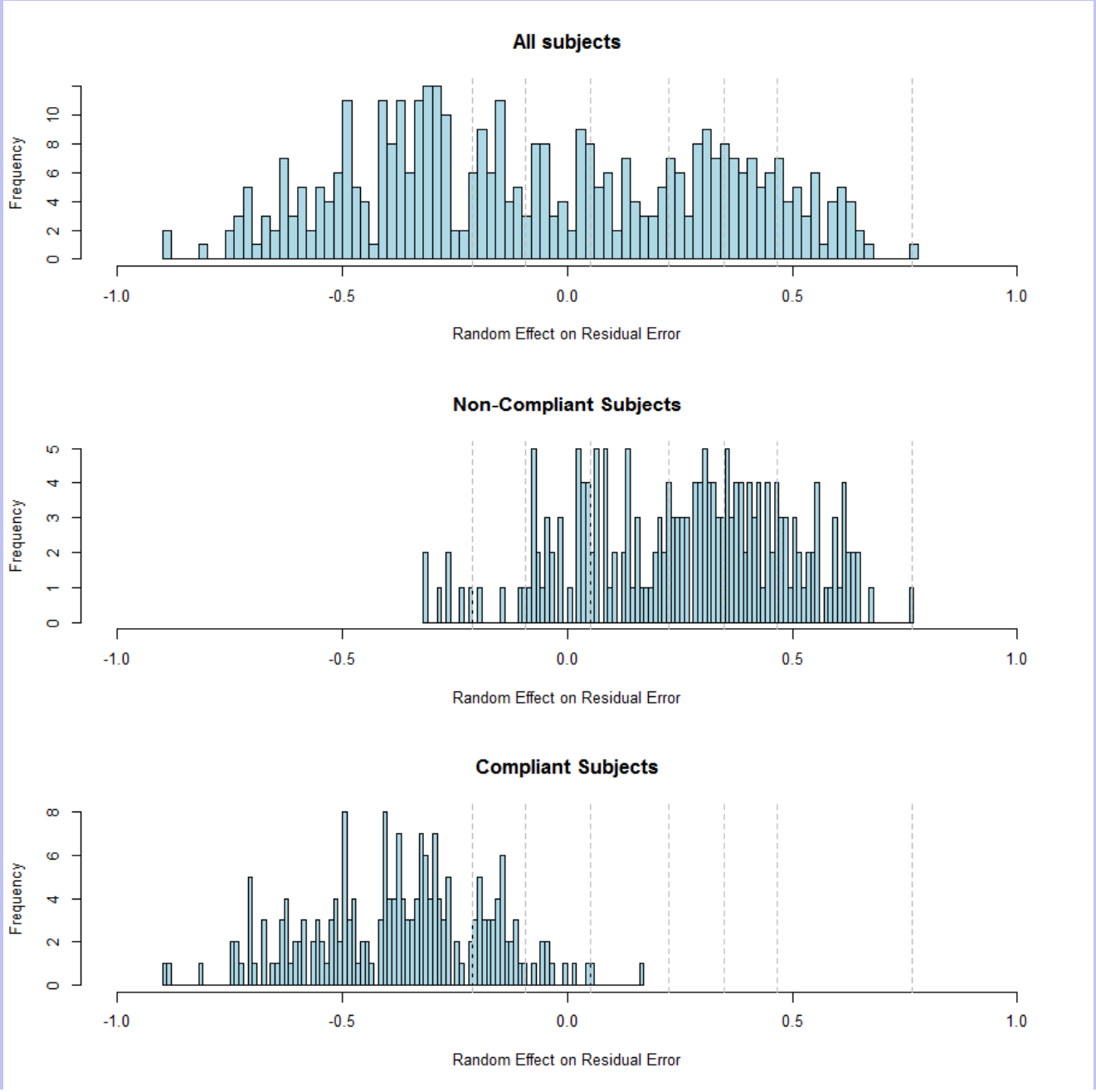
- Sparse data from 400 subjects;
- All subjects: pre-dose samples on weeks 4, 6, 8, 10, 12, and 24;
- 80 PK subjects: Additional post-dose samples at about 3 and 6.5 hours post-dose on weeks 4, 6, 8, 10, 12, and 24

CM1 Results: η_ε Distribution

The data were simulated with non-compliance and zero inter-subject variability of residual error.

