Blinded Sample Size Recalculation in Longitudinal Clinical Trials Using Generalized Estimating Equations

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DIA Stat Community & PSI

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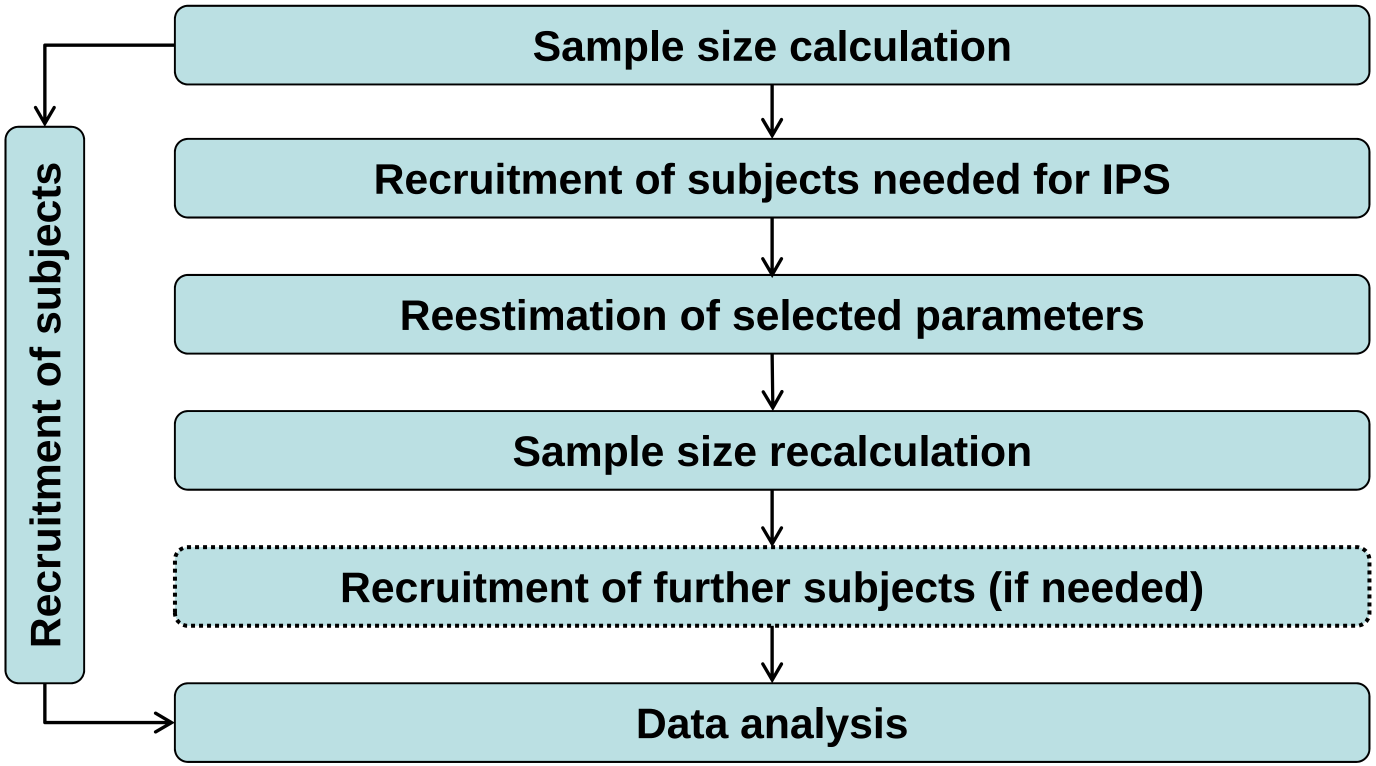
Background

- Uncertainty related to initial parameter estimates in the planning stage of clinical trials
- Increased complexity of sample size calculation in longitudinal clinical trials (intra subject correlation)
- <u>One</u> analysis approach: Generalized Estimating Equations (GEE)

- Chance to correct for initial misspecifications would be helpful
- <u>One</u> Solution: Blinded sample size recalculation with Internal Pilot Study (IPS) Design

- Primary question: Is type I/II error preserved within recalculation procedure?

