Influence of the size of the cohorts in adaptive design for nonlinear mixed effect models: an evaluation by simulation for a pharmacokinetic (PK) and pharmacodynamic (PD) model in oncology

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Outline

- Context
- Objectives
- Methods
- Simulation Study
- Results
- Conlusion and Perspectives

Context: Optimal design in NLMEM

- Choosing a good design for a planned study is essential
  - Number of patients
  - Number of sampling times for each patient
  - Sampling times (allocation in time)

- Optimal design depends on prior information (model and parameters)

- D-optimality criterion
  - Local Designs
  - Robust designs

Atkinson, Optimum Experimental Designs. (1995)
Dodds et al., J Pharmacokinet Pharmacodyn. (2005)
Pronzato and Walter, Math Biosci. (1988)

Context: Adaptive design

- AD: clinical trial designs that use accumulating information to decide how to modify predefined aspects of the study
  - Areas of interest: predicting clinical data; Phase 1 studies
  - ADs are useful to provide some flexibility but were rarely used for NLMEM
- Two-stage designs could be more efficient than fully adaptive design (not yet tested in NLMEM)
- Dumont et al. implemented two-stage AD in NLMEM
- AD questions:
  - How many adaptations? (e.g stages)
  - How many patients in each cohort? (i.e. cohorts size)

Foo et al., Pharm Res. (2012)
Mentré et al., CPT Pharmacometrics Syst Pharmacol. (2013)
Fedorov et al., Stat Med. (2012)
Dumont et al., Commun Stat. (2014)

Objectives

1. To compare by simulation one and two-stage designs using a PKPD model in oncology

2. To study the influence of the size of each cohort in two-stage designs

3. To test extensions of two-stage adaptive design as three- and five-stage adaptive designs

Methods: Basic mixed effect model

- Individual model (one continuous response)

  $y_i = f(\phi_i, \xi_i) + \varepsilon_i$ vector of n_i observations

    - ξ_i : individual sampling times t_{ij} j=1, ... n_i
    - ϕ_i : individual parameters (size p)
    - f : nonlinear function defining the structural model
    - ε_i : gaussian zero mean random error
    - var (ε_i) = $(\sigma_{inter} + \sigma_{slope} f(\phi_i, \xi_i))^2$ combined error model

- Random-effects model

  - $\phi_i = \beta \times \exp(b_i)$
  - $b_i \sim N(0, \Omega)$ here Ω diagonal: ω_k^2 = Var(b_{ik})

- Population parameters: Ψ (size P)

  - β (fixed effects)

  - unknowns in Ω (variance of random effects)

  - σ_{inter} and/or σ_{slope} (error model parameters)

Methods: Basic population design

- Assumption
  - N individuals i
  - same elementary design ξ in all N patients ($\xi_i = \xi$) with $t_1, \ldots, t_n$ sampling times
  - $n_{tot} = N \times n$
    - n = number of samples for each individual
- Population design
$$\Xi = \{\xi, N\}$$

Methods : Fisher Information Matrix (FIM)

- Elementary FIM: $M_F(\Psi, \xi) = E\left(\frac{-\partial^2 L(y;\Psi)}{\partial\Psi\partial\Psi^T}\right)$

- no analytical expression for FIM → FO approximation

- Population Fisher Information Matrix for one group design
$$M_F(\Psi, \Xi) = N \times M_F(\Psi, \xi)$$

- M_F is implemented in the R function « PFIM »

- In PFIM 4.0 (April 2014) it is possible to include prior information on FIM for two-stage design
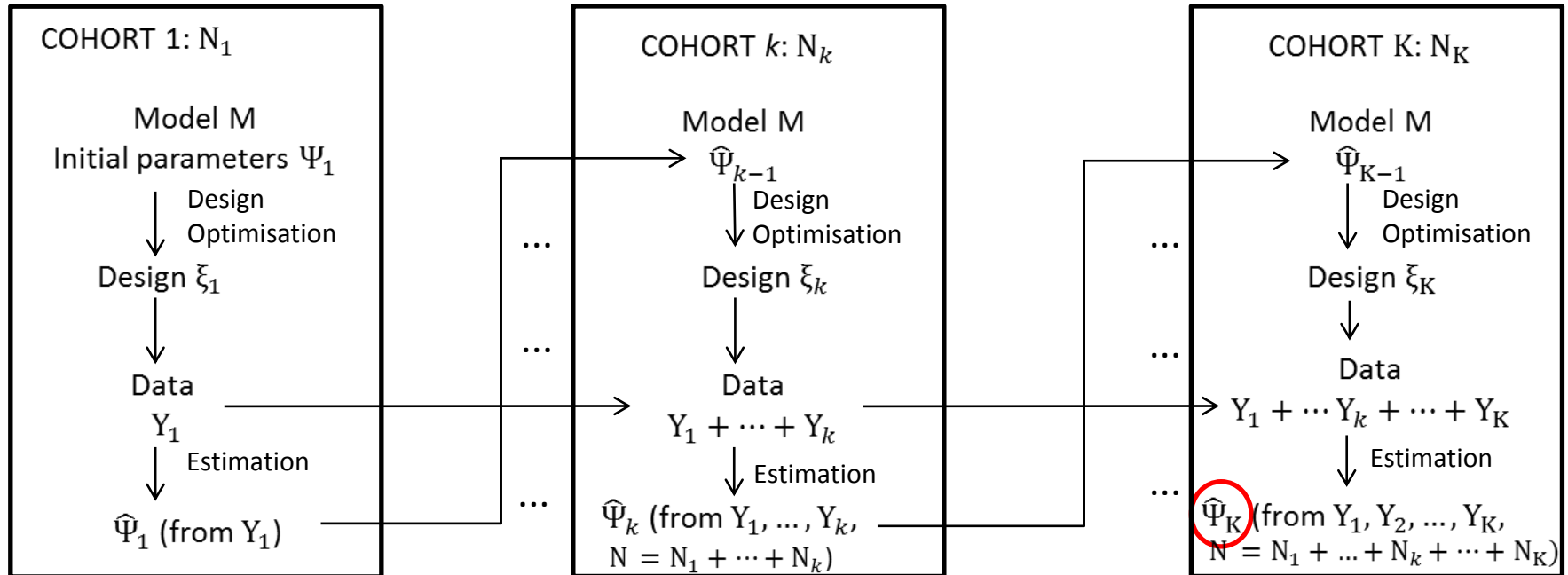
Mentré et al., Biometrika (1997)
Bazzoli et al., Comput Methods Programs Biomed. (2010)
Mentré et al., PAGE Abstr 3032 (2014)
Dumont et al., Commun Stat. (2014)
www.pfim.biostat.fr

Method: K-stage Adaptive Design

1st stage:
    from a priori Ψ_1, find ξ_1 that maximizes determinant of

$$M_F(\Psi_1, N_1 \xi) = N_1 M_F(\Psi_1, \xi)$$

k^{th} stage:
    using estimated $\hat{\Psi}_{k-1}$, find ξ_k that maximizes determinant of

$$M_F(\hat{\Psi}_{k-1}, N_1\xi_1 + \ldots + N_k \xi) = N_1 M_F(\hat{\Psi}_{k-1}, \xi_1) + \ldots + N_{k-1} M_F(\hat{\Psi}_{k-1}, \xi_{k-1}) + N_k M_F(\hat{\Psi}_{k-1}, \xi)$$

Simulation Study: PKPD Model

- 2 responses model, developed for a novel oral transforming growth factor β (TGF − β)