The estimation assumed full compliance.

The random effect on the residual error was included and estimated by the model.

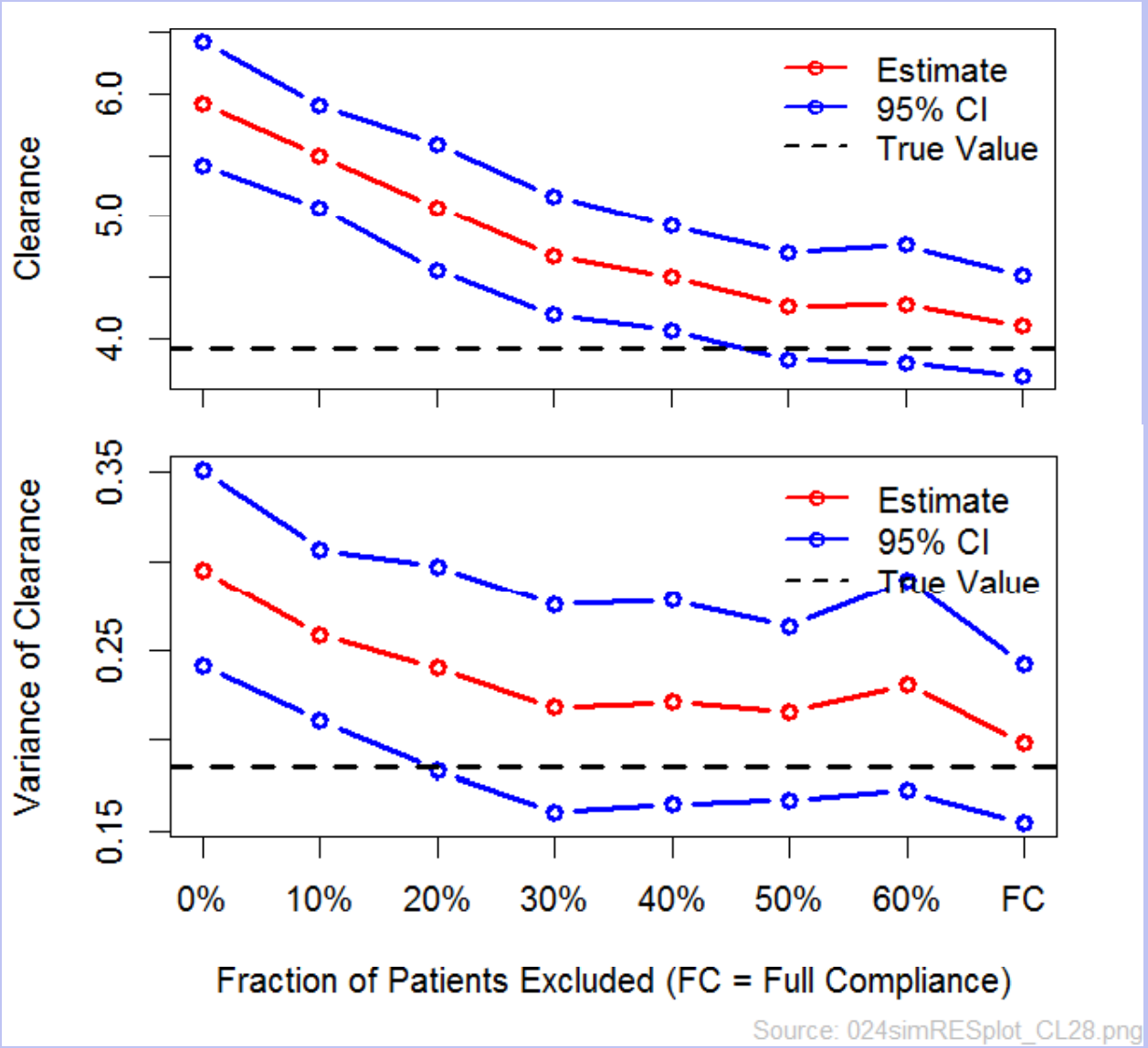


CM1 Results: Estimates of Clearance

Simulated data:

50% of non-compliers,
60% of missed doses

X% of all subjects (those with the highest η_ε) were excluded from the dataset.



