

Normal fat mass cannot be reliably estimated in typical pharmacokinetic studies

RE Wasmann^{1,2}, EM Svensson^{1,3}, SJ Schalkwijk¹, RJM Brüggemann^{1,2}, R ter Heine¹

(1) Department of Pharmacy, Radboud Institute of Health Sciences, Radboud university medical center, Nijmegen, The Netherlands (2) Center of Expertise in Mycology Radboudumc/CWZ, Nijmegen, The Netherlands; (3) Department of Pharmaceutical Bioscience, Uppsala University, Uppsala, Sweden

Background

An important covariate for pharmacokinetics (PK) is (body) size. Choosing the correct size descriptors for your PK model is important since these might determine individual dose, especially when dosing a drug with a narrow therapeutic index (e.g. aminoglycosides) and even more in populations with extreme body size. Recently, the method of estimation of normal fat mass (NFM) has been advocated.¹ NFM is calculated by:

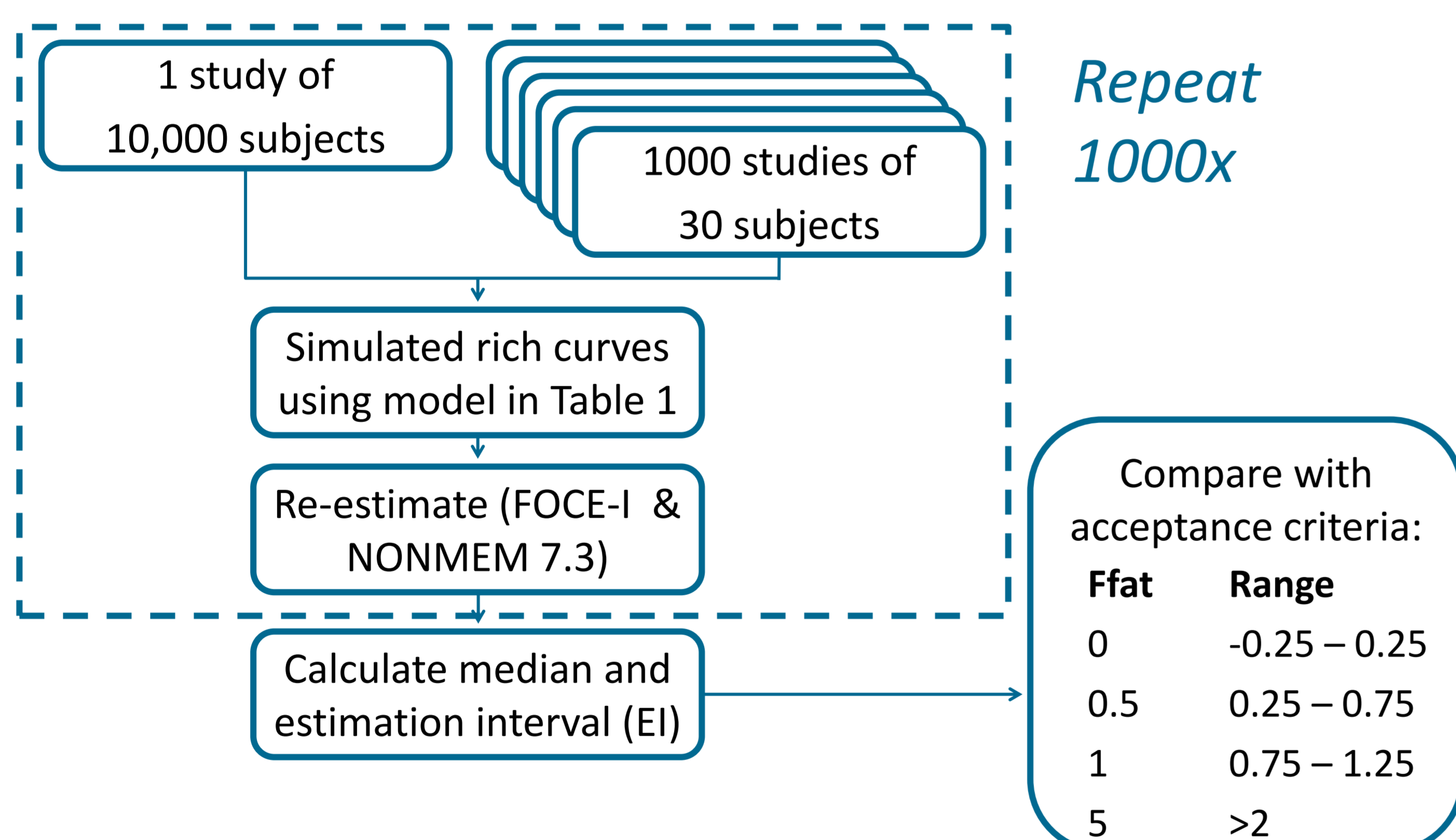
$$\text{NFM} = \text{FFM} + Ffat \cdot (\text{TBM} - \text{FFM})$$

Here *Ffat* is the estimated fraction of fat contributing to the PK, relative to FFM. *Ffat* is drug specific and when *Ffat* is 1 then NFM=TBW while if *Ffat* is 0, then NFM=FFM. However, it remains unclear whether NFM (with estimation of *Ffat*) can be reliably estimated in typical PK studies (n=30).