Recalculation procedure (generic)



Simulation study (1)

- Investigated setting
  - Model: $$\boldsymbol{y_{ij} = \beta_1 + \beta_2 r_i + \beta_3 j + \beta_4 r_i j + \varepsilon_{ij}}$$
    - y_{ij} Continuous outcome for subject *i* at time *j*
    - β Model coefficients
    - r_i Treatment indicator of subject *i*, balanced designs investigated
    - j Measurement time *j* of a subject, *j*={1,2,3,4,5,6}
    - ε_{ij} Model error term related to measurement *j* of subject *i*
  - Two randomized treatments
  - Parallel group design
  - Balanced treatment allocation
  - Parameter of interest: β_4
  - Generalized estimating equations: ε_{ij} correlated within subjects

Simulation study (2)

- Sample size calculation
  - Formula of Jung and Ahn (2003)

$$n = \frac{\sigma^2 s_t^2 (z_{1-\alpha/2} + z_{1-\gamma})^2}{\beta_{40}^2 \mu_0^2 \sigma_r^2 \sigma_t^4}$$

$$\sigma^2 = Var(\varepsilon_{ij}). \qquad s_t^2 = \sum_{j=1}^{K} \sum_{j'=1}^{K} p_{jj'} \rho_{jj'} (t_j - \mu_1)(t_{j'} - \mu_1).$$

$$\mu_k = \mu_0^{-1} \sum_{j=1}^{K} p_j t_j^k, k = 1, 2. \qquad \mu_0 = \sum_{j=1}^{K} p_j \qquad \sigma_t^2 = \mu_2 - \mu_1^2.$$

  - Constant risk of dropout per period, only permanent dropouts
  - Correlation according to the damped exponential family of correlation structures (Munoz (1992)): $Corr(y_{ij}, y_{ij+t}) = \rho^{t^\theta}, 0 \leq \rho, \theta \leq 1$
  - Significance level: 5%, Power: 80%

Simulation study (3)

- Reestimation of selected parameters
  - Size of internal pilot study: $n_{IPS} = \pi \cdot n, 0 \leq \pi \leq 1$

  - Reestimating covariance matrix
    - Simultaneously estimate $\rho,\ \theta,\ \sigma^2$
    - Damped exponential family of correlation structures (Munoz (1992))
    - Variability of error term identical for treatment groups, subjects and measurement occasions, $Var(\varepsilon_{ij}) = Var(\varepsilon)$
    - Non-linear model
    - Starting values $\rho,\ \theta,\ \sigma^2 = 1$
    - Minimize unweighted sum of deviations between model based and empirical covariance matrix

  - Reestimating constant risk of dropout
    - Derive from rate of observed values at last measurement time
    - Assume identical risk of dropout for both treatment groups
    - $\hat{h}_{IPS} = 1 - \sqrt[5]{\hat{p}_6}$

Simulation study (4)

- Sample size recalculation
  - Use updated parameter estimates
  - Blinded procedure
  - Unrestricted design (Birkett/Day (1994))
  - $n_{total} = MAX(\pi \cdot n_{ini}, n_{recalc})$

- Analysis
  - (Weighted) GEE (Robins/Rotnitzky (1995))
  - Inverse probability weighting, weights only differ between measurement times
  - Working correlation matrix = Independent (Mancl/Leroux (1996), Ziegler/Vens (2010))
  - Test $\beta_4 = 0$, one-sided significance level 2.5%