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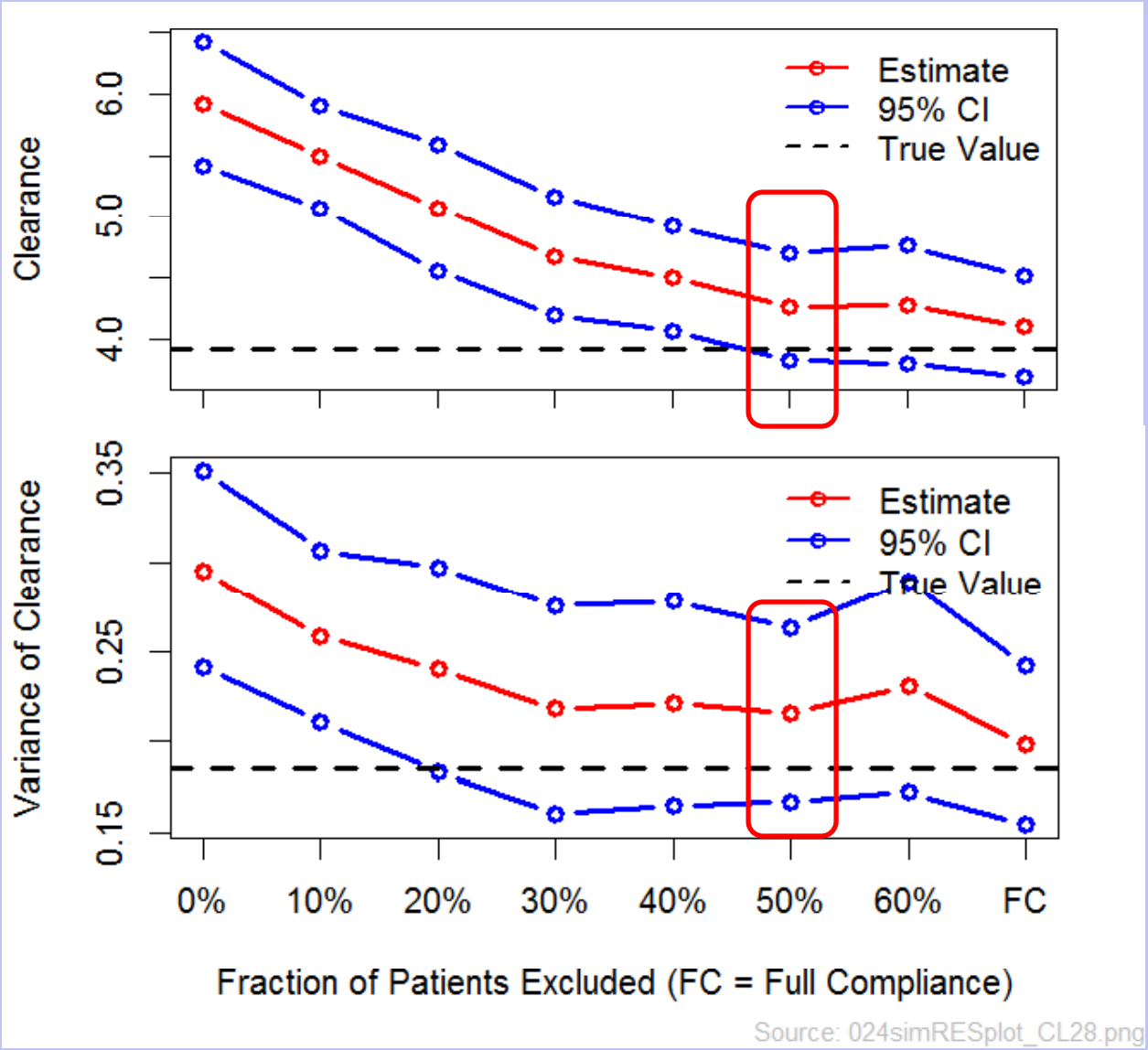
CM1 Results: Estimates of Clearance

Simulated data:

50% of non-compliers, 60% of missed doses.