PK: concentration

$$f_{PK}(\phi, t) = \frac{DOSE}{V} \frac{k_a}{k_a - k} (e^{-kt} - e^{-k_a t}),$$

$$k = \frac{CL}{V}$$

Parameters: k_a, V, CL

PD: relative inhibition of TGF-β

$$\frac{df_{PD}(\phi, t)}{dt} = k_{out} \frac{I_{max} \cdot f_{PK}(\phi, t)}{f_{PK}(\phi, t) + IC_{50}} - k_{out} \cdot f_{PD}(\phi, t),$$

$$I_{max} = 1$$

Parameters: k_{out}, IC_{50}

ka → Concentration → CL/V

ksyn Effect kout

Gueorguieva et al., Comput Methods Programs Biomed. (2007)
Gueorguieva et al., Br J Clin Pharmacol. (2014)
Bueno et al., Eur J Cancer. (2008)
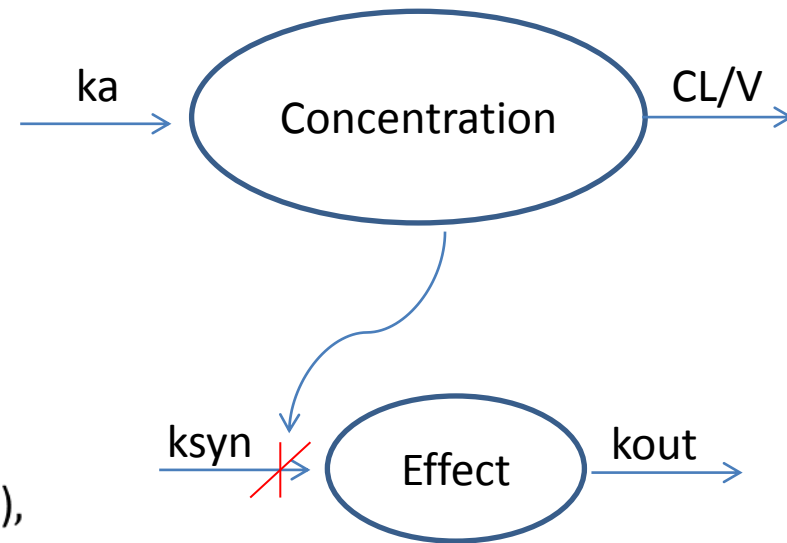
Simulation Study: Parameters

PK Parameters	Prior (Ψ^0)	True ($\Psi*$)
k_a (h^{-1})	2	2
V (L)	100	100
CL (Lh^{-1})	**40**	**10**
$\omega^2_{k_a}$	0	0
ω^2_V	0.49	0.49
ω^2_{CL}	0.49	0.49
$\sigma_{inter,PK}$	0	0
$\sigma_{slope,PK}$	0.2	0.2

PD Parameters	Prior (Ψ^0)	True ($\Psi*$)
k_{out} (h^{-1})	**2**	**0.2**
IC_{50} (mg/L)	0.3	0.3
$\omega^2_{k_{out}}$	0.49	0.49
ω^2_{IC50}	0.49	0.49
$\sigma_{inter,PD}$	0.2	0.2
$\sigma_{slope,PD}$	0	0

Single Dose 80 mg
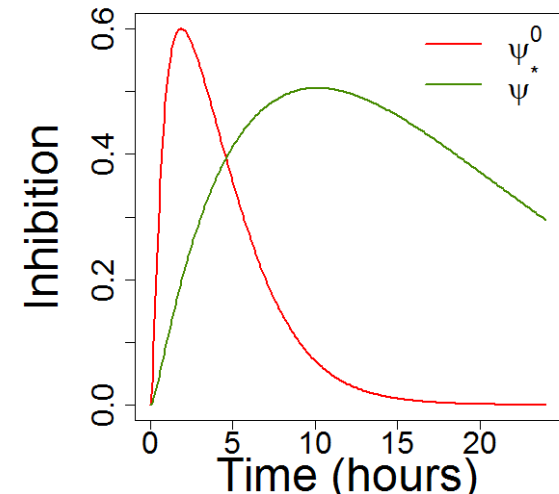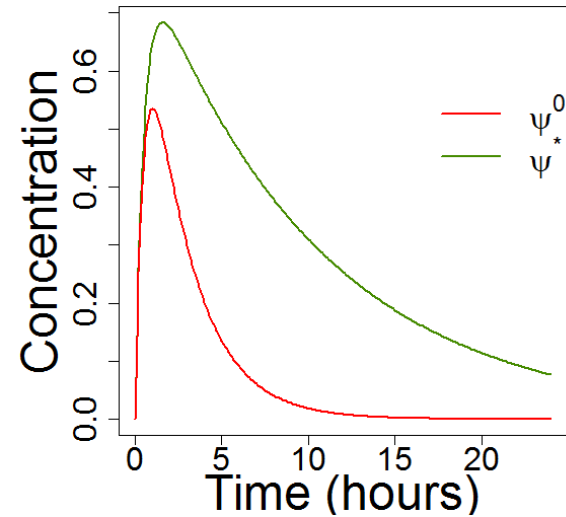
Simulation Study: Evaluated designs

- N=50

One-stage designs

- Rich design, n=6 sampling times: $\xi_{rich} = (0.1, 0.5, 1.5, 4, 6, 12)$
- 2 optimal designs, n=3 sampling times among the 6 of ξ_{rich}:
  - $\xi_0 = \{\xi_0^{PK} = (0.1, 4, 12); \xi_0^{PD} = (0.5, 1.5, 4)\}$ (D-optimal for Ψ^0)
  - $\xi_* = \{\xi_*^{PK} = (0.1, 4, 12); \xi_0^{PD} = (4, 6, 12)\}$ (D-optimal for Ψ^*)
  - mixed design ξ_{0*} (N_1=25 patients with ξ_0; N_2=25 patients with ξ_*)

Two-stage designs

- Balanced: ξ_{25-25} (N_1=N_2=25)
- Various sizes for cohorts 1 and 2: ξ_{10-40}, ξ_{15-35}, ξ_{35-15}, ξ_{40-10}

Three-stage designs

- Small size for cohorts 1 (N_1=10): $\xi_{10-20-20}$, $\xi_{10-10-30}$

Five-stage design

$\xi_{10-10-10-10-10}$ (N_1=N_2=N_3=N_4=N_5=10)

Simulation Study: Clinical Trial Simulation

- 100 data sets simulated with parameters Ψ^* and design ξ_{rich}
  - For the designs to be evaluated were kept only the corresponding sampling times

  Parameter estimation: SAEM algorithm in MONOLIX 4.3

  - 5 chains, initial estimates: Ψ^0

- Comparison of one-, two-,three- and five- stage designs from 100 estimated $\widehat{\Psi}_1, \widehat{\Psi}_2, \widehat{\Psi}_3, \widehat{\Psi}_5$:
  - Relative Estimation Error (REE)
  - Relative Bias (RB)
  - Relative Root Mean Squared Error (RRMSE)

