UPPSALA UNIVERSITET

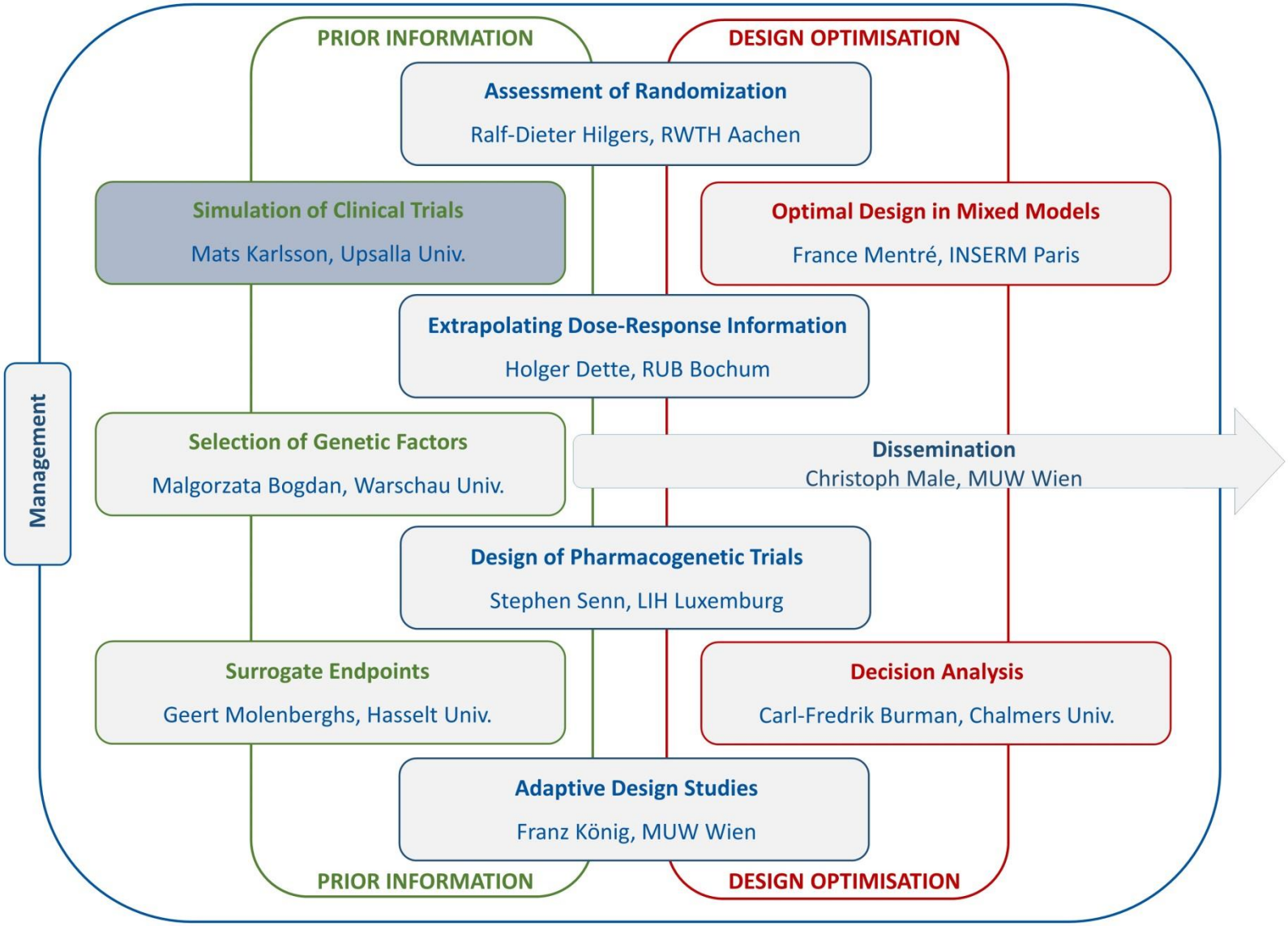
WP7: Simulation of clinical trials in small population groups

A Sampling Importance Resampling Procedure for Estimating Parameter Uncertainty

Oct 11, 2016

Mats Karlsson
Uppsala University

Workpackage structure



Considerations in small population groups

- Difficult to run trials with many subjects
- How can all relevant information be utilized in making decisions?
  - Nonlinear mixed effects models (**NLMEM**) incorporating drug and disease characteristics offer an attractive alternative

NLMEM – why attractive?

- Integrate information in data across
  - subjects
  - time (longitudinal analysis)
  - variables
  - covariates/predictors
- Allow prior knowledge to be incorporated
  - Drug/Disease driven structural models
  - Parameter constraints from biological/pharmacological knowledge
  - Other knowledge/assumptions as appropriate

Trial/treatment decisions using NLMEM

- Informed by
  - Model contrasts (hypothesis tests)
  - Parameter uncertainty distributions
  - Prediction distributions with uncertainty

Decisions using NLMEM – model contrasts

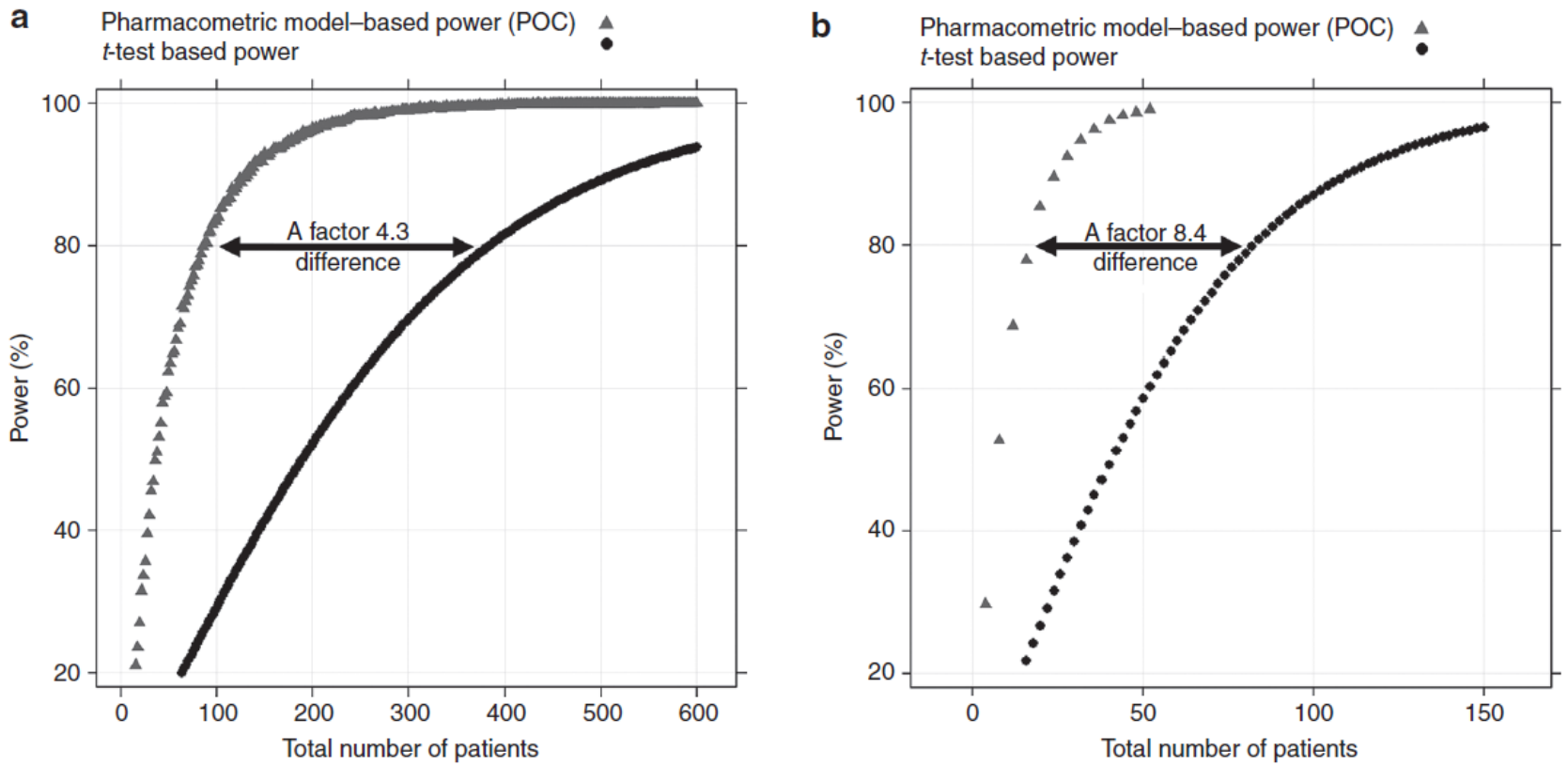


Figure 3 Power curve comparison between the pharmacometric model–based power (gray triangles) and the *t*-test based power (black diamonds), for the proof-of-concept scenario. (**a**) The power curves for the stroke example in which the difference in study size is a factor of 4.3 (90 vs. 388 total number of patients) is displayed. (**b**) In the diabetes example, the difference in study size was 8.4-fold (10 vs. 84 total number of patients) in favor of the pharmacometric approach.