- Simulations based on 10.000 samples under H_0 and H_a

Scenarios

Scen.	ρ	θ	σ^2	h	π	n	n_{IPS}
1	0.25	0.5	1	0.00	0.5	203	102
2	0.25	0.5	1	0.00	0.2	203	41
3	0.25	0.5	1	0.00	0.8	203	162
4	0.7	0.1	1	0.00	0.5	67	34
5	0.7	1	1	0.00	0.5	223	112
6	0.25	0.5	5	0.00	0.5	1015	508
7	0.1	0.1	1	0.00	0.5	172	86
8	0.1	0.9	1	0.00	0.5	197	98
9	0.25	0.5	1	0.01	0.2	208	42
10	0.25	0.5	1	0.05	0.2	231	46
11	0.25	0.5	1	0.01	0.8	208	166
12	0.25	0.5	1	0.05	0.8	231	185

Results (1)

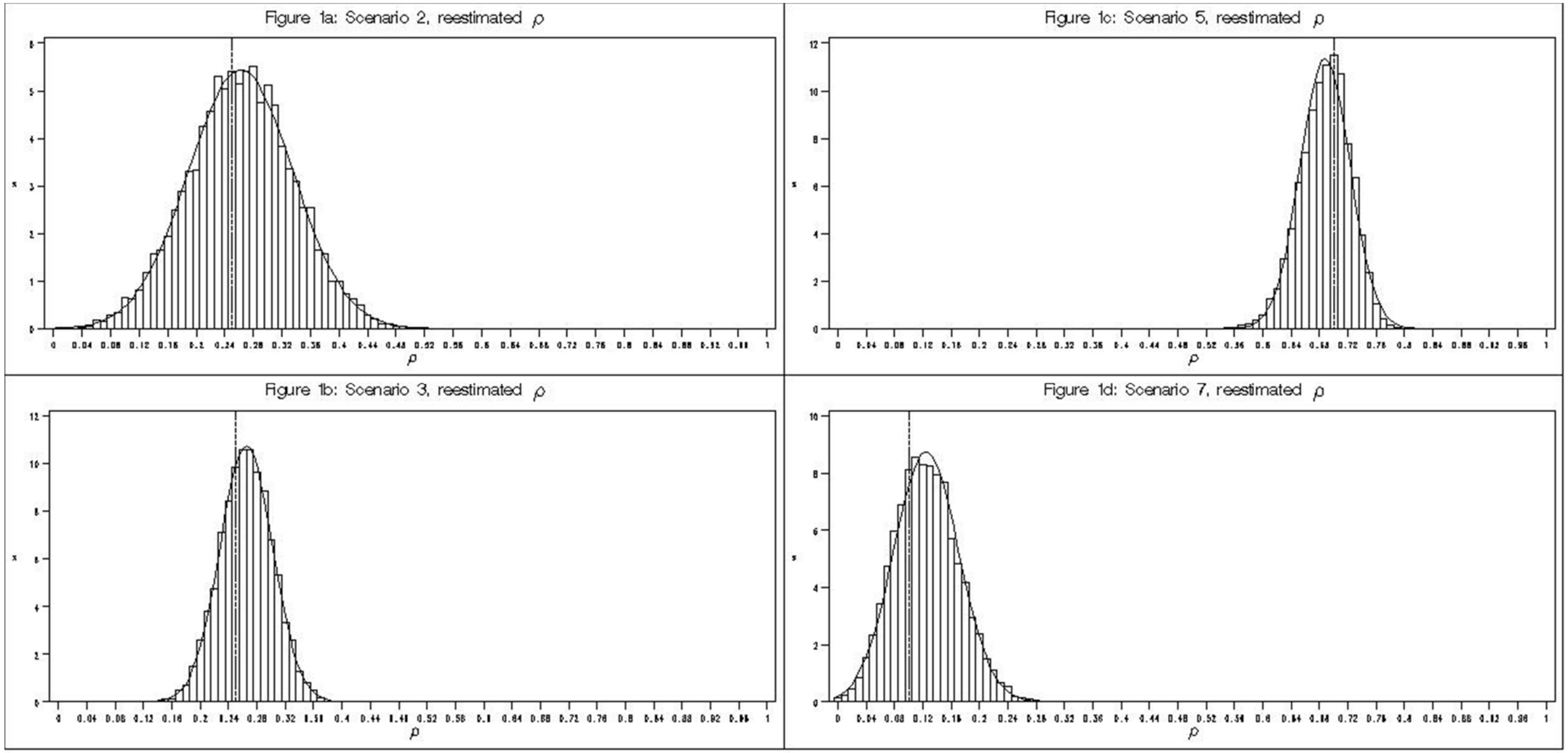


Figure 1a: Scenario 2, reestimated ρ
Figure 1c: Scenario 5, reestimated ρ
Figure 1b: Scenario 3, reestimated ρ
Figure 1d: Scenario 7, reestimated ρ
ρ

Results (2)