Results: 1-stage vs 2-stage balanced design

- Relative Estimation Error (REE) for PK parameters Ka and CL

Ka
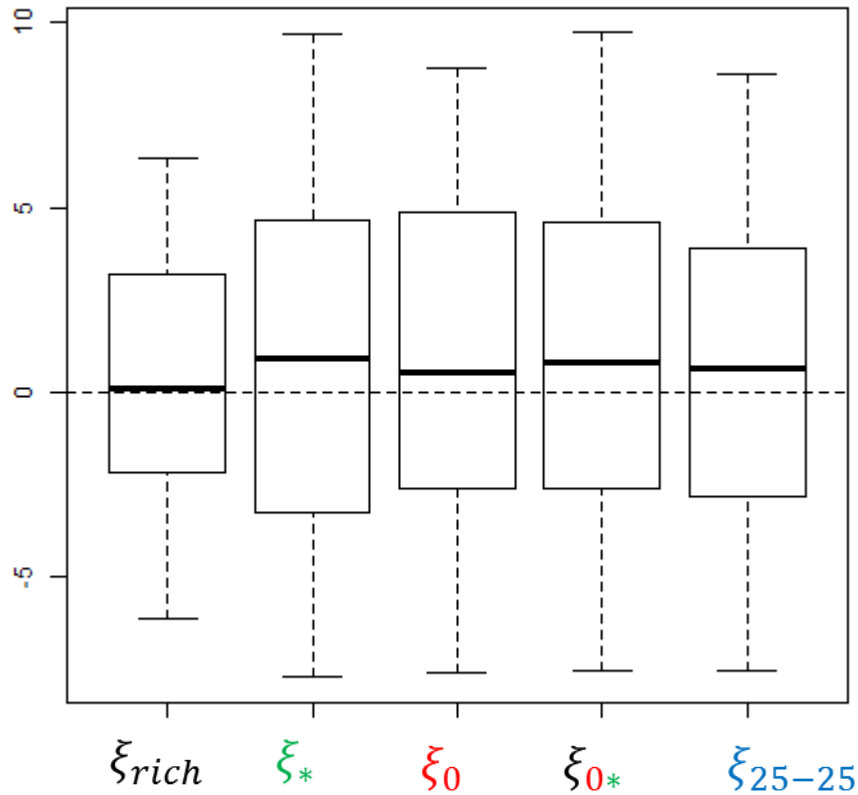
RB	0.4	0.9	1.0	1.1	0.5

CL
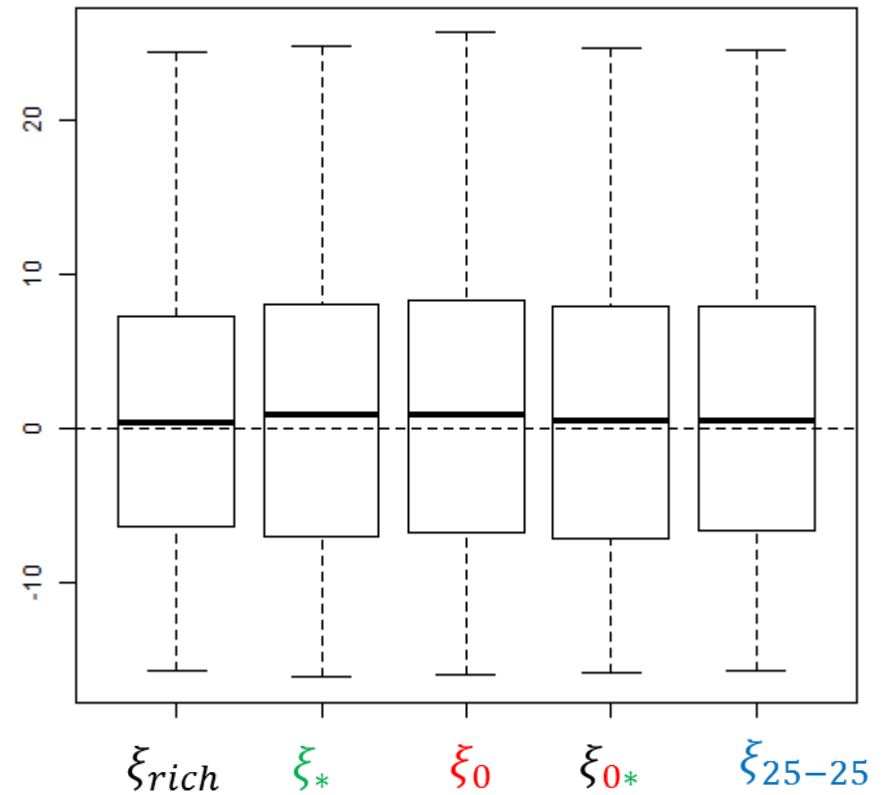
RB	1.6	1.7	1.7	1.7	1.8

Results: 1-stage vs 2-stage balanced design

- Relative Estimation Error (REE) for PD parameters Kout and IC50

Kout
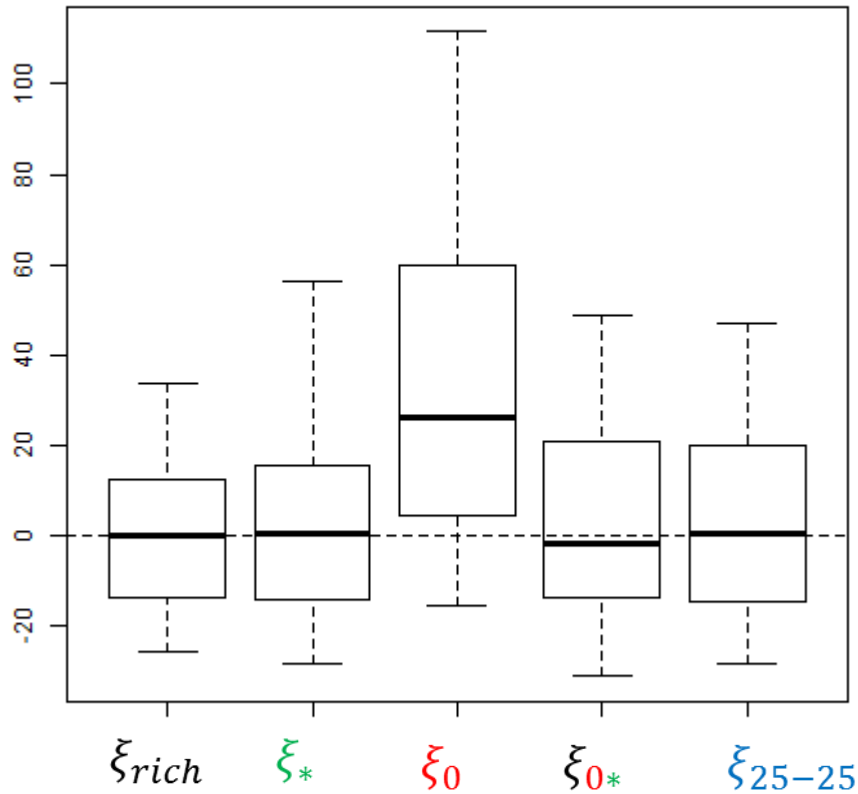