Objective Investigate the identifiability of NFM as a size descriptor for allometric scaling in typical PK studies.

Methods

We used stochastic simulation and estimation to investigate the identifiability of *Ffat* in 16 virtual drugs consisting of all possible combinations of *Ffat* (0, 0.5, 1 and 5) for CL and V. We chose a balanced study population (50% male) with three arms: 1/3 non-obese (BMI<30), 1/3 obese (BMI30-40) and 1/3 morbidly obese (BMI>40) sampled from the NHANES database.²



Results

- Figure 1: *Ffat* was estimated with **low bias** and **high precision** in **large studies** with 10,000 subjects, indicated by **narrow 95% EIs**
- Table 1: **PK parameters** are estimated with **low bias** and **high precision** in **typical studies** with 30 subjects. Indicating a **robust setup** to estimate these parameters.
- Figure 2: *Ffat* was estimated with **bias** and **low precision** in **typical studies** with 30 subjects. **95%EIs** are **large** and mostly **overlapping**. Indicating that *Ffat* is **not identifiable**.
- Figure 2: **None** of the 16 virtual drugs **passed** the acceptance criteria.

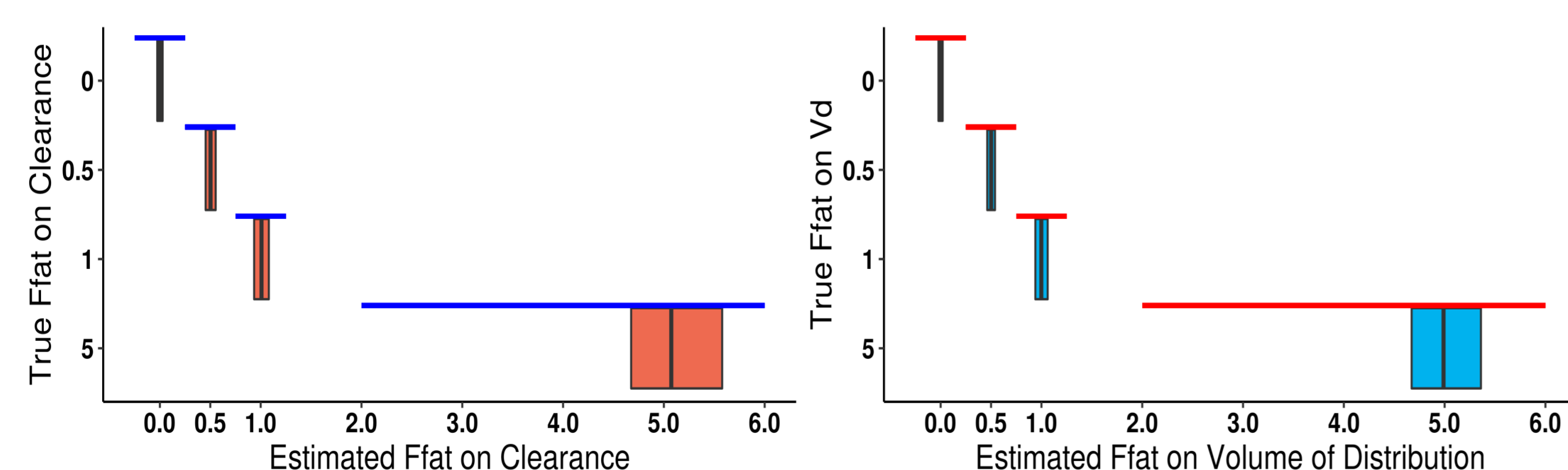


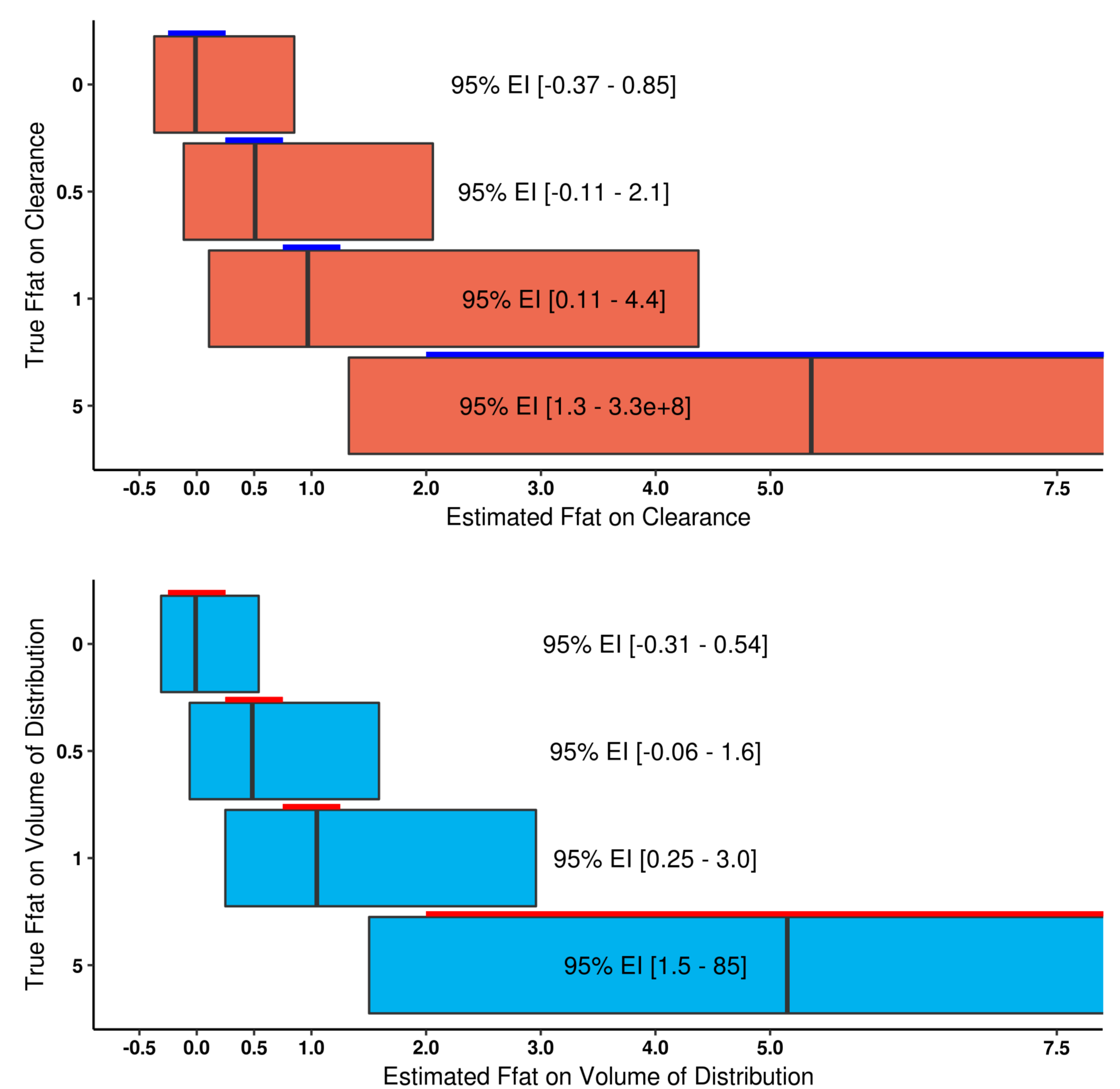
Figure 1. 95% Estimation interval (EI) of the large studies with 10,000 subjects for the four values of *Ffat* for clearance (left panel) and volume of distribution (right panel). The thin horizontal lines represent (arbitrary) acceptance criteria.