X% of all subjects (those with the highest η_ε) were excluded from the dataset.

When 50% of subjects were removed, parameters versus X curves flatten close to the true values.



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CM1 Results: Estimates of η_ε Variance

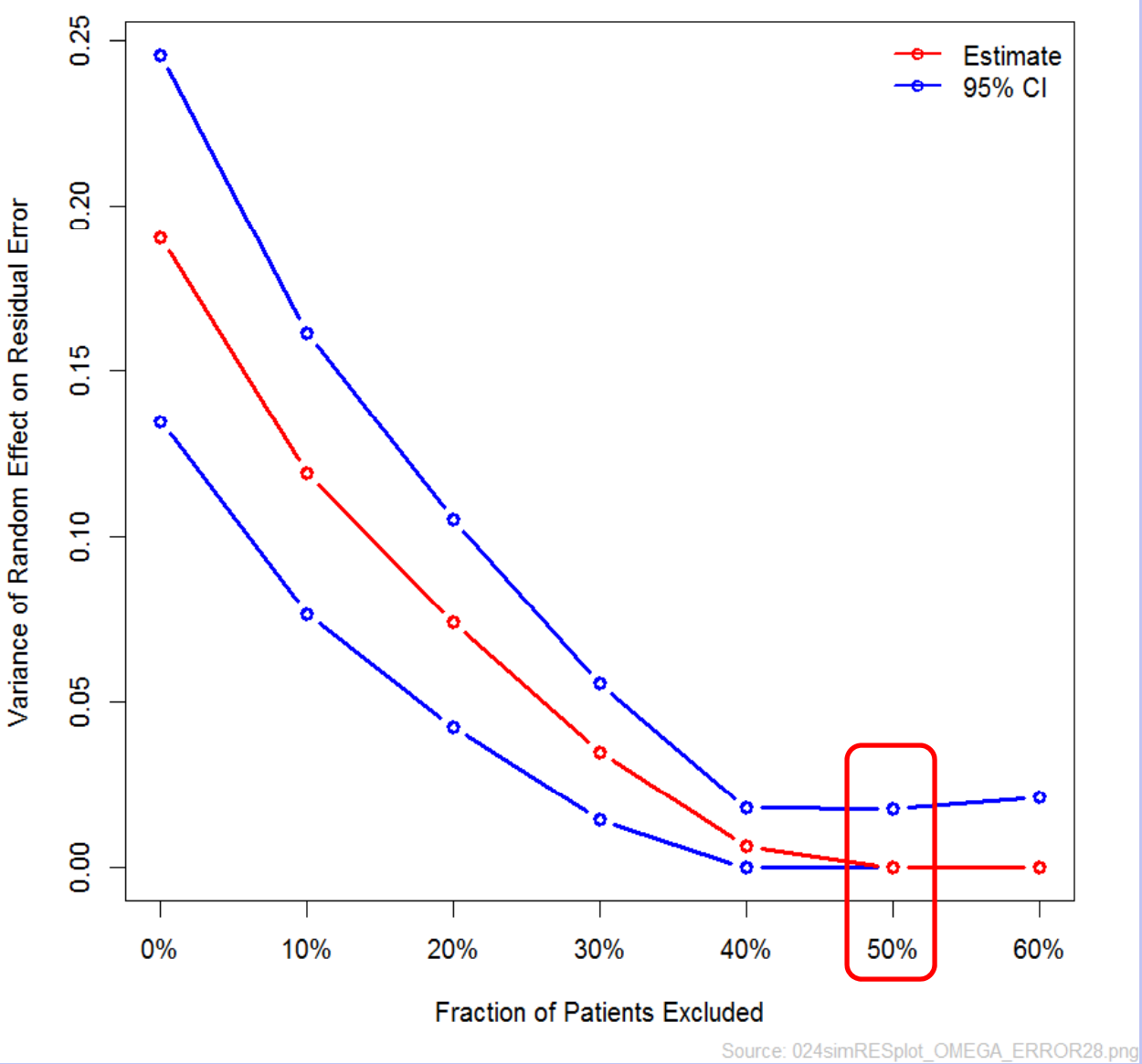
Simulated data:

50% of non-compliers, 60% of missed doses, 2-days drug holidays.