RB	0.6	2.6	**34.2**	3.2	3.7

IC50
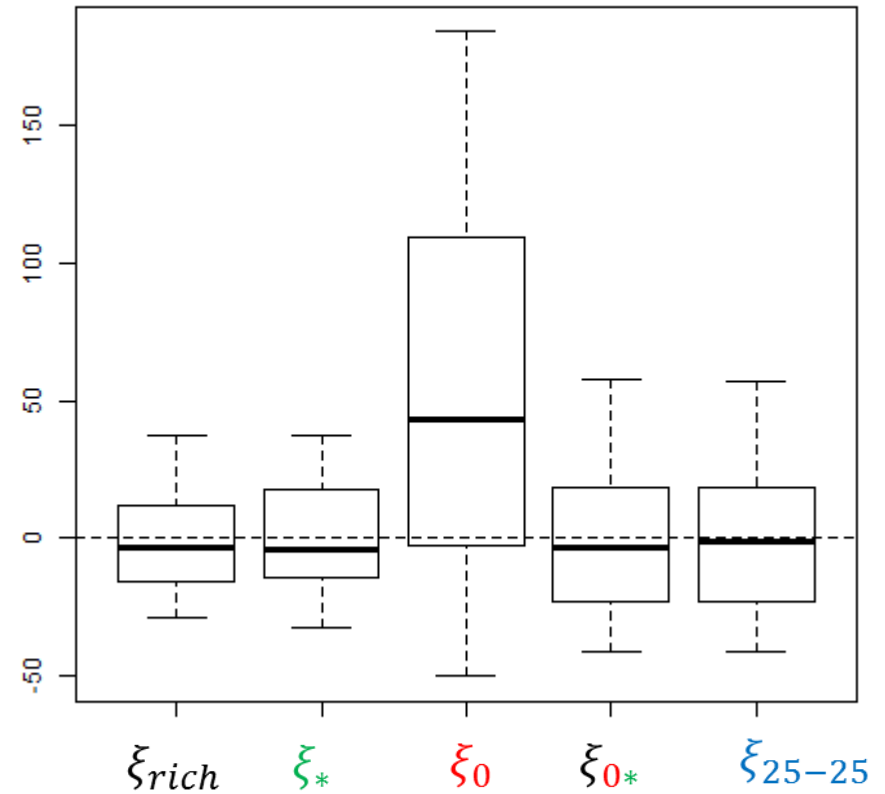
RB	-0.5	-0.3	**53.1**	0	1.5

Results: 1-stage vs 2-stage balanced design

- Relative Root Mean Squared Error (RRMSE) for PD parameters
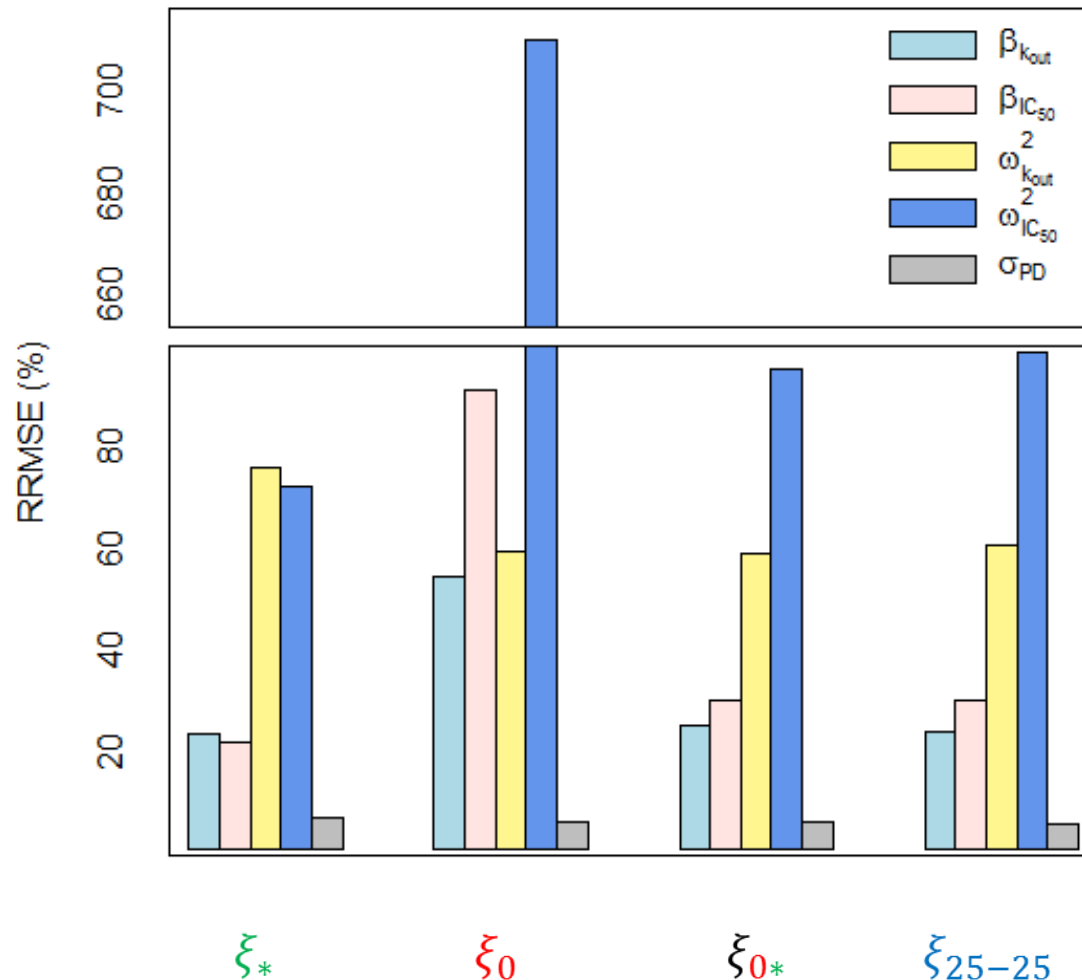
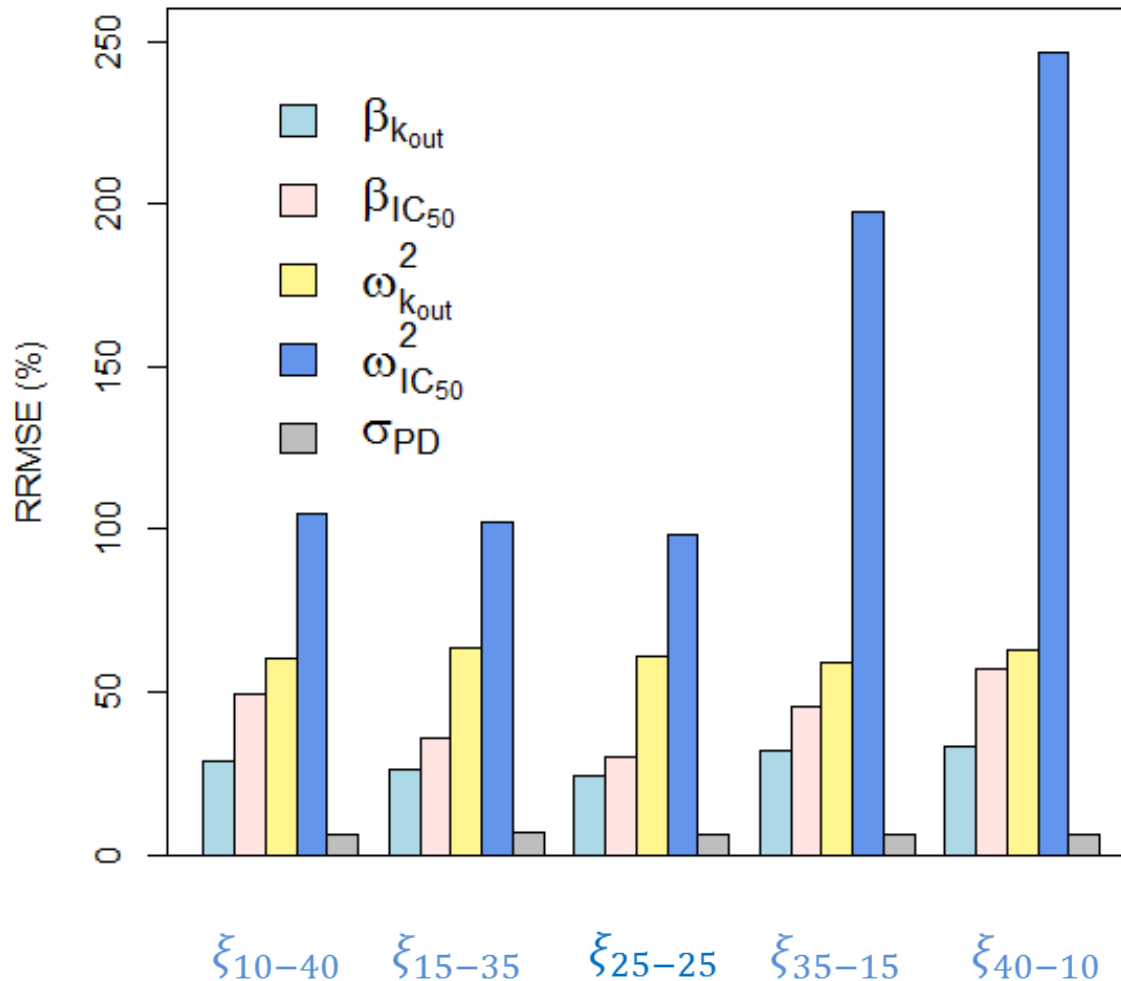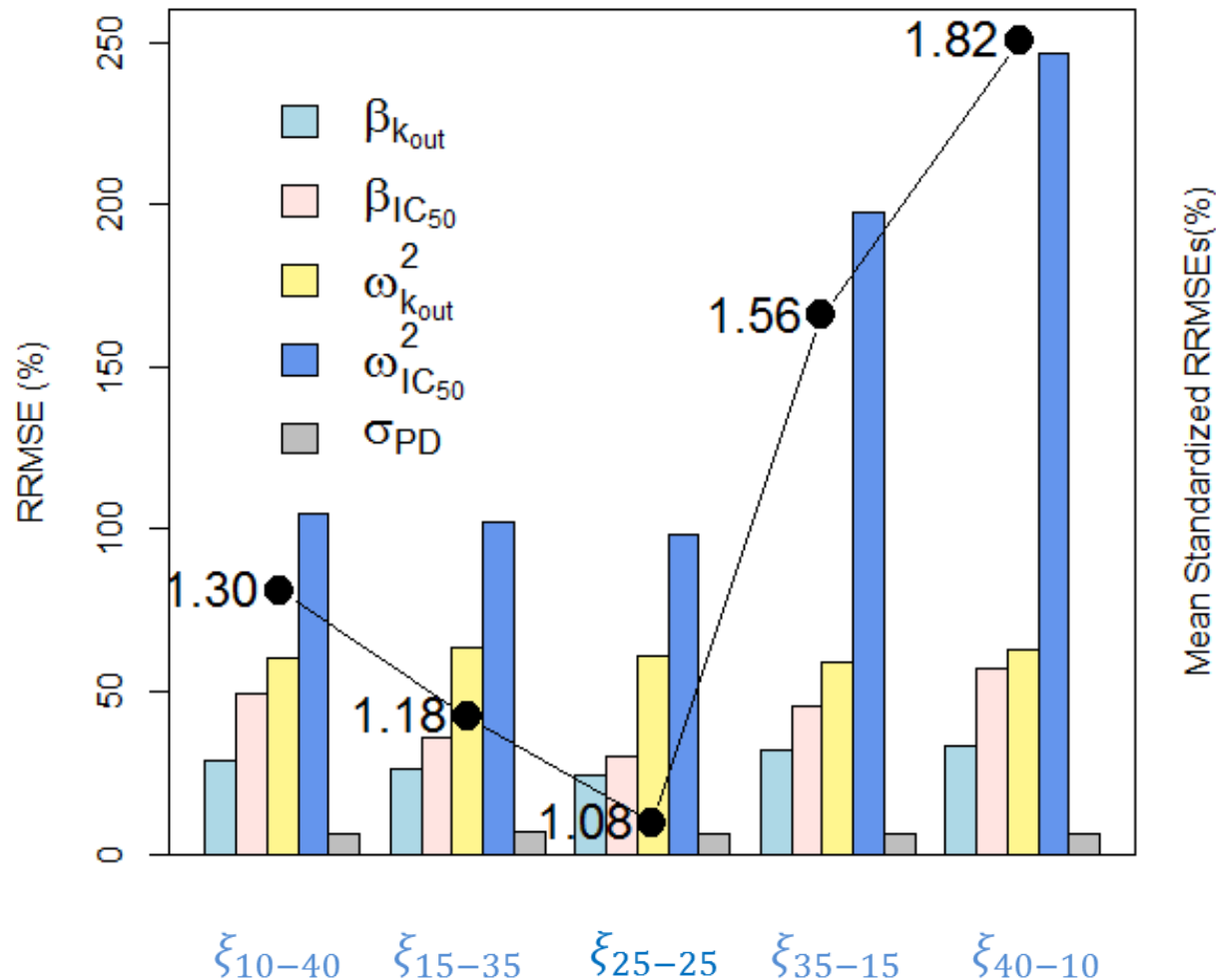# Results: 1-stage vs 2-stage balanced design