Karlsson et al. CPT:PSP 2:e23 (2013)

Decisions using NLMEM – parameter uncertainty

Clarification on Precision Criteria to Derive Sample Size When Designing Pediatric Pharmacokinetic Studies

J Clin Pharmacol 2012 52: 1601

Yaning Wang, PhD, Pravin R. Jadhav, PhD, Mallika Lala, PhD, and Jogarao V. Gobburu, PhD

One of the important goals of the pediatric PK study is to ensure the precise estimate of important PK parameters, such as clearance and volume of distribution, to justify the choice of a safe and effective dose from a PK perspective. To achieve this goal, a standard regulatory requirement has been drafted and communicated to the sponsors, where applicable, as follows:

> The study must be prospectively powered to target a 95% CI [confidence interval] within 60% and 140% of the geometric mean estimates of clearance and volume of distribution for DRUG NAME in each pediatric sub-group with at least 80% power.

Internal decision making – predictive distributions

Model-Based Drug Development: A Rational Approach to Efficiently Accelerate Drug Development

PA Milligan[1], MJ Brown[2], B Marchant[3,10], SW Martin[1], PH van der Graaf[4,1], N Benson[4,11], G Nucci[5], DJ Nichols[5], RA Boyd[6], JW Mandema[7], S Krishnaswami[6], S Zwillich[8], D Gruben[2], RJ Anziano[2], TC Stock[9] and RL Lalonde[6]

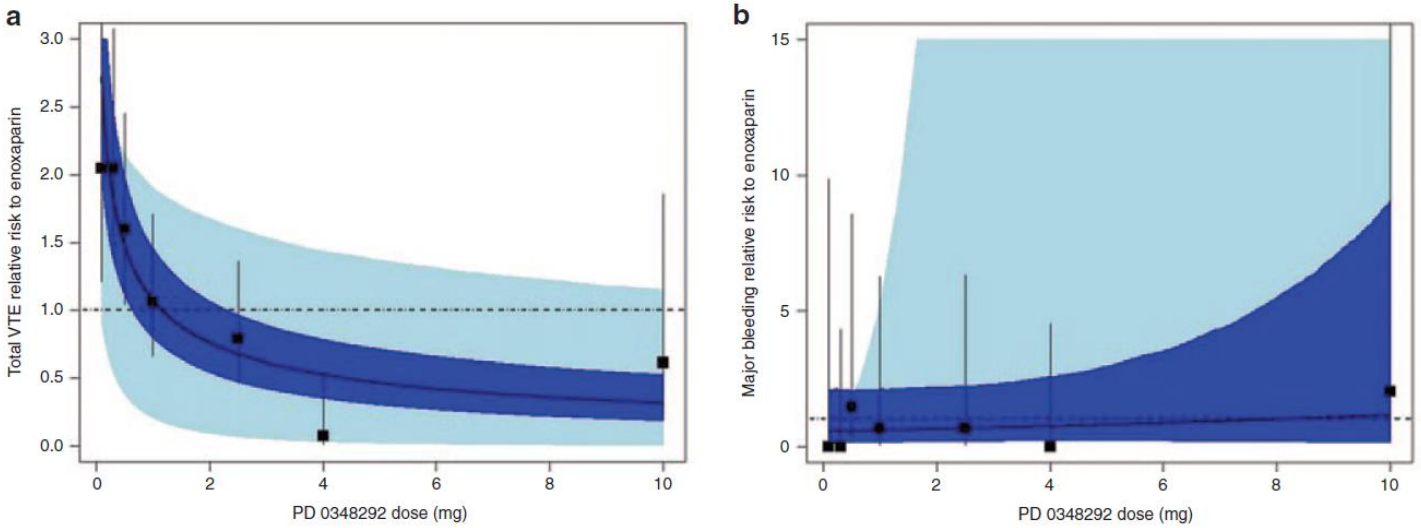


Figure 6 Observed relative risk of PD 0348292 vs. enoxaparin (symbols with 95% confidence intervals (CIs)) for (**a**) VTE and (**b**) MB and logistic regression model fit (solid line with dark blue area covering the 90% CI) in an adaptive phase II study. The light blue area covers the 90% CI before the trial based on the PK–PD model for inhibition of thrombin generation. MB, major bleeding; PK–PD, pharmacokinetics–pharmacodynamics; VTE, venous thromboembolism.

Clin Pharmacol Ther 2013

Good Practices in Model-Informed Drug Discovery and Development: Practice, Application, and Documentation

EFPIA MID3 Workgroup: SF Marshall[1]*, R Burghaus[2], V Cosson[3], SYA Cheung[4], M Chenel[5], O DellaPasqua[6], N Frey[3], B Hamrén[7], L Harnisch[1], F Ivanow[8], T Kerbusch[9], J Lippert[2], PA Milligan[1], S Rohou[10], A Staab[11], JL Steimer[12], C Tornøe[13] and SAG Visser[14]

: CPT Pharmacometrics Syst. Pharmacol. (2016) 5, 93–122;