Table 1. Pharmacokinetic parameters of the 1-comp model and estimates of the virtual drug with an *Ffat* of 0.5 set on both CL and V.

Parameter	True	Estimated median [95% EI]
CL	L/h	0.69
V	L	1.0
IIV CL	%	30
IIV V	%	30
Res.error	%	15

CL, clearance; V, volume of distribution; IIV, interindividual variability; Res.error, proportional residual error; 95% EI, 95% estimation interval.

Figure 2. 95% Estimation interval (EI) of the typical studies with 30 subjects for the four values of *Ffat* for clearance (upper panel) and volume of distribution (lower panel). The thin horizontal lines represent the (arbitrary) acceptance criteria.



Conclusions

In this work we investigated the identifiability of *Ffat* used in the normal fat mass approach. Low precision was observed for estimates of *Ffat* in studies with a realistic study size despite a best case scenario. Estimating an incorrect value of *Ffat* could have consequences for dosing drugs with a narrow therapeutic index at extreme weights. Therefore, NFM must be used with caution and should be preceded with study design evaluation.

Clinical Relevance

Our study shows that NFM cannot be reliably estimated in typical clinical pharmacokinetic (best case scenario) studies. In our case, estimation of NFM could have resulted in a dose advice with a >25% difference from the correct dose.