- Relative Root Mean Squared Error (RRMSE) for PD parameters
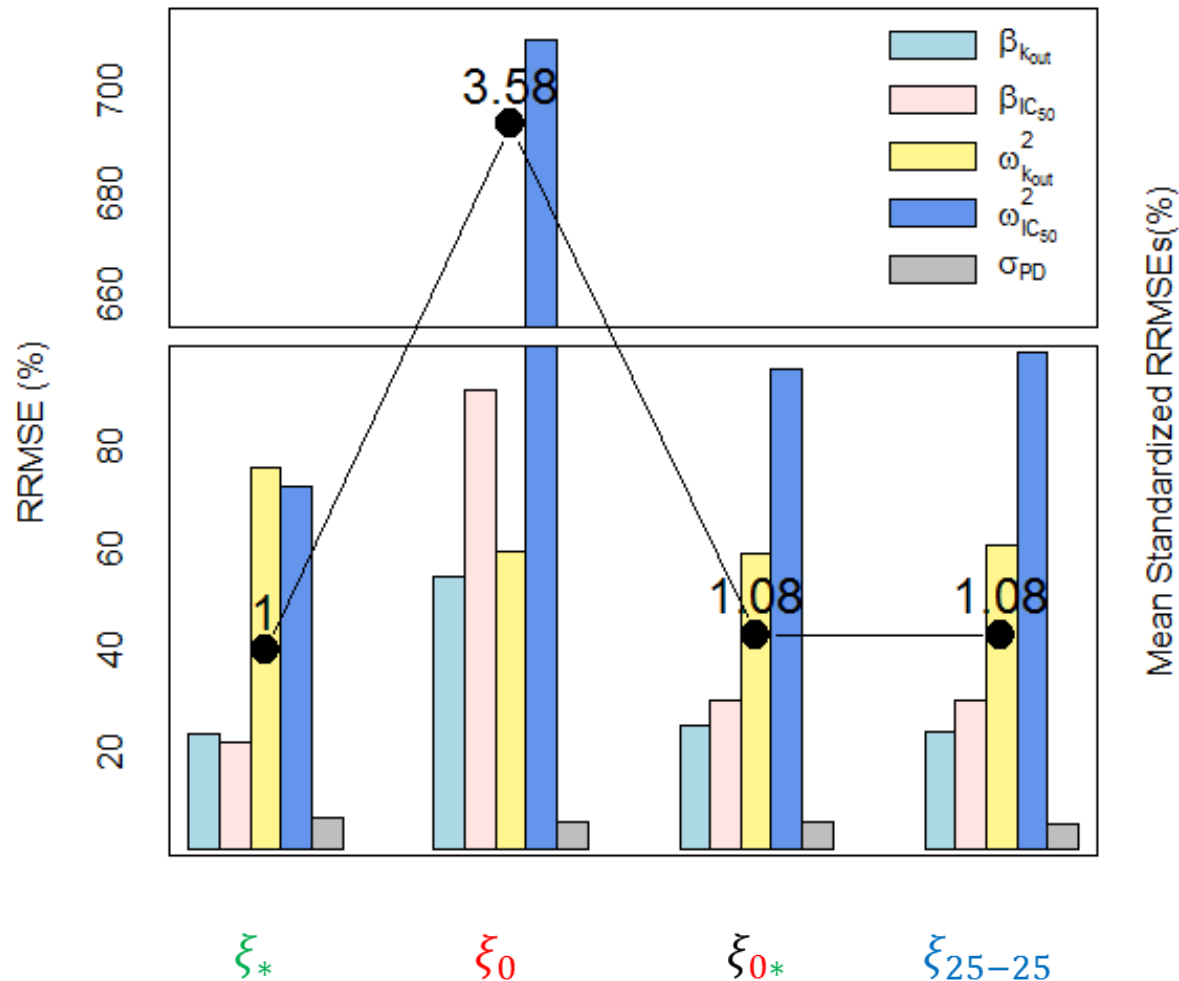
* RRMSEs standardized to ξ_* (best 1-stage design)