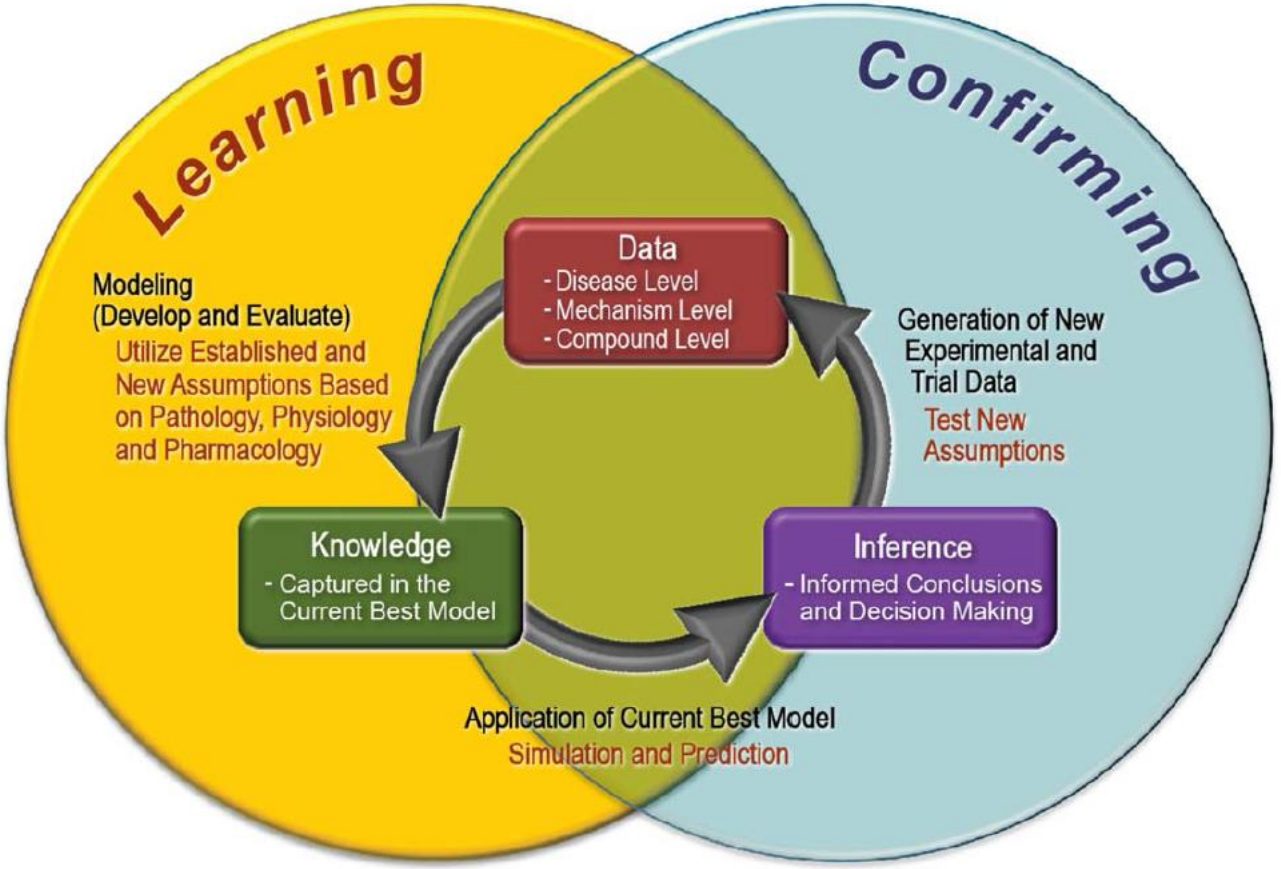
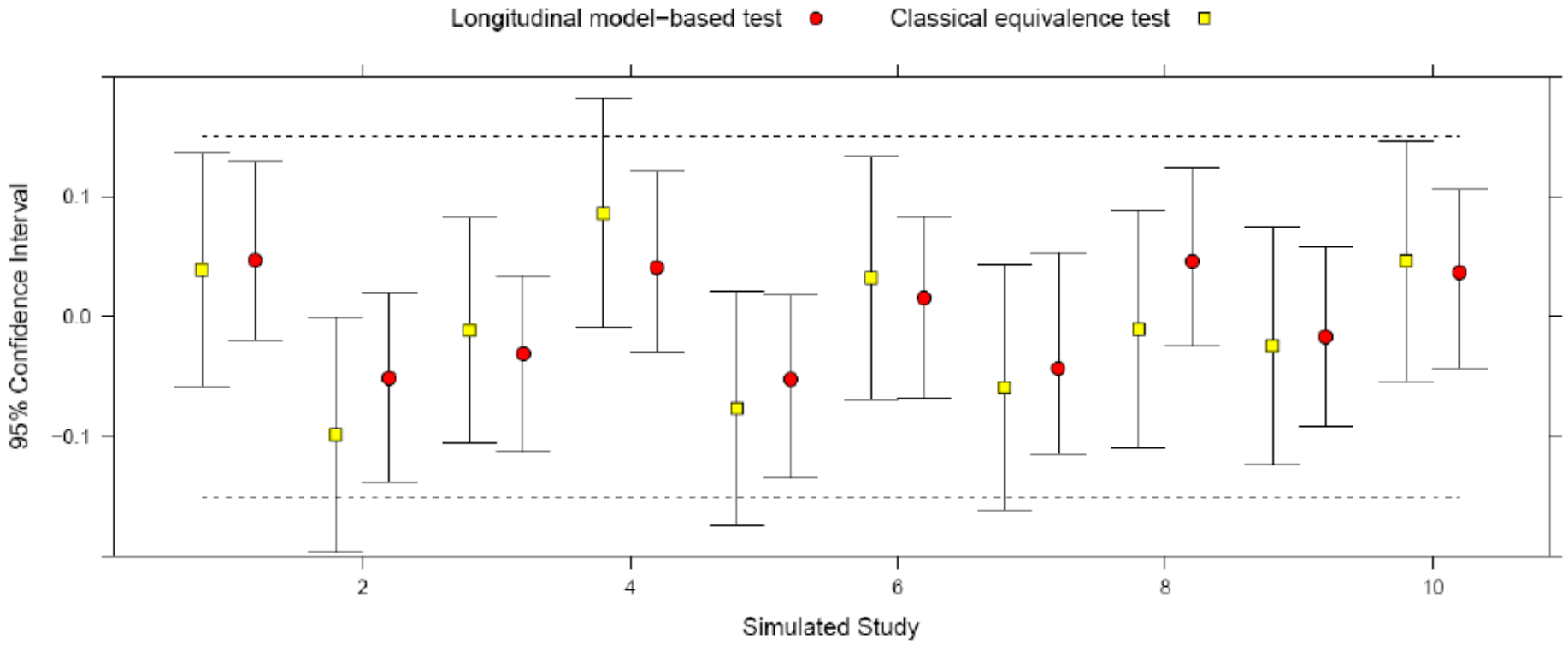


Figure 3 MID3: a quantitative framework for prediction and extrapolation centered on knowledge and inference generated from integrated models of compound, mechanism, and disease level data aimed at improving the quality, efficiency, and cost-effectiveness of decision-making. The colored boxes represent essential components of the "Learn and Confirm Cycle". The arrows represent processes that link these components.

Regulatory decision making – predictive distributions

Model-based analyses for pivotal decisions,
with an application to equivalence testing for biosimilars
Bieth et al, PAGE 2012



NLMEM in trial/treatment evaluations

- Power calculations
  - How to do timely power calculations?
- Hypothesis tests
  - How to achieve type 1 error control?
- Model uncertainty
  - What if the NLMEM is not appropriate?
- Adaptive designs for small populations
  - NLMEM-Based Adaptive Optimal Design
- Parameter uncertainty (PU)
  - Diagnostics for adequacy of PU
  - Sampling-Importance-Resampling (SIR)

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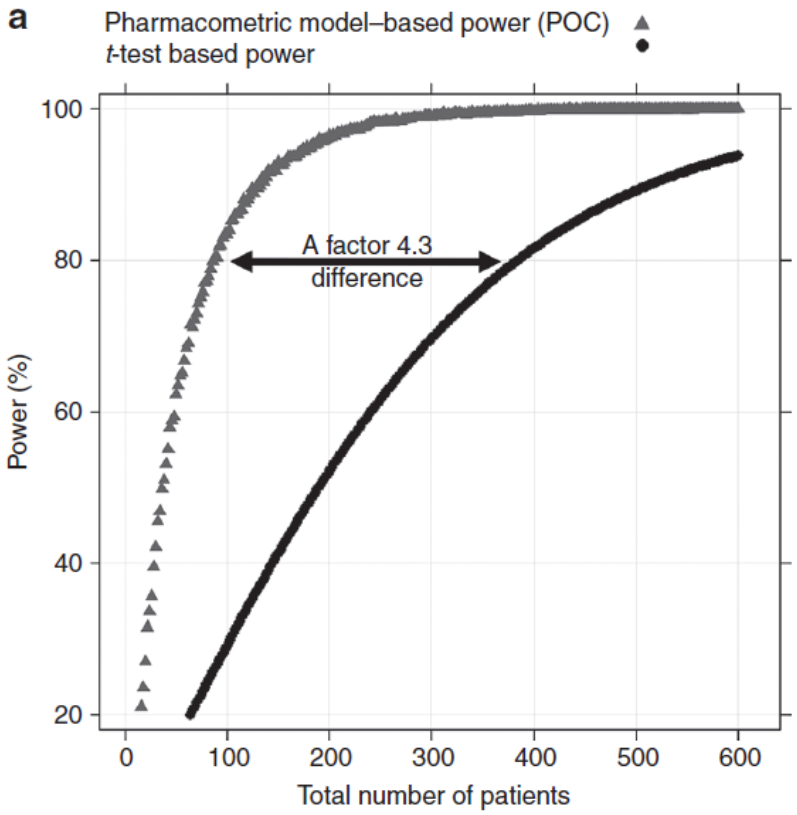

Increased speed in power calculations

- **Monte Carlo Mapped Power (MCMP)**
- Simulate 1 data set with large N
- Fit full and reduced model
- Obtain dOFVi for each subject
- Resample dOFVi to obtain power for study size of interest
- Vong et al., AAPS J 2012

- **Parametric Power Estimation (PPE)**
- Simulate X data sets with N subjects
- Fit full and reduced model
- Estimate λ from dOFV assuming non-central chi-square distribution
- Extrapolate to other study sizes using λ
- Ueckert et al., JPKPD 2016