X% of all subjects (those with the highest η_ε) were excluded from the dataset.

When 50% of subjects were removed, η_ε variance approaches zero.

Can be used for diagnostics: exclude subjects until η_ε variance approaches zero.



CM1 Method: Range of Simulated Examples

Non-compliance patterns:

- 30%, 50%, or 100% of non-compliers
- 10 to 80% of missed doses.

Subjects and samples:

- Sparse data from 400 subjects;
- All subjects: pre-dose samples on weeks 4, 6, 8, 10, 12, and 24 or
  pre-dose samples on weeks 4, 8, and 24;
- In-patient doses (on sample days) assumed to be administered;
- 80 PK subjects: Additional post-dose samples randomly sampled for the time windows 2-4 hours and 5-8 hours post-dose.

Parameters of interest:

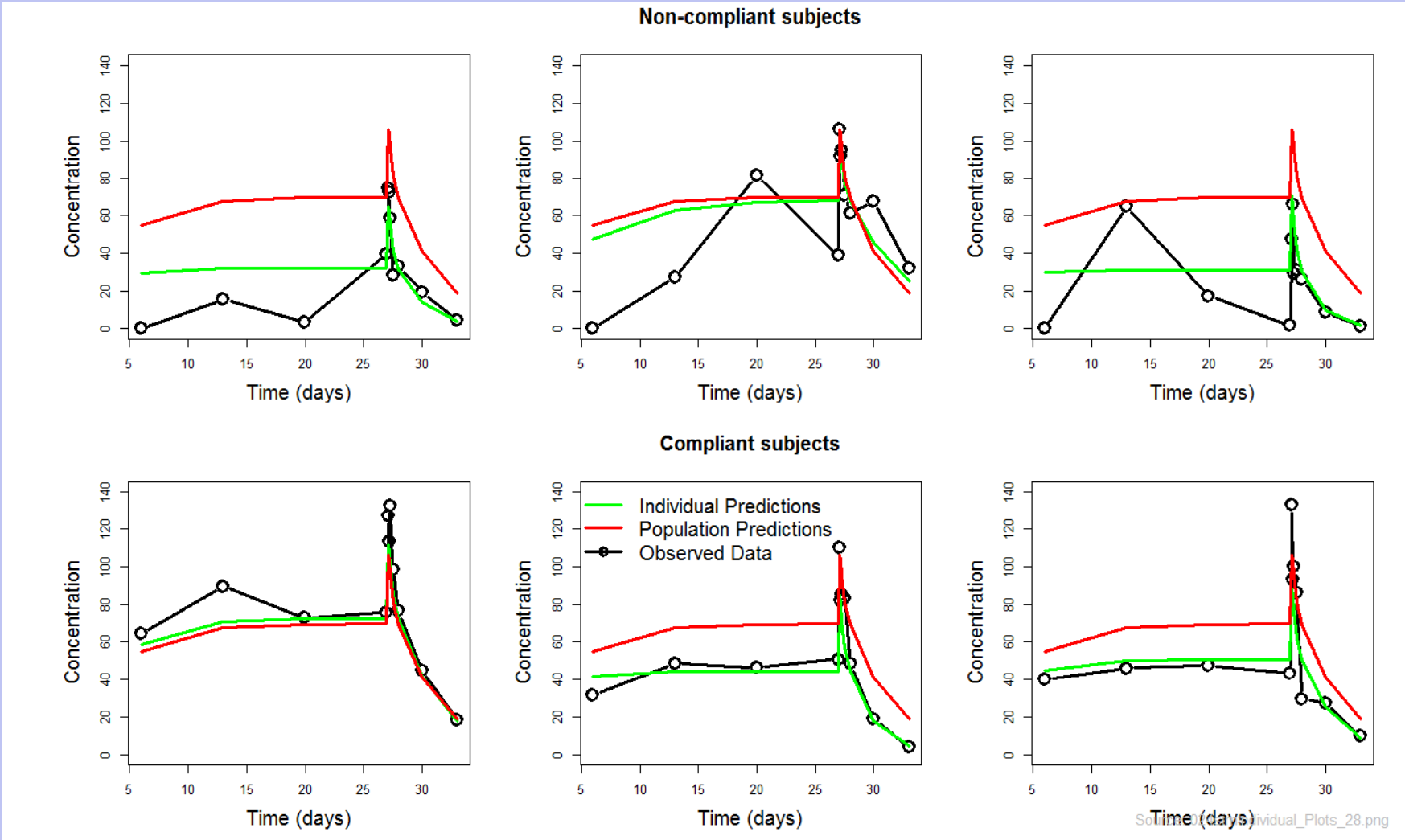
- Clearance and variance of the random effect on clearance.