Results: Cohort size influence in 2-stage design

- Relative Root Mean Squared Error (RRMSE) for PD parameters
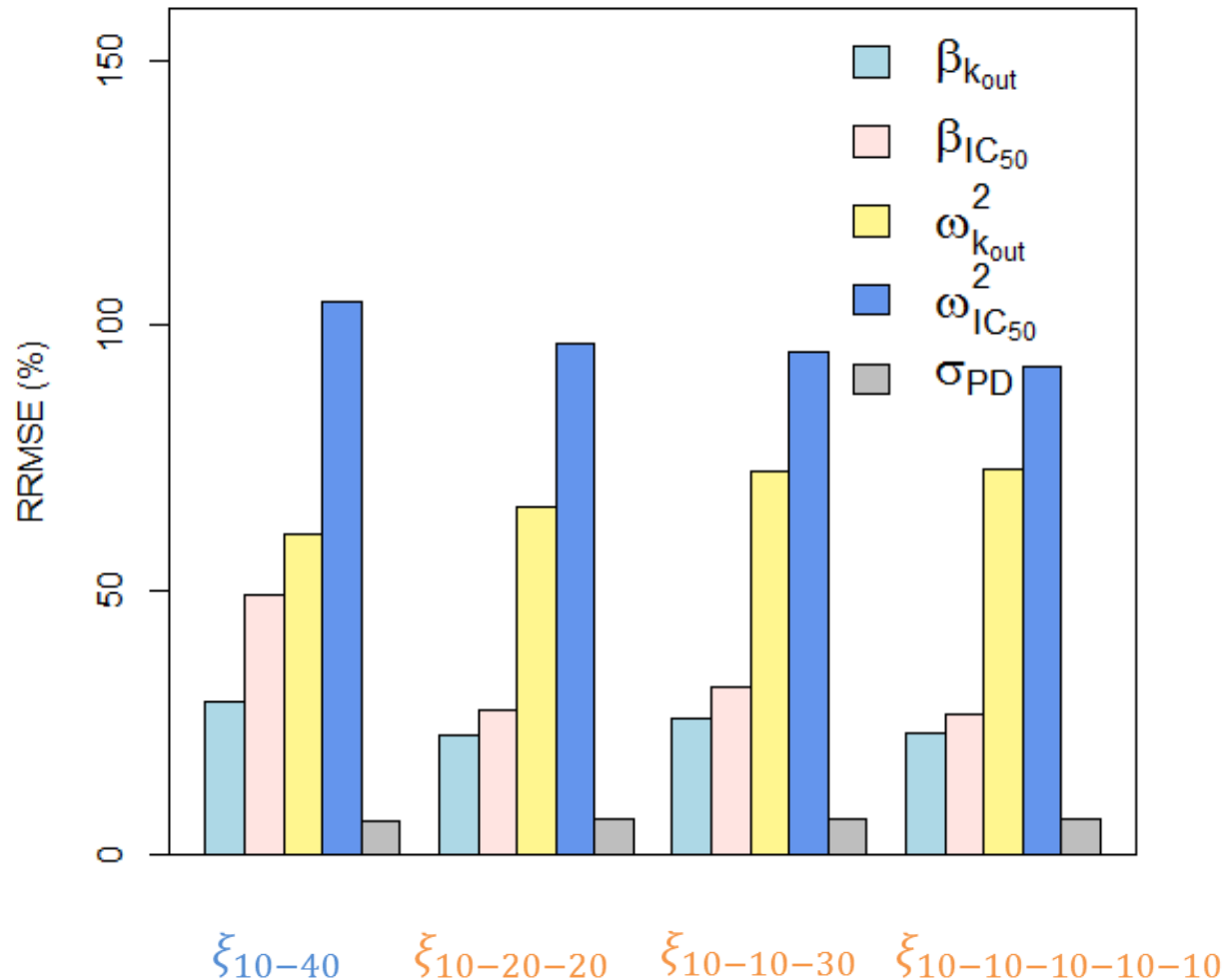
Results: Cohort size influence in 2-stage design

- Relative Root Mean Squared Error (RRMSE) for PD parameters

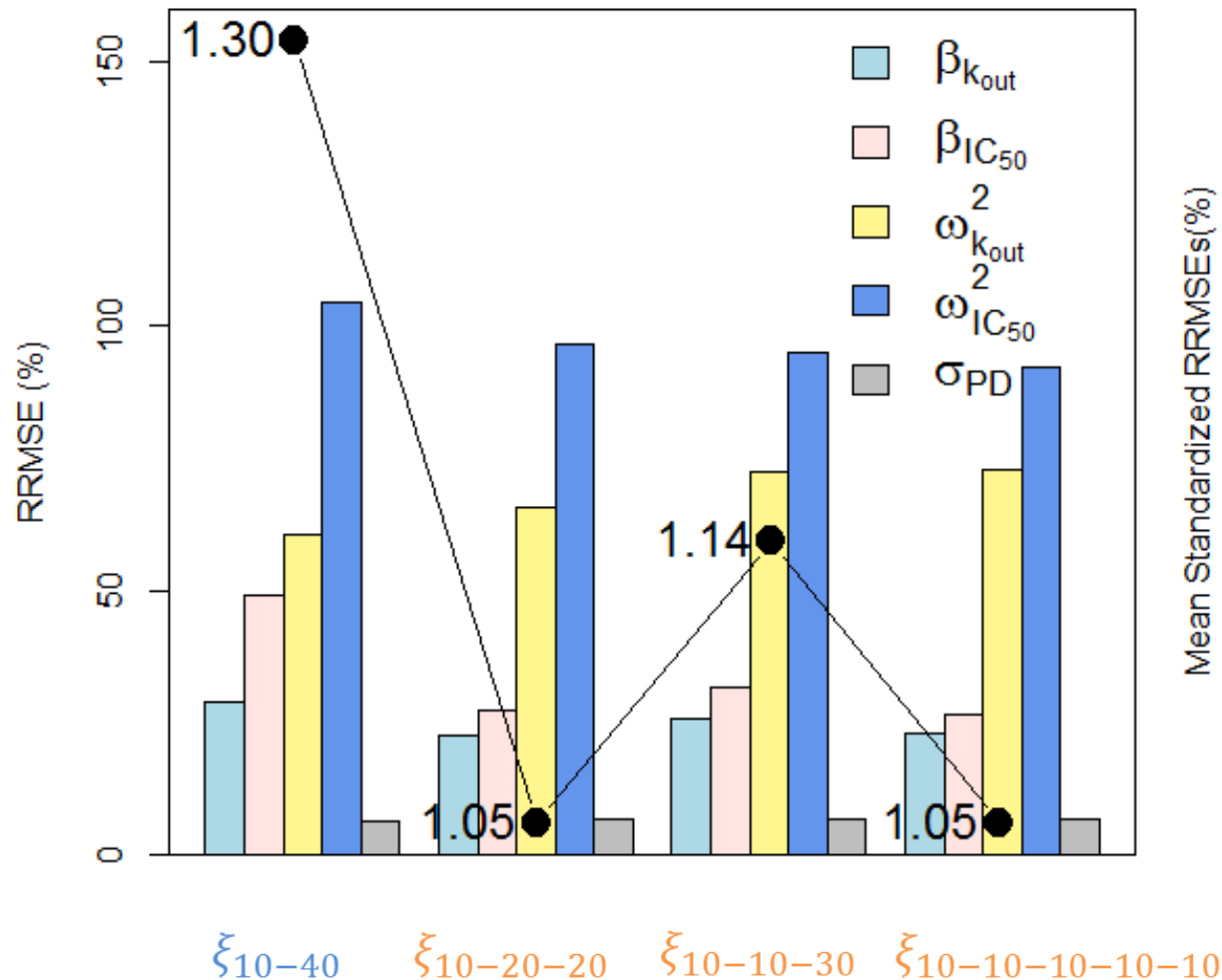* RRMSEs standardized to ξ_* (best 1-stage design)