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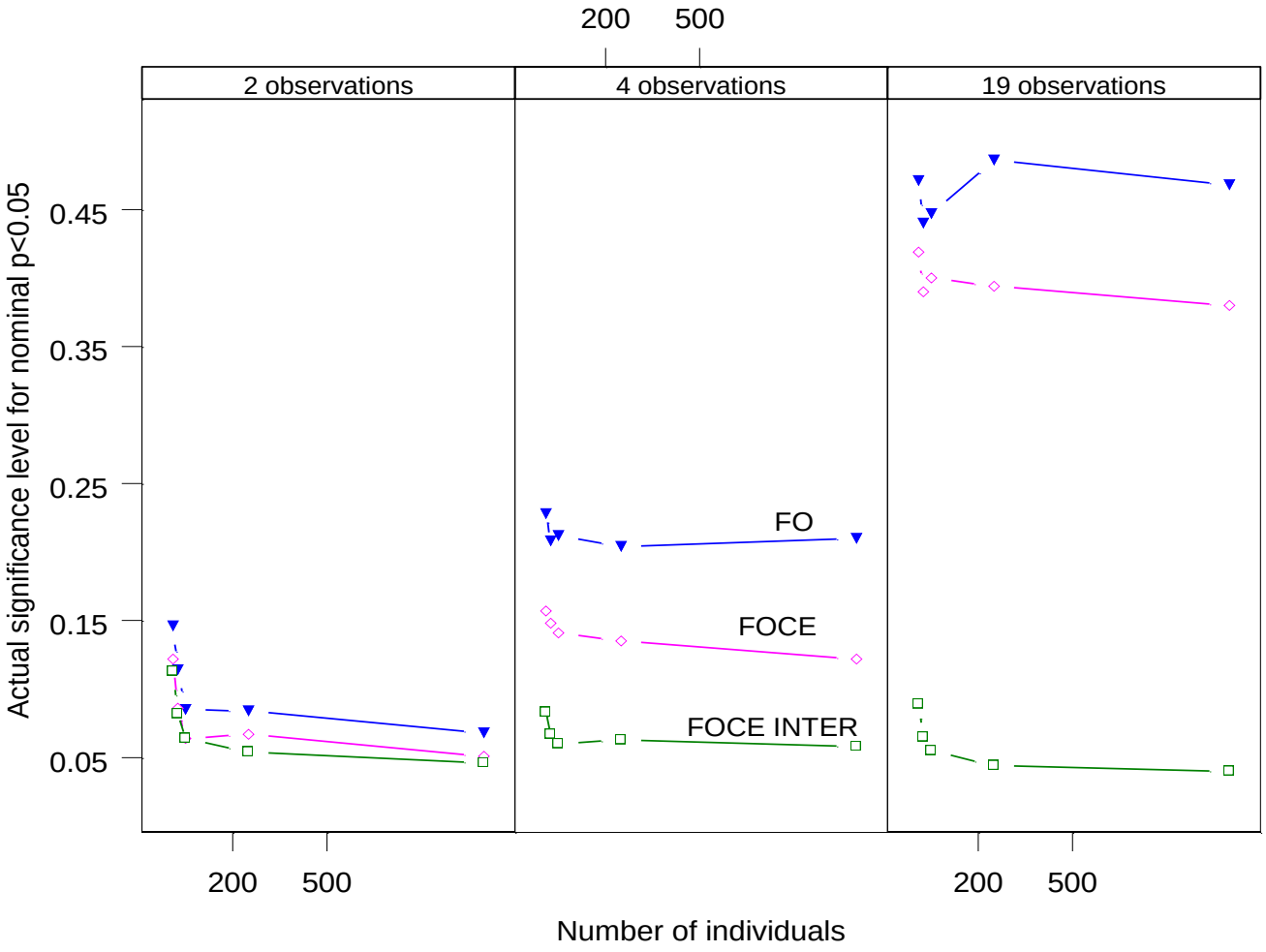
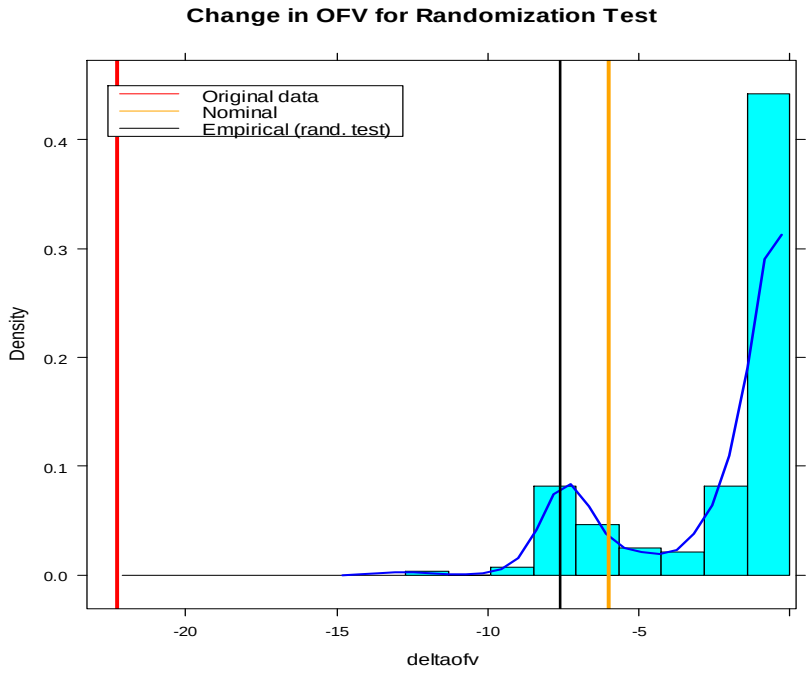
NLMEM – Type 1 error control

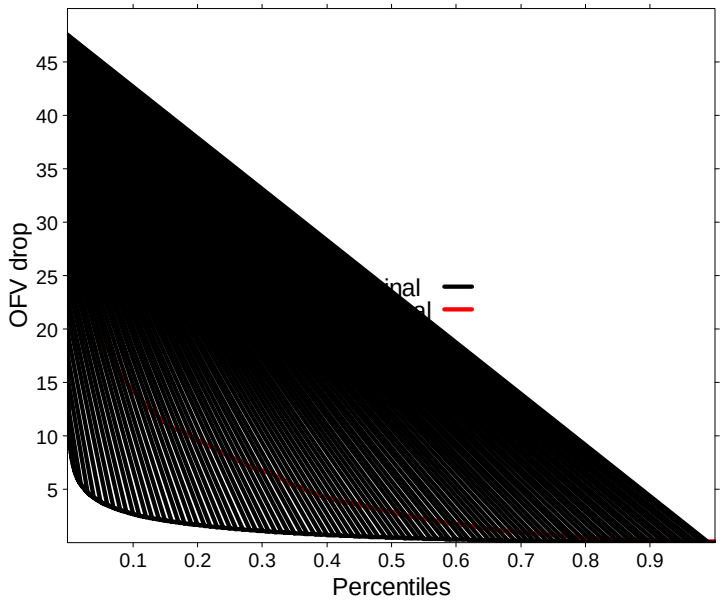


Wählby U et al., J Pharmacokinet Pharmacodyn 28:231-52 (2001)

Permutation (Randomisation) tests for NLMEM

- Permutation test for
  - prespecified NLMEM model
  - (mixture) model built using blinded data





Deng et al. PAGE 2015, Harling et al. PAGE 2016,

NLMEM in trial/treatment evaluations

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Model-averaging

- Model-averaging for
  - longitudinal dose–response*
  - biosimilar superiority testing**
  - confidence interval-based QT-test***

*Aoki et al., PAGE 2014, PAGE 2016
**Dosne et al., in manuscript
***Dosne et al, PAGE 2016