CM1 Method: Summary of Results

- For the models that did not account for non-compliance, clearance estimates were biased, with bias approximately equal to the fraction of missed doses;
- Introduction of the random effect on the residual error reduced bias in many cases but did not eliminate it;
- When subjects with the highest η_ε were incrementally removed from the datasets, bias due to non-compliance was reduced or eliminated. At the same time, the variance of η_ε decreased towards zero;
- Most (but not all) removed subjects were non-compliers while most (but not all) retained subjects were compliant;
- Magnitude of bias and bias reduction using CM1 method depends on study design, fraction of non-compliers, and non-compliance patterns;
- As expected, for the datasets with all non-compliant subjects, CM1 method was not able to reduce the parameter bias.

Illustration of the problem: rich data

QD oral administration; steady-state trough values; rich data following the last dose; proportional residual error (CV=20%); simulated with non-compliance; estimated assuming full compliance.



CM2 Method: Motivation

Ref. [2] proposed to account for non-compliance using only data that follow the in-patient (compliant) doses:

- Considered a **one-compartment model** with absorption half-life much shorter than inter-dose interval
- In this case, concentrations that follow in-patient doses can be computed as

$$\mathbf{C(t) \approx C_0 \exp(-k_e t) + A[\exp(-k_e t) - \exp(-k_a t)]},$$

  where the parameters C_0, A, k_e, and k_a can be estimated from only the reliable data that follow the in-patient doses. C_0 reflects the contribution of outpatient doses.
- The proposed procedure ignored all the data except those that immediately preceded or followed the in-patient (compliant) doses.

[2] Gupta P, Hutmacher MM, Frame B, Miller R, An alternative method for population pharmacokinetic data analysis under noncompliance. J Pharmacokinet Pharmacodyn. 2008; 35(2):219-33.

CM2 Method: Derivation

Linear Multi-Compartment Model

If the absorption half-life is short relative to the inter-dose interval, concentration-time profile following known dose can be presented as a superposition of the multi-exponential decay and concentration-time profile following the single dose:

$$C(t) \approx \sum_i C_{0i} \exp(-k_i t) + A\left[\sum_i \alpha_i \exp(-k_i t) - \sum_i \alpha_i \exp(-k_a t) \right]$$

If the distribution half-lives are short relative to the inter-dose interval:

$$C(t) \approx C_0 \exp(-k_{term} t) + A\left[\sum_i \alpha_i \exp(-k_i t) - \sum_i \alpha_i \exp(-k_a t) \right]; \quad k_{term} = \min(k_i)$$

Here k_{term} depends on model parameters while C_0 depends on model parameters and preceding dosing history. In particular, it depends on compliance pattern of preceding doses.

CM2 Method: Key Idea

Linear Multi-Compartment Model

C_0 is also proportional to bioavailability of those doses.

➡ **IDEA**

Assume full compliance for all doses, but estimate bioavailability of the out-patient doses. This would effectively estimate C_0.