Results: 2-stage vs 3- and 5-stage adaptive designs

- Relative Root Mean Squared Error (RRMSE) for PD parameters

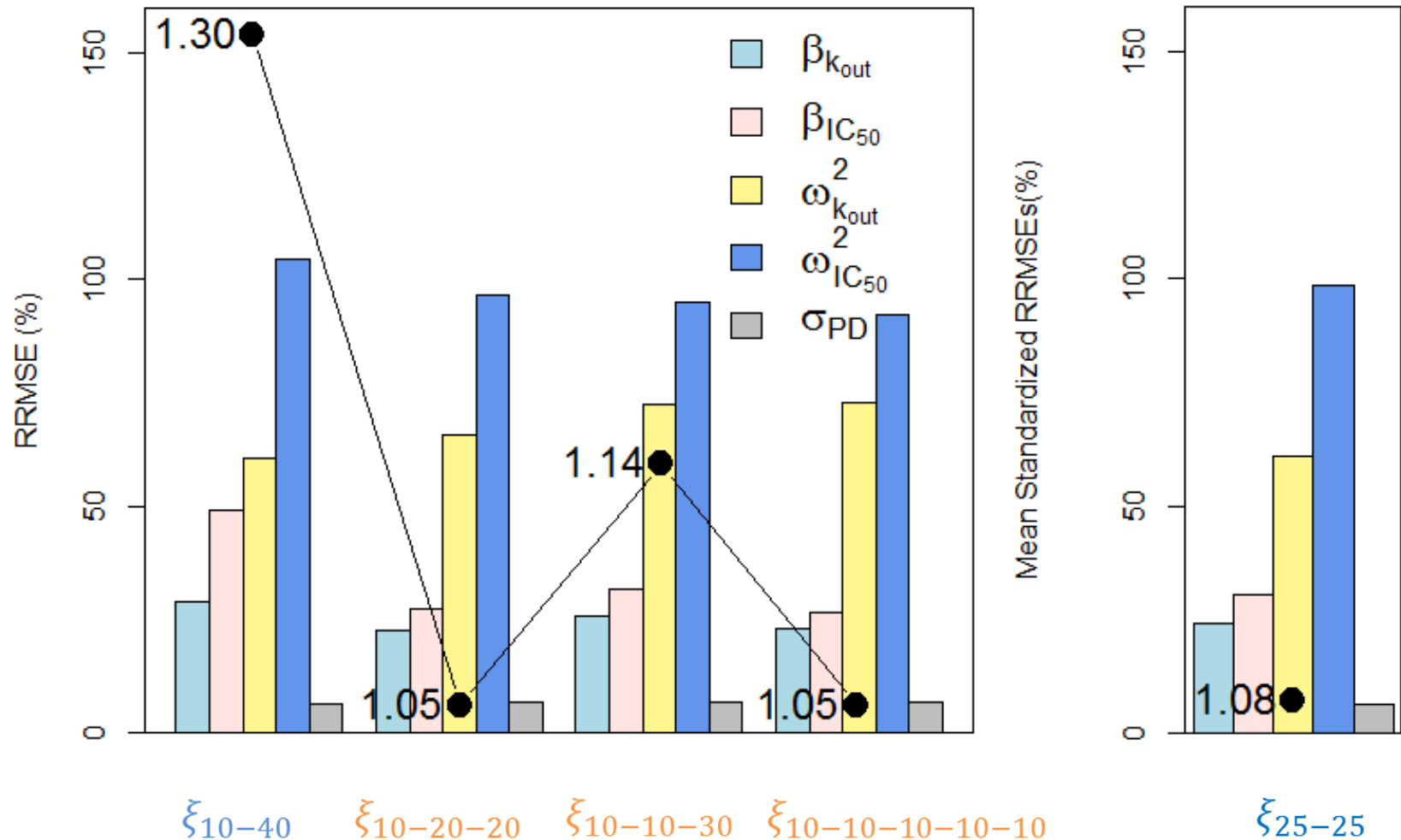# Results: 2-stage vs 3- and 5-stage adaptive designs

- Relative Root Mean Squared Error (RRMSE) for PD parameters

* RRMSEs standardized to ξ_* (best 1-stage design)

Results: 2-stage vs 3- and 5-stage adaptive designs

- Relative Root Mean Squared Error (RRMSE) for PD parameters

* RRMSEs standardized to ξ_* (best 1-stage design)

Conclusions

1. With the balanced two-stage design ξ_{25-25}
   - results are very close to those of ξ_* and are much better than those of ξ_0
2. The balanced ξ_{25-25} was the best two-stage design compared to unbalanced cohort size, especially if the second cohort was of small size
3. In case of small first cohort, more adaptive steps are needed, but these designs are more complex to implement
- Perspectives:
  - Use robust approach for first stage
  - Expand the approach for dose-finding
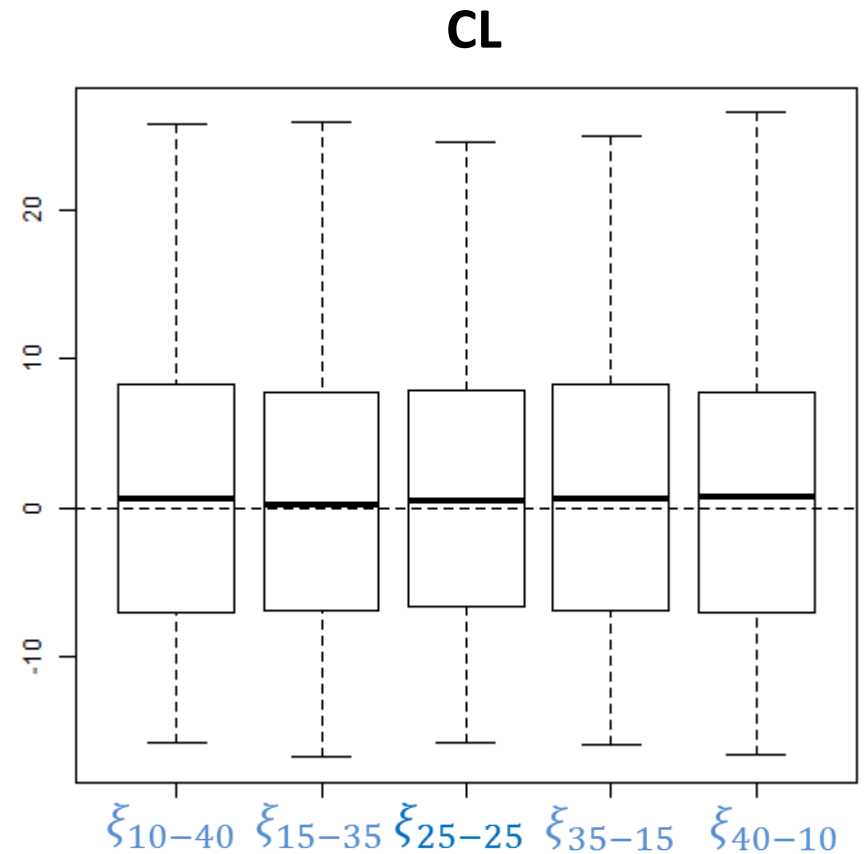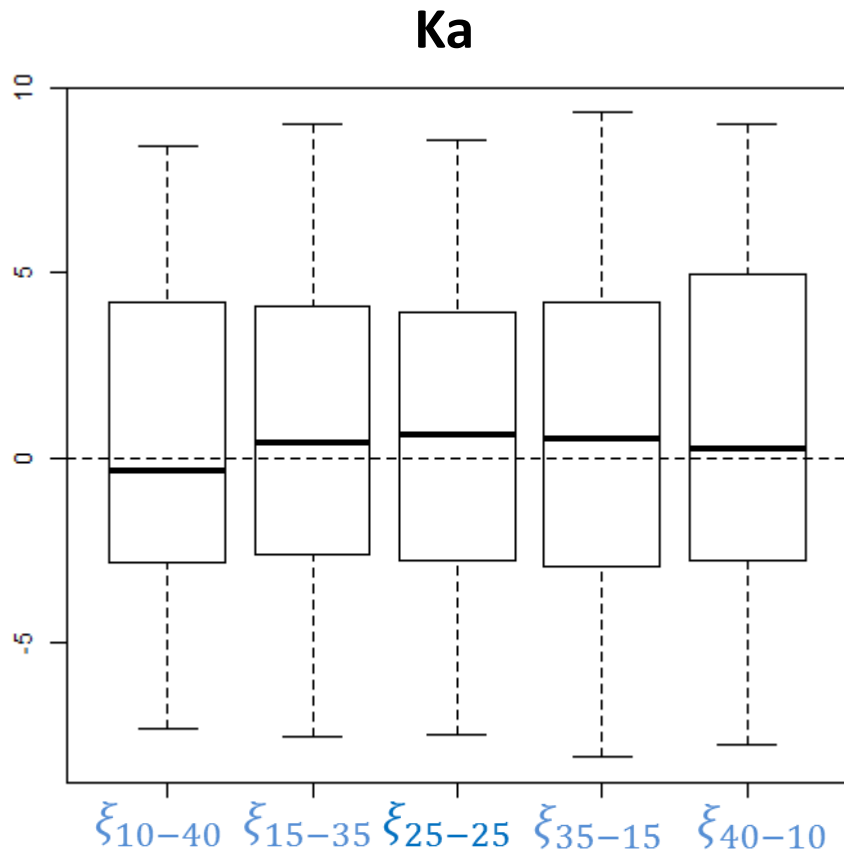 - Perform other studies