NLMEM in treatment evaluations

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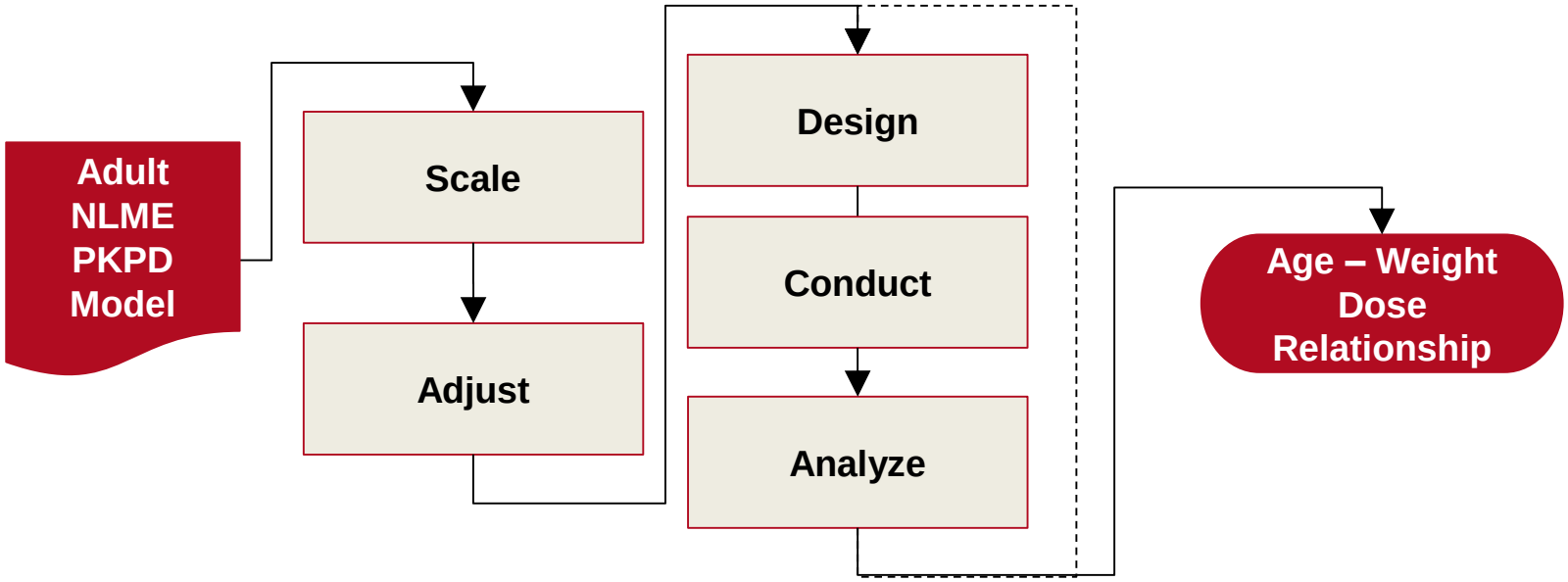
Model-based adaptive optimal design

Simulated model based adaptive optimal design of adult to children bridging study using FDA stopping criteria

- Interim analysis after every cohort
- Update of design for next cohort
- Stopping if precision is sufficient



Strömberg and Hooker. PAGE 2015; Karlsson EMA Workshop 2016

NLMEM in treatment evaluations

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Parameter uncertainty (PU)

- Parameter uncertainty distributions provide decision basis for probability and confidence interval (CI)-based decisions
- Several ways to estimate PU
  - Cov-matrix, bootstrap, …
- Different methods provide different PU and have different properties
  - Which one to use?

Parameter uncertainty – covariance matrix

- Covariance matrix
  - Not always retrievable or suitable
  - Assumes symmetry & linear correlations
- NLMEM CIs often assymetric
  - Non-linear model
  - (Interindividual) Variability parameters
  - Context-driven parameter boundaries

Parameter uncertainty – bootstrap

- Bootstrap: sensitivity to sample size
  - For simple models, robust down to small sample sizes (N≈10-12)
  - For NLME models, sample size dependence less well explored/understood

Bootstrap of NLME models

- Factors likely to increase sample size demand
  - Simultaneous estimation of multiple parameters
  - Hierarchical models with ≥2 levels of random-effects
  - Heterogeneous designs including covariate distributions
  - Data-driven model development
  - Model misspecification

dOFV distribution - a diagnostic for PU

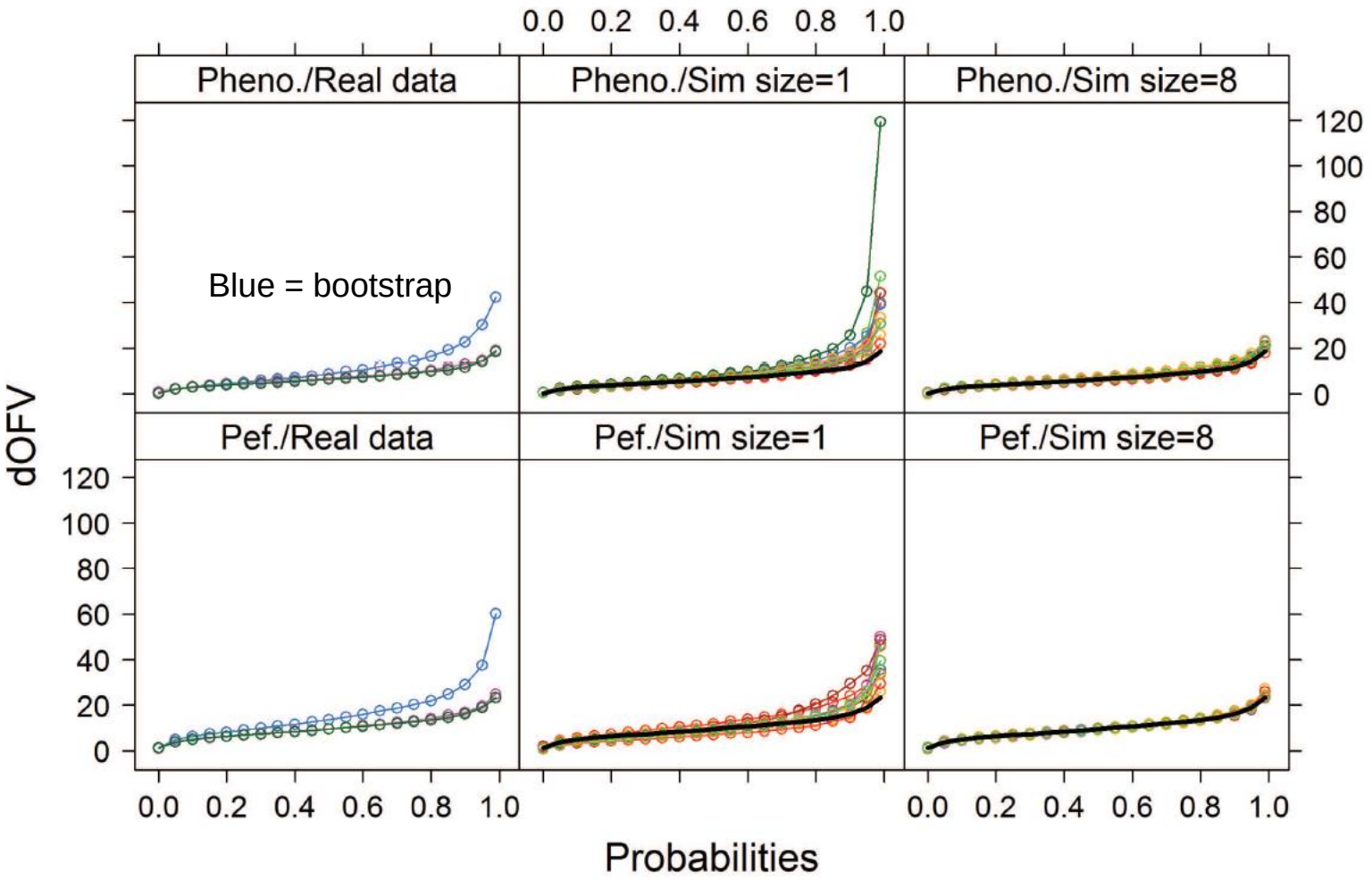
- Objective:
  - Provide a diagnostic for the adequacy of an estimate of parameter uncertainty