THEN

- Estimation of bioavailability for **ANY** dosing history is equivalent to estimation of C_0 !
- Knowledge of the specific dosing history, and analytical expressions for C_0 and k_{term} are not required for implementation of the method. Nonmem and numerical equation solver can handle this part while required flexibility is provided by estimation of bioavailability of out-patient doses.

CM2 Method: Implementation

- Does not require an explicit expression for concentration;
- Use only data from samples immediately preceding or following the in-patient doses.
- Assume full compliance but introduce individual relative bioavailability (with high and fixed variance) for out-patient doses.
- If more than one sampling period with in-patient doses is available, allow separate bioavailability parameters for out-patient doses preceding each of these periods.

```
F1  = 1

IF(outpatient dose) F1= 0.5*EXP(ETA(1))
….
$OMEGA  10  FIX                          ; ETA-F1
```

CM2 Method: Advantages and limitations

- Can be applied to both linear and non-linear models when absorption and distribution half-lives are much shorter than inter-dose interval;
- Simple to implement without analytical solution of underlying equations;
- Relies on the availability of sufficient data following in-patient doses;
- For a one-compartment linear model, reduces to the method proposed in [2].

CM2 Method: Simulated Example

Model: two-compartment linear; QD administration; relatively long (2 days) half-life and significant drug accumulation (C_{trough} accumulation ratio of about 5).

Non-compliance pattern

- 50% of non-compliers;
- Non-compliers:
  - ✓ Missed 40% of doses (randomly);
  - ✓ Shortest drug holiday: 6 days; longest drug holiday: 12 - 24 days;
- In-patient doses (on sample days) assumed to be administered.

Subjects and samples:

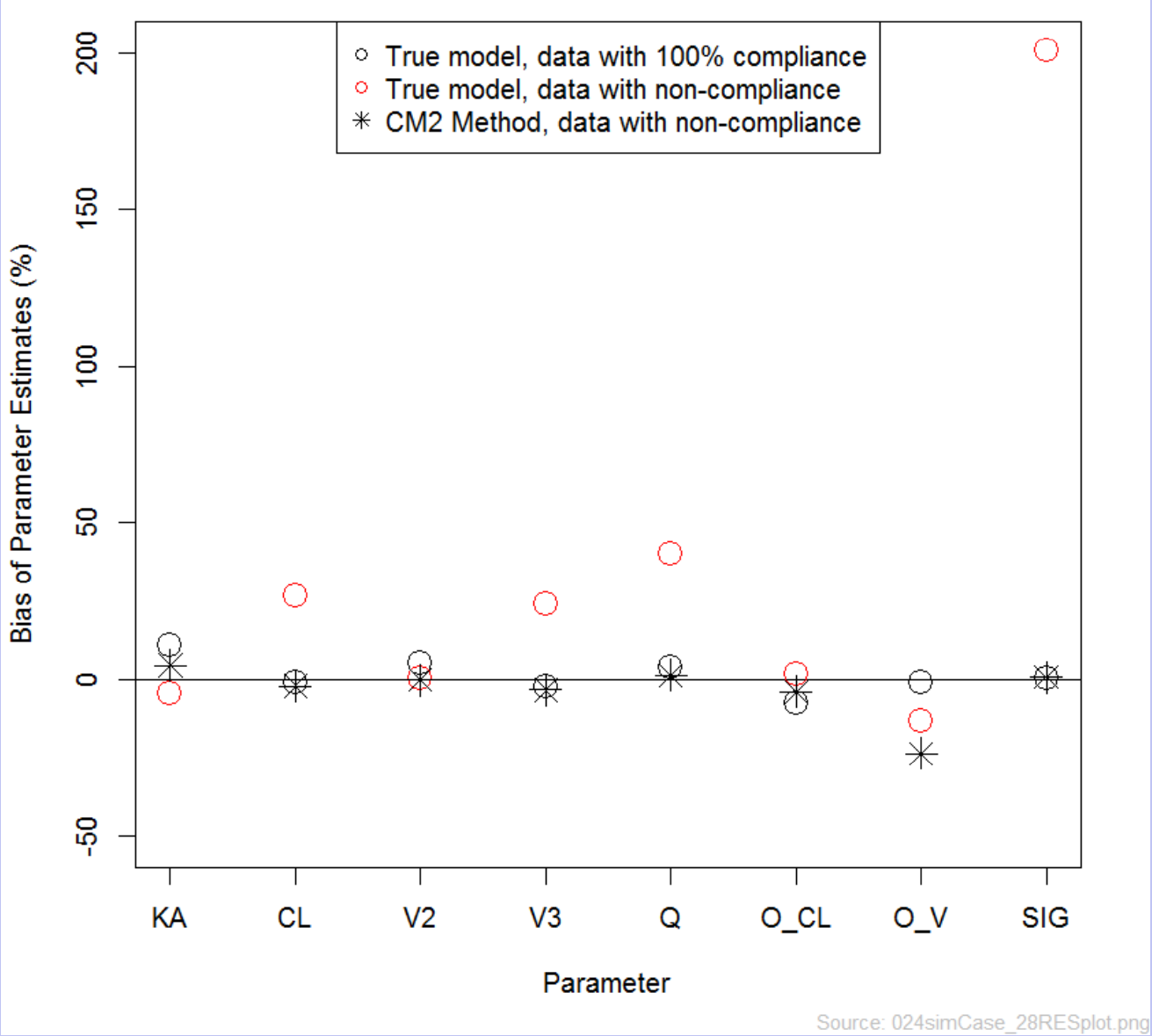
- 400 subjects;
- Pre-dose samples on weeks 1, 2, 3, and 4;
- Rich data following the last dose: 2, 4, 6, 12, 24, 72, and 144 hours.