Thank you for your attention !

Back up

Results: Cohort size influence in 2-stage design

- Relative Estimation Error (REE) for PK parameters Ka and CL

Ka

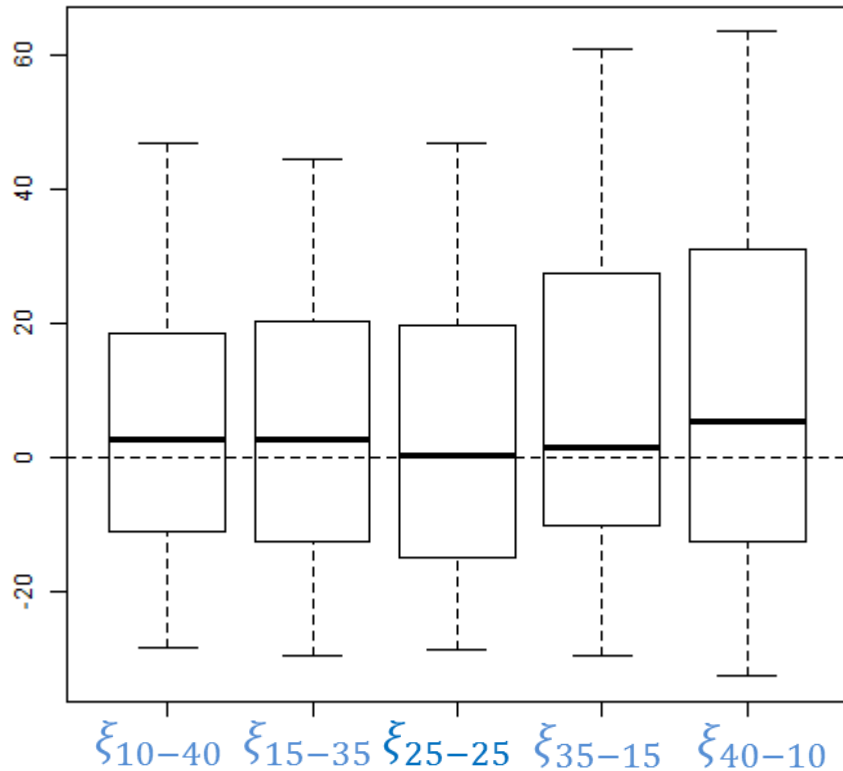| RB	0.5	0.8	0.5	0.7	0.9

CL

RB	1.7	1.7	1.8	1.8	1.8

Results: Cohort size influence in 2-stage design

- Relative Estimation Error (REE) for PD parameters Kout and IC50

Kout

RB	5.9	5.0	3.7	8.9	10.4

IC50
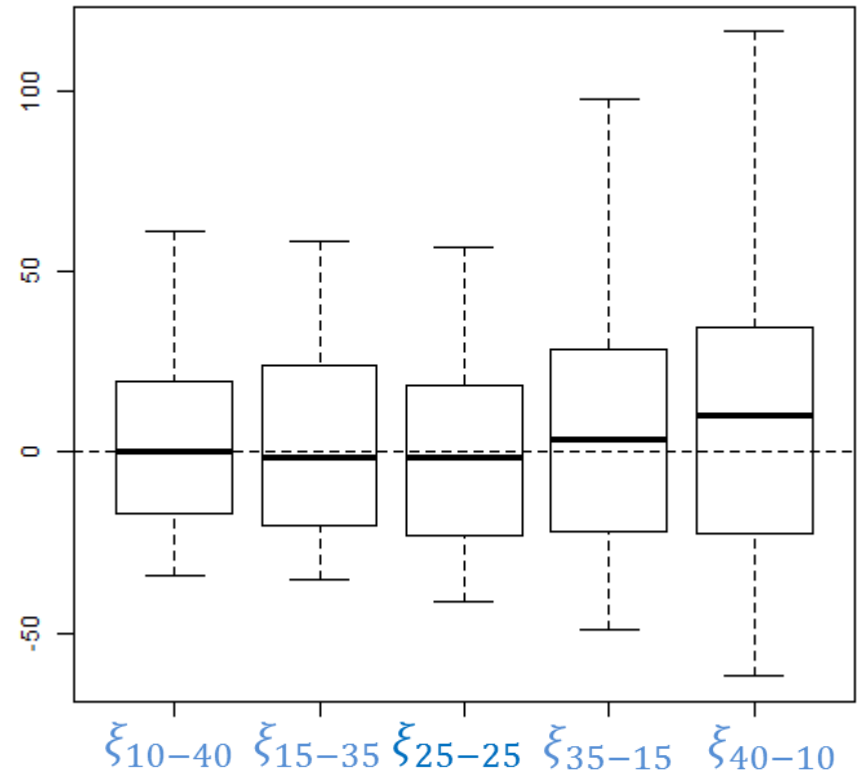
RB	8.3	5.3	1.5	8.8	12.7

Results: number of different elementary designs ($n_{designs}$) and number of datasets with $\xi = \xi_*$ ($n_{datasets}$) in two-, three- and five- stage design

Designs	2nd Stage		3rd Stage		4th Stage		5th Stage	
	$n_{designs}$	$n^*_{datasets}$	$n_{designs}$	$n^*_{datasets}$	$n_{designs}$	$n^*_{datasets}$	$n_{designs}$	$n^*_{datasets}$
Two-stage								
ξ_{10-40}	12	24						
ξ_{15-35}	8	35						
ξ_{25-25}	6	49						
ξ_{35-15}	6	47						
ξ_{40-10}	6	45						
Three-stage								
$\xi_{10-20-20}$	12	27	5	71				
$\xi_{10-10-30}$	12	28	6	61				
Five-stage								
$\xi_{10-10-10-10-10}$	12	28	7	60	4	69	4	76