Dosne et al. JPKPD 2016 (in press)

dOFV distribution

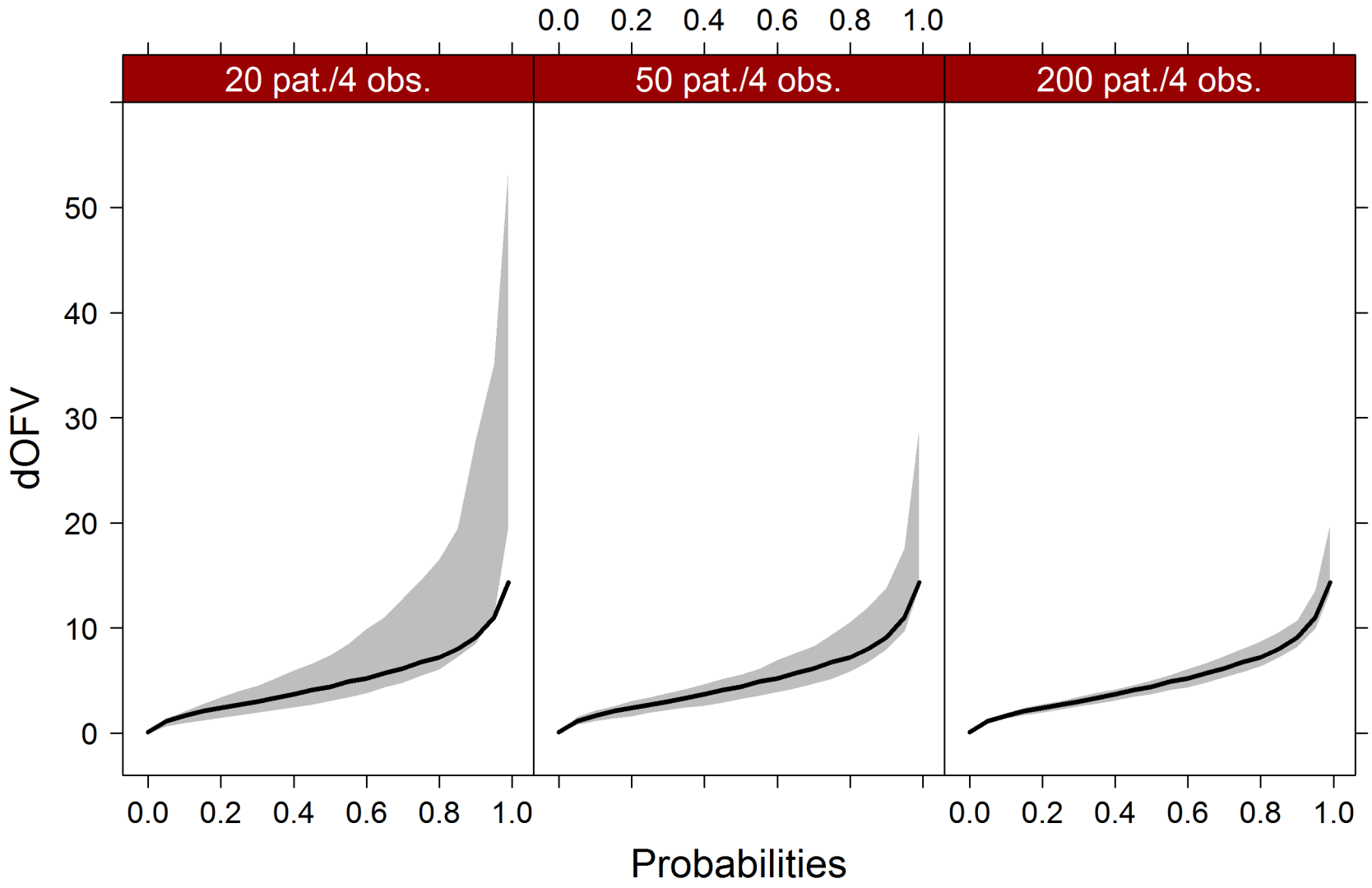
1. Evaluate parameter vectors sampled from PU distribution on original dataset
2. Subtract OFV of the final model for original data set
3. Compare bootstrap dOFV distribution with reference (chisq) dOFV distribution

Comparison with expected distribution

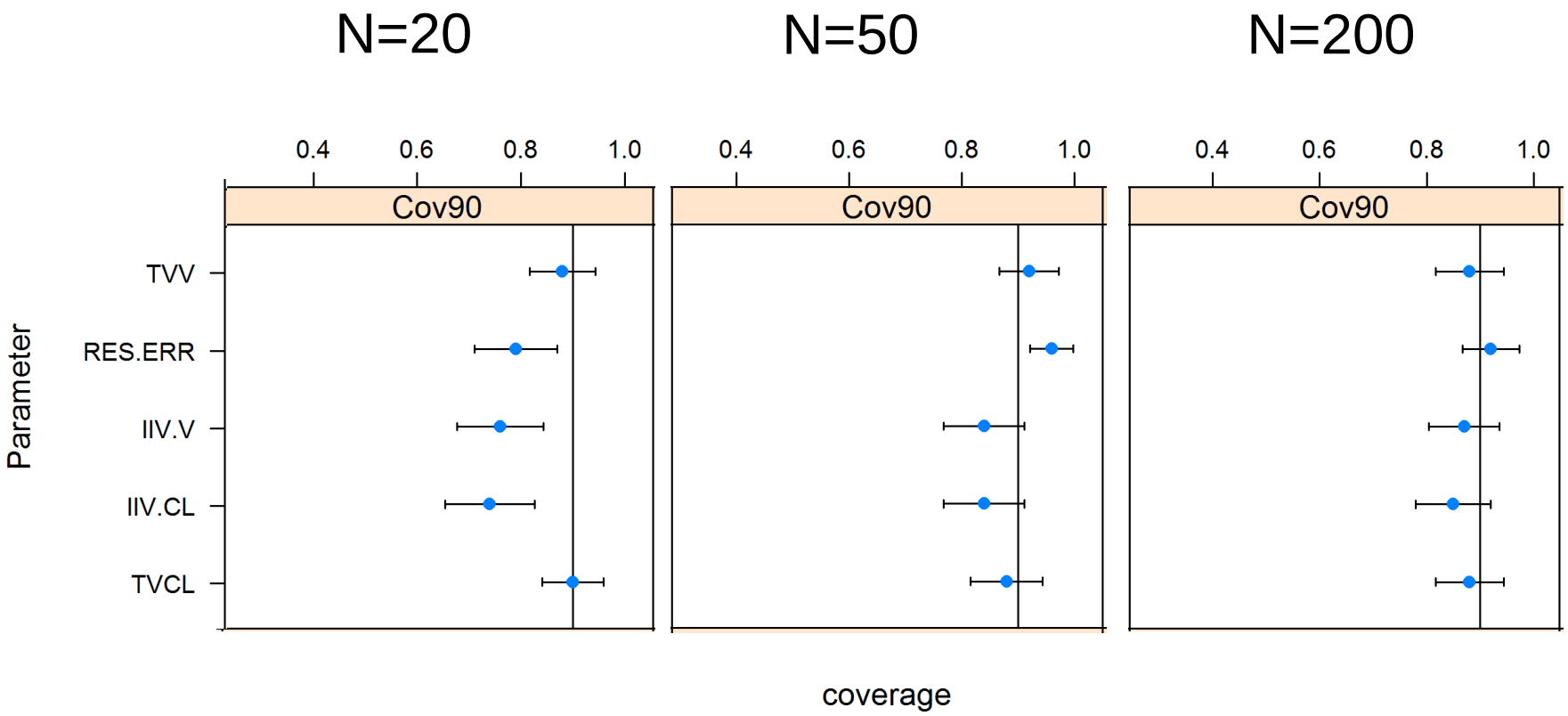


Dosne et al. JPKPD 2016 (in press)

Simulation example 1



Simulation example 1



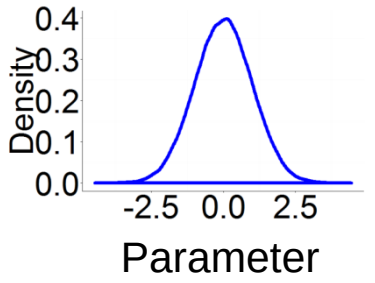
Parameter uncertainty estimation

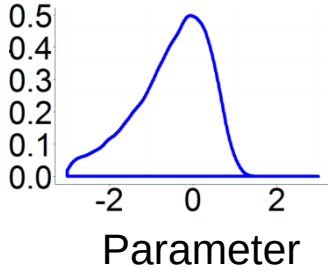
- Covariance matrix
  - Not always retrievable or suitable
  - Assumes symmetry & linear correlations
- Bootstrap
  - Empirically shown to be inadequate for small/medium-sized data
  - Computationally problematic (time & stability)
- Need for additional PU estimation methods
  - **S**ampling – **I**mportance – **R**esampling (**SIR**)