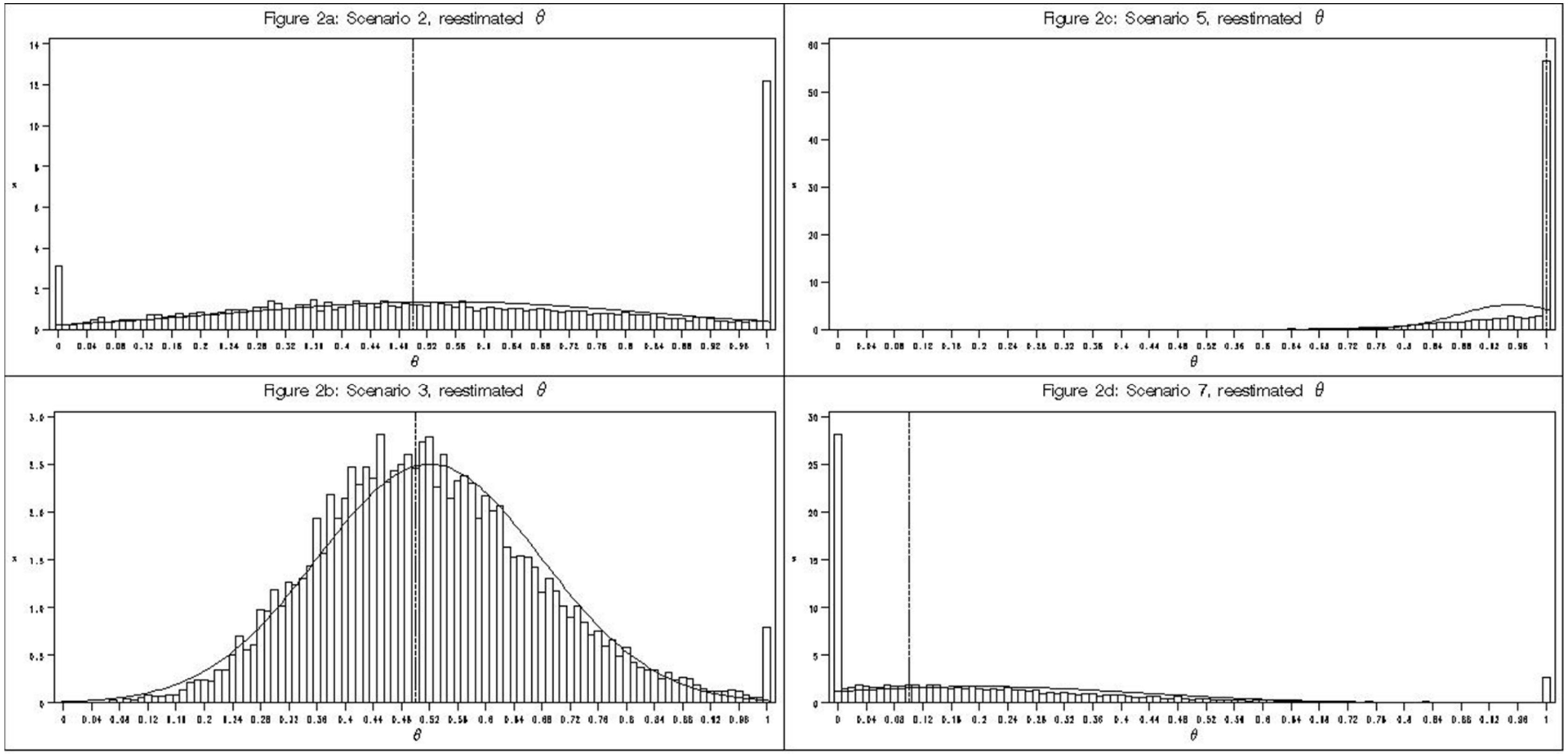


Figure 2a: Scenario 2, reestimated θ
Figure 2c: Scenario 5, reestimated θ
Figure 2b: Scenario 3, reestimated θ
Figure 2d: Scenario 7, reestimated θ
θ

Illustration of results of θ estimates

- $$\rho_{ij} = \begin{pmatrix} 1 & 0.5 & 0.5 & 0.5 \\ 0.5 & 1 & 0.5 & 0.5 \\ 0.5 & 0.5 & 1 & 0.5 \\ 0.5 & 0.5 & 0.5 & 1 \end{pmatrix}, \rho = 0.5, \theta = 0$$

- $$\rho_{ij} = \begin{pmatrix} 1 & 0.5 & 0.375 & 0.301 \\ 0.5 & 1 & 0.5 & 0.375 \\ 0.375 & 0.5 & 1 & 0.5 \\ 0.301 & 0.375 & 0.5 & 1 \end{pmatrix}, \rho = 0.5, \theta = 0.5$$

- $$\rho_{ij} = \begin{pmatrix} 1 & 0.5 & 0.25 & 0.125 \\ 0.5 & 1 & 0.5 & 0.25 \\ 0.25 & 0.5 & 1 & 0.5 \\ 0.125 & 0.25 & 0.5 & 1 \end{pmatrix}, \rho = 0.5, \theta = 1$$

Results (3)