CM2 Results: Bias of Parameter Estimates

Simulated data:

400 subjects, 50% of non-compliers, 40% of missed doses.

CM2 method was able to estimate all population model parameters without significant bias.



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CM2 Method: Range of Simulated Examples

Non-compliance patterns:

- 50% or 100% of non-compliers;
- 10 to 80% of missed doses.

Subjects and samples:

- Rich data from 400 subjects;
- Pre-dose samples on weeks 1, 2, 3, and 4 (last dose);
- Rich data following the last dose: 2, 4, 6, 12, 24, 72, and 144 hours

Parameters of interest:

- All population PK parameters.

CM2 Method: Summary of Results

- CM2 method provided unbiased estimates of the population PK parameters in the datasets with any fraction of non-compliant subjects;
- CM2 method should be able to provide unbiased estimates of the individual PK parameters of all subjects, including non-compliers;
- CM2 method results do not depend on non-compliance patterns;
- Most (but not all) non-compliant subjects were estimated to have lower bioavailability during outpatient dosing.

CM1 and CM2 Methods: Comparison

CM1 and CM2 methods can be viewed as complementary, each with its own advantages and limitations:

CM2 Method:

- Provides unbiased parameter estimates for any non-compliance patterns;
- Can be applied only for the specific sampling schemes that include relatively rich data following in-patient (fully compliant) doses;

CM1 method:

- Is not based on any assumptions about the sampling schemes;
- More applicable to Phase 3 data (only sparse sampling usually available);
- Unlikely to account for the non-compliance if it is present in the majority of patients.

CM1 and CM2 Methods: Combination

- CM1 and CM2 methods can be combined for the datasets that contain mixture of sparse and rich data;
- Simulations confirmed that combined CM1/CM2 method provided better results than each of them separately;
- Possible extension: apply CM2 method only to subjects with high residual error (identified by CM1 procedure).

Conclusions

For a number of simulated datasets with various sampling schemes and various fractions of non-compliant patients, the proposed methods allowed to identify subjects with non-compliance and to obtain the unbiased estimates of model parameters;

These methods can be used to evaluate the influence of non-compliance on the population PK parameter estimates;

Real-life performance of the methods (especially CM1) can be influenced by the underlying PK model, inter-occasion variability of model parameters, dosing and sampling schedules, non-compliance prevalence and patterns.