SIR principle:
Sampling, Importance weighting, Resampling

- → Approximate unknown posterior distribution by weighted known distribution[1]

S	**SAMPLING** *Step 1*	• **Sample** *p* parameter vectors from covariance matrix
I	**IMPORTANCE WEIGTHING** *Step 2*	• **Calculate weights** based on fit to original data
R	**RESAMPLING** *Step 3*	• **Resample** *M* vectors based on weights from step 2 • Compute confidence intervals





[1] Rubin DB, Bayesian Statistics. 1988;3:395-402

Importance ratios (IR)

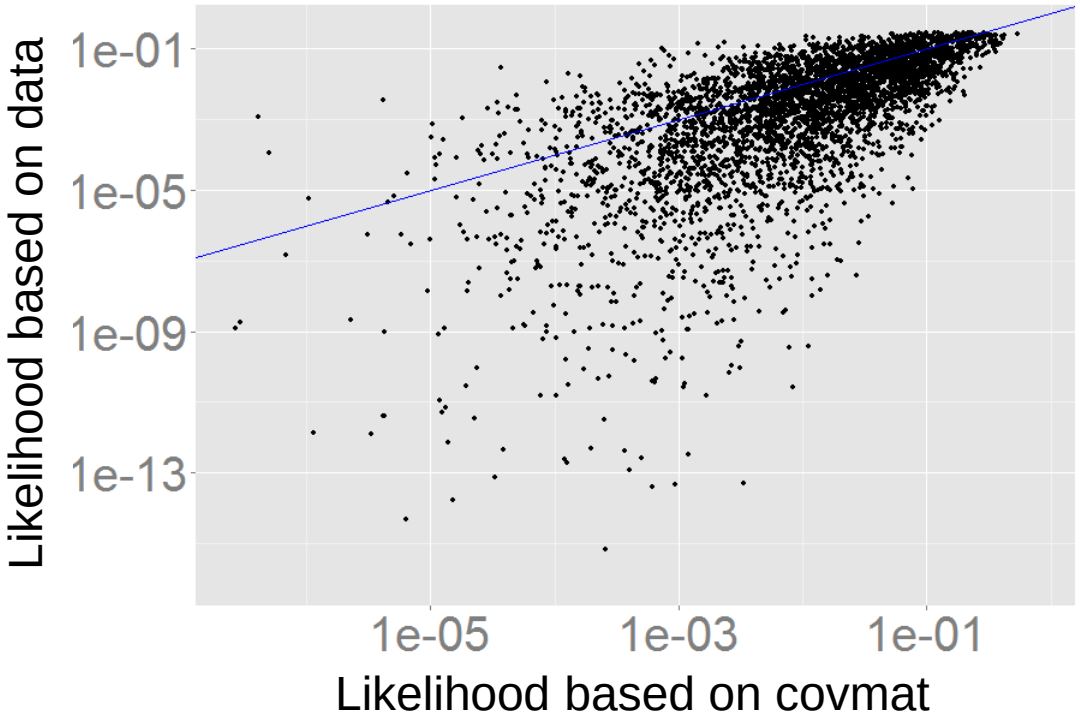
- **Resampling probabilities:**

$$IR = \frac{lik(Y|\theta)}{h(\theta)}$$

- Likelihood of data given parameter vector divided by likelihood of vector in proposal
- How well vector fits data compared to how well it should fit data
- $IR = 1$: as expected → not reweighted in resampling
- $IR > 1$: better than expected → upweighted
- $IR < 1$: worse than expected → downweighted

Components of Importance Ratios

- Many vectors do not fit as well as expected



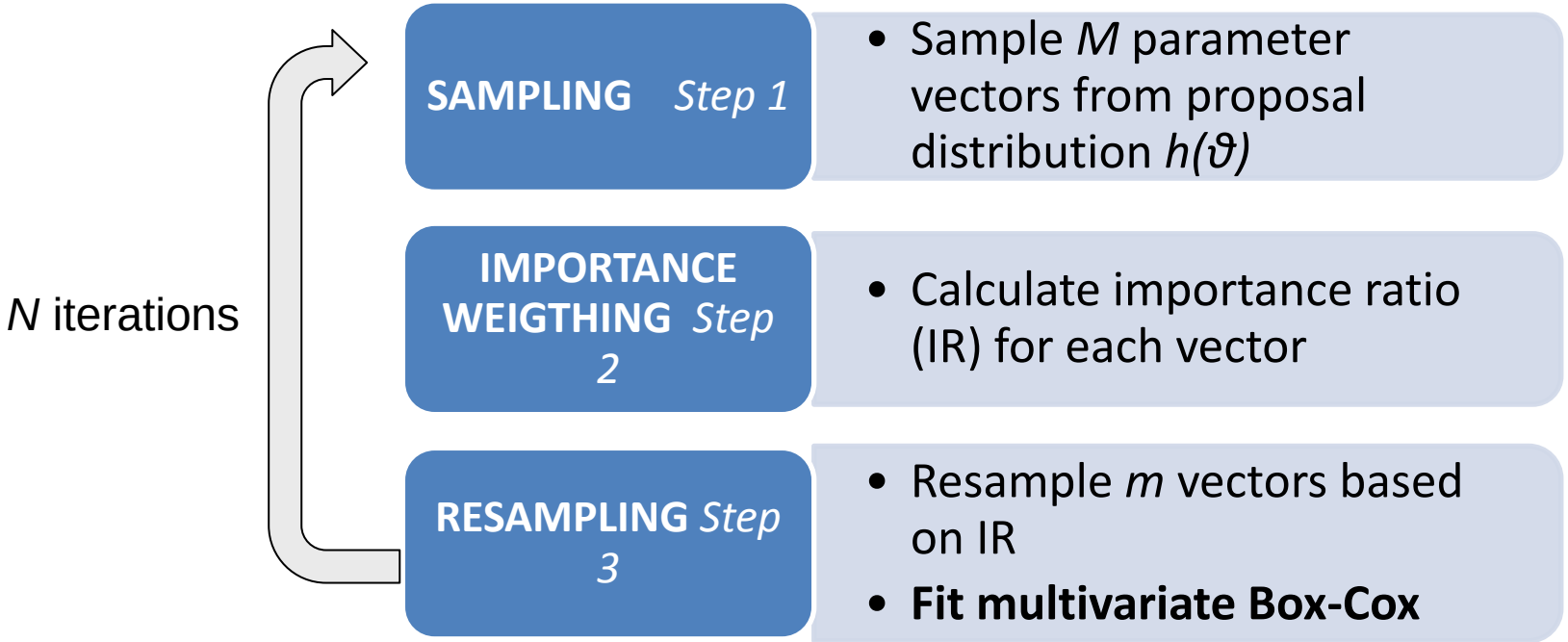
SIR optimization I

- SIR is a procedure with options

Number of initial samples	• The higher number the better • A costly way of increasing precision
Resampling	• Resampling can improve efficiency – but also decrease performance • With or without replacement?
Inflation of sampling distribution	• A too wide proposal is better than a too constrained – basis for inflation?