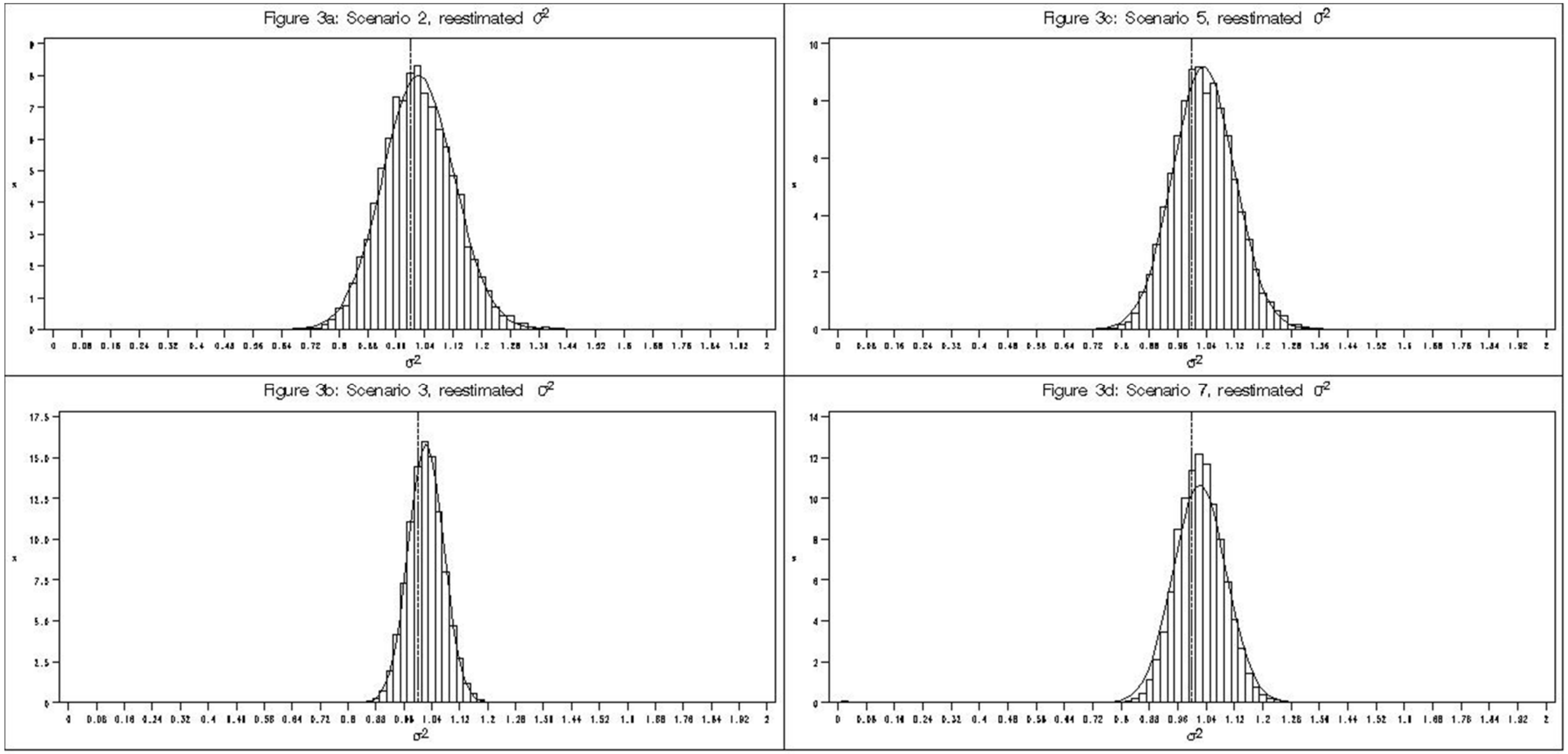


Figure 3a: Scenario 2, reestimated σ^2
Figure 3c: Scenario 5, reestimated σ^2
Figure 3b: Scenario 3, reestimated σ^2
Figure 3d: Scenario 7, reestimated σ^2
σ^2

Results (4)