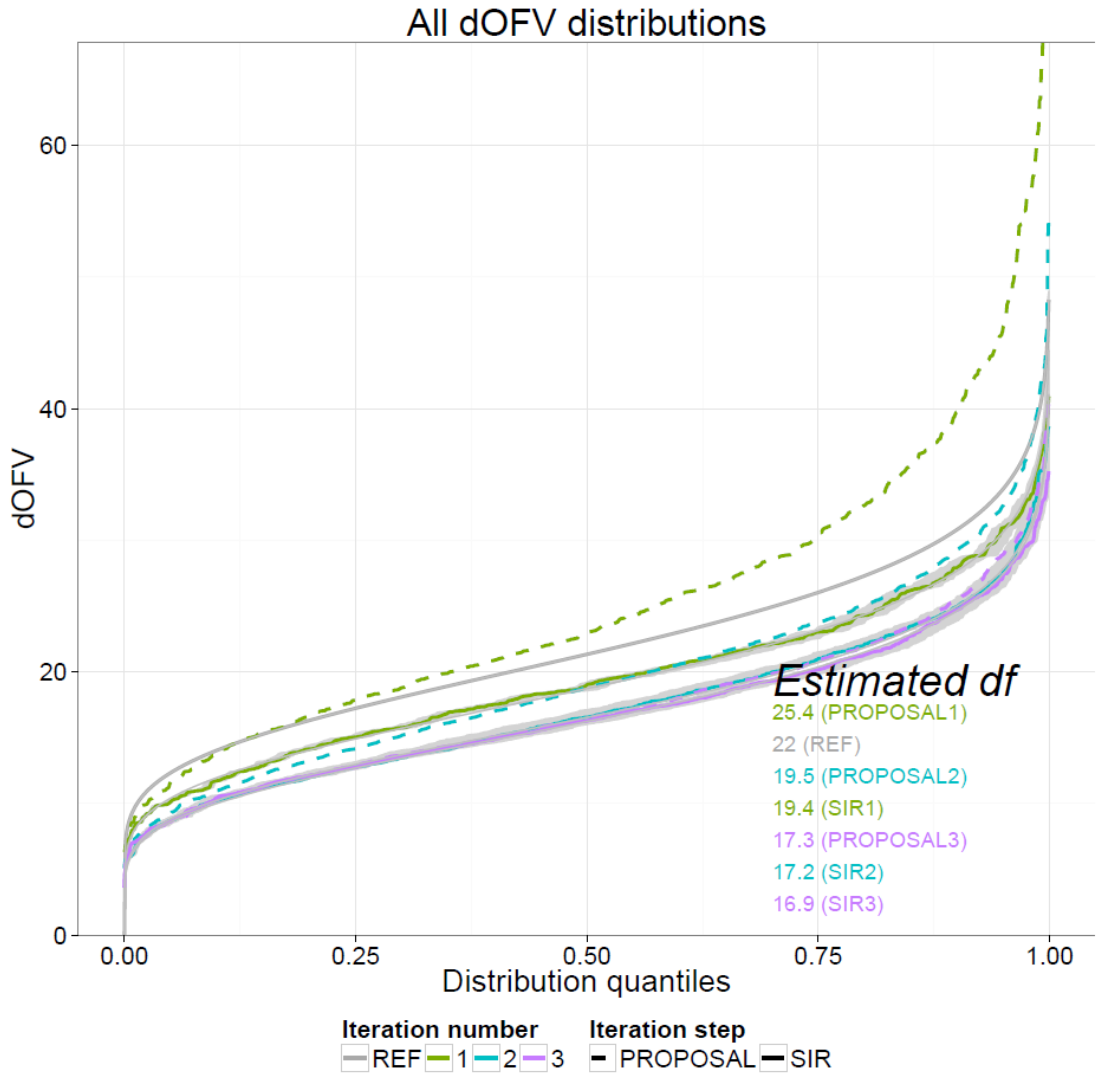
SIR optimization II - make SIR iterative

- Updating of proposal is more efficient than increasing initial sampling
- Fit multivariate Box-Cox to SIR output and use as new proposal



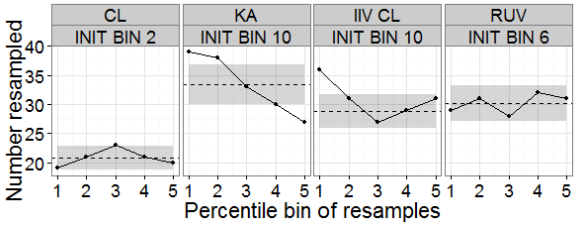
Dosne et al., PAGE 2016

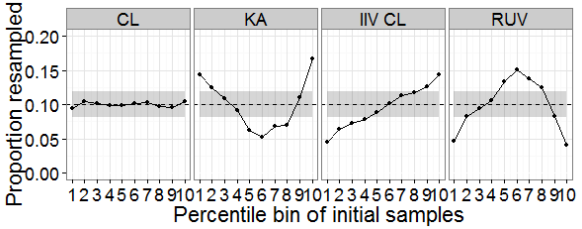
dOFV plot iterative SIR – convergence check

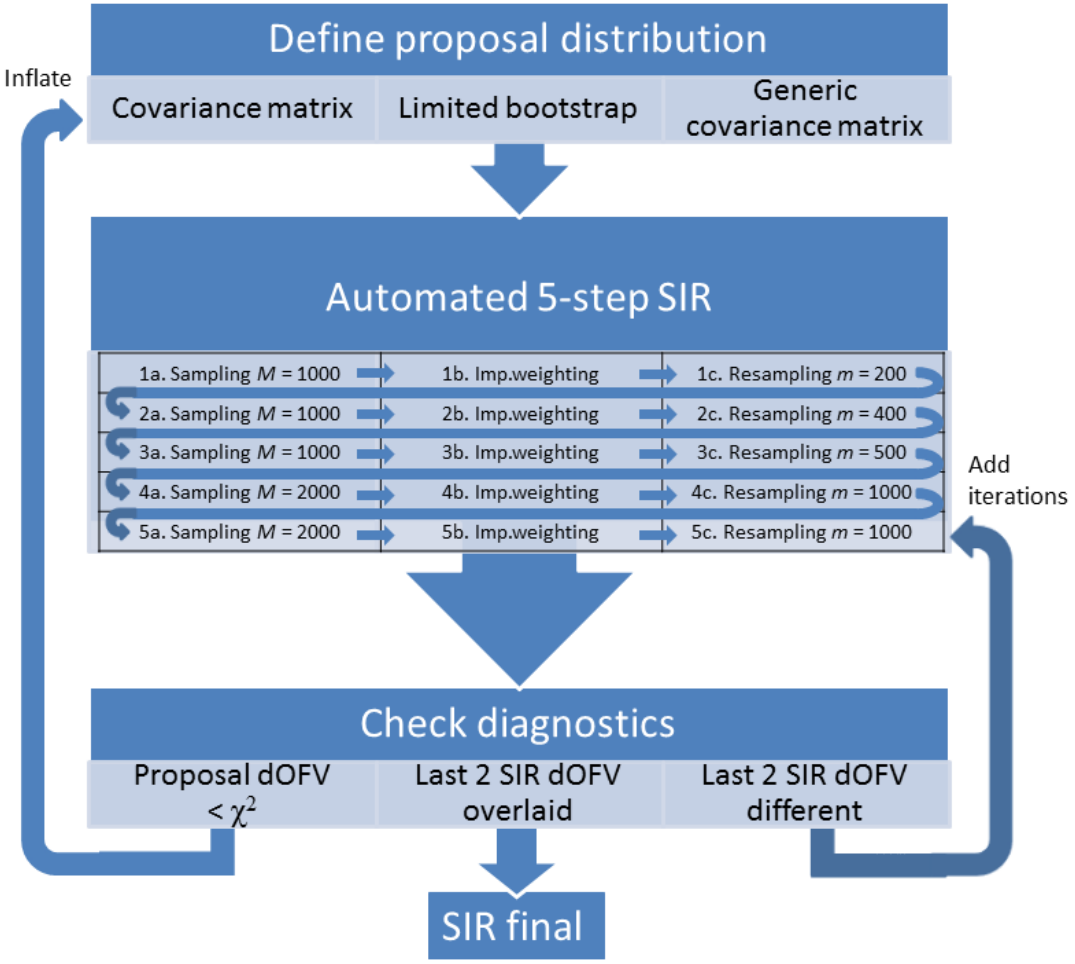


- ✓ dOFV distribution $\sim \chi^2$
- ✓ $df \leq n\,params$
- ✓ dOFV distribution stable over last 2 iterations

Implementation of SIR in PsN/NONMEM







Dosne et al., PAGE 2016

Conclusion SIR

- SIR

✓ allows for asymmetry in uncertainty distribution

✓ does not require parameter re-estimation

- "Fast and stable" method to assess parameter uncertainty, in particular if:
  - ✓ long estimation times
  - ✓ bootstrap convergence issues
  - ✓ unbalanced/small study designs
  - ✓ model-based meta-analysis
  - ✓ informative priors in model

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Team @ UU

- Mats Karlsson – Prof
- Andrew Hooker – Assoc Prof
- Kristin Karlsson – Researcher
- Sebastian Ueckert – Researcher
- Yasunori Aoki – Postdoc
- Ronald Niebecker – Postdoc
- Chenhui Deng - Postdoc
- Anne-Gaelle Dosne – PhD student
- Eric Strömberg – PhD student
- Kajsa Harling – System developer
- Rikard Nordgren – System developer