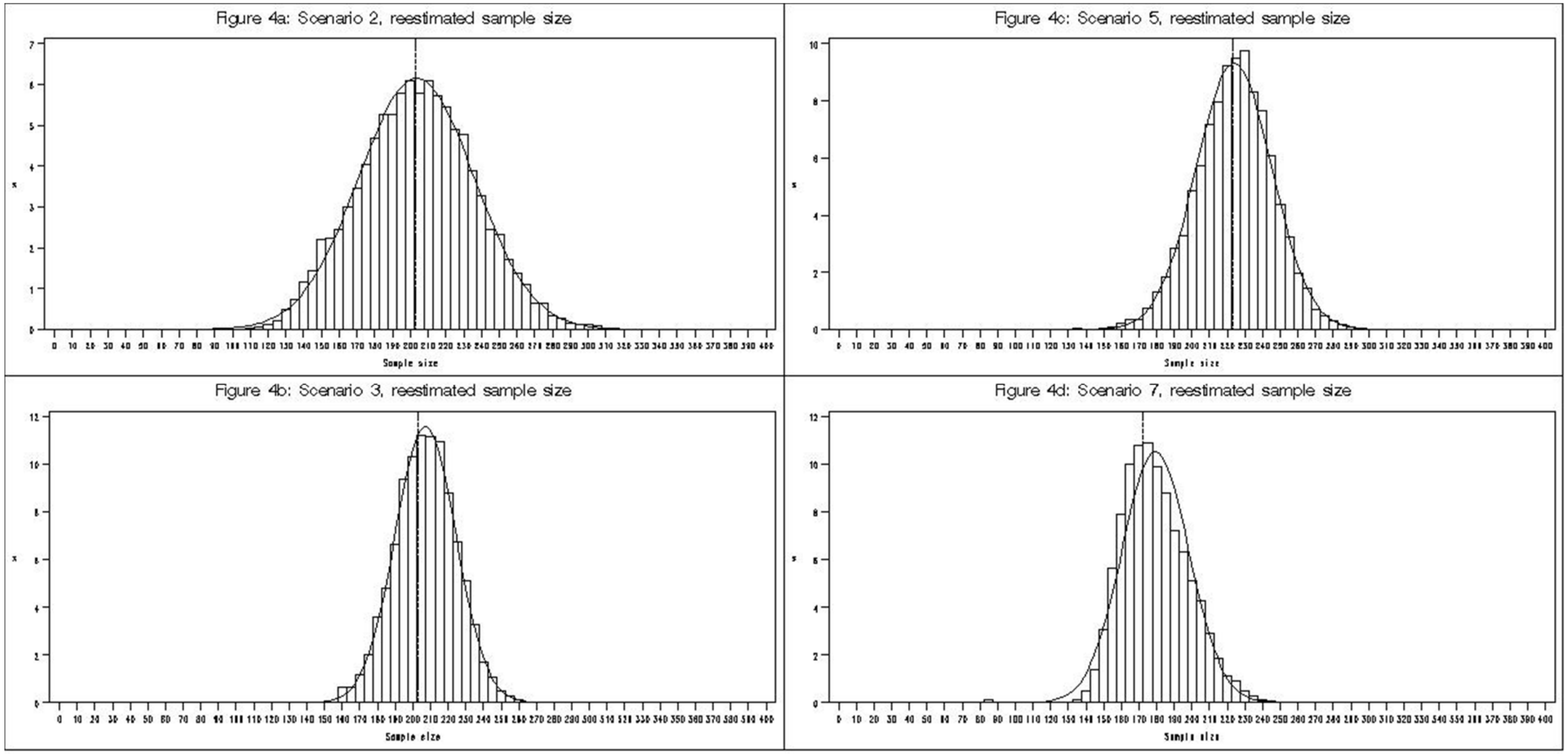


Figure 4a: Scenario 2, reestimated sample size
Figure 4c: Scenario 5, reestimated sample size
Figure 4b: Scenario 3, reestimated sample size
Figure 4d: Scenario 7, reestimated sample size
Sample size

Results (5)

Scenario	n	n_{IPS}	α_{FIXED}	$(1-\gamma)_{FIXED}$	α_{IPS}	$(1-\gamma)_{IPS}$
1	203	102	2.37	80.34	2.70	80.61
2	203	41	2.87	80.42	2.56	79.20
3	203	162	2.51	80.20	2.49	80.69
4	67	34	2.73	79.93	3.19	82.66
5	223	112	2.67	79.90	2.78	79.90
6	1015	508	2.54	80.36	2.38	79.88
7	172	86	2.54	80.68	2.53	81.23
8	197	98	2.55	80.15	2.54	79.49
9	208	42	2.86	79.88	2.64	79.10
10	231	46	2.57	80.09	2.34	79.37
11	208	166	2.60	80.50	2.66	81.03
12	231	185	2.86	80.01	2.75	80.52

Summary

- Mostly unbiased estimation of ρ, σ^2
- Estimation of θ associated with high variability and risk of bias
- Sample size on average near (slightly above) the fixed sample size results
- Results confirmed in the presence of missing data
- Impact of IPS size on estimates and resulting sample size distribution
- Type I error mostly very near to nominal value
- Robust power results
- Few limitations
  - Starting values for reestimating covariance parameters
  - Bound effects / biased estimates can be anticipated by simulating extreme scenarios
  - Simplified assumptions for investigated setting