FRAMEWORK FOR TIMING INTERIM ANALYSES IN LONGITUDINAL TRIALS WITH MISSING DATA: THE ROLE OF BLINDING AND SAMPLE SIZE

NEŽA DVORŠAK [1], CHRISTOPHER JENNISON [1], ROBIN MITRA [2], JIANMEI WANG [3], THOMAS BURNETT [1],
[1] UNIVERSITY OF BATH, [2] UNIVERSITY COLLEGE LONDON, [3] ROCHE UK

TIMING INTERIM ANALYSES IN LONGITUDINAL TRIALS

- Planned using an **information fraction**

UNIVERSITY OF BATH

TIMING INTERIM ANALYSES IN LONGITUDINAL TRIALS

- Planned using an **information fraction**
- Outcomes repeatedly measured over time

TIMING INTERIM ANALYSES IN LONGITUDINAL TRIALS

- Planned using an **information fraction**
- Outcomes repeatedly measured over time
- Challenge of **missing data**

TIMING INTERIM ANALYSES IN LONGITUDINAL TRIALS

- Planned using an **information fraction**
- Outcomes repeatedly measured over time
- Challenge of **missing data**
- Our framework

FRAMEWORK

Missing data patterns

FRAMEWORK

Missing data patterns

Pattern	Visit 1	Visit 2
1	✓	✓
2	✗	✓
3	✓	✗

FRAMEWORK

Missing data patterns

Pattern	Visit 1	Visit 2
1	$\bar{X}_{11}$	$\bar{X}_{12}$
2	$Missing$	$\bar{X}_{22}$
3	$\bar{X}_{31}$	$Missing$

Row groups: n_1 (pattern 1), n_2 (pattern 2), n_3 (pattern 3)

Column means: μ_1 (Visit 1), μ_2 (Visit 2)

UNIVERSITY OF BATH

FRAMEWORK

Missing data patterns

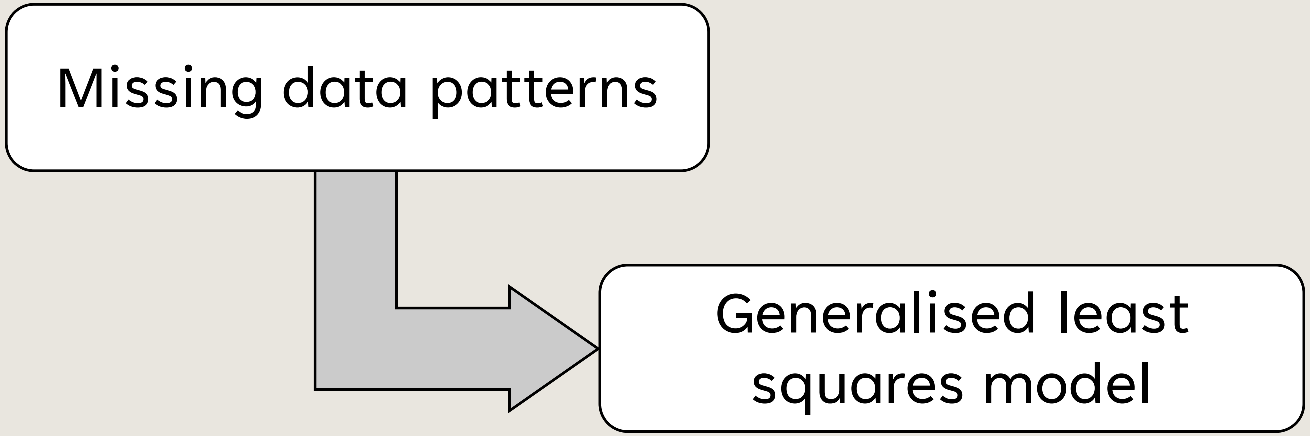
Pattern	Visit 1	Visit 2	
1	$\bar{X}_{11}$	$\bar{X}_{12}$	n_1
2	*Missing*	$\bar{X}_{22}$	n_2
3	$\bar{X}_{31}$	*Missing*	n_3
	μ_1	μ_2	

$$(\bar{X}_{11}, \bar{X}_{12}) \sim N\left(\begin{bmatrix}\mu_1 \\ \mu_2\end{bmatrix}, \frac{\sigma^2}{n_1}\begin{bmatrix}1 & \rho^2 \\ \rho^2 & 1\end{bmatrix}\right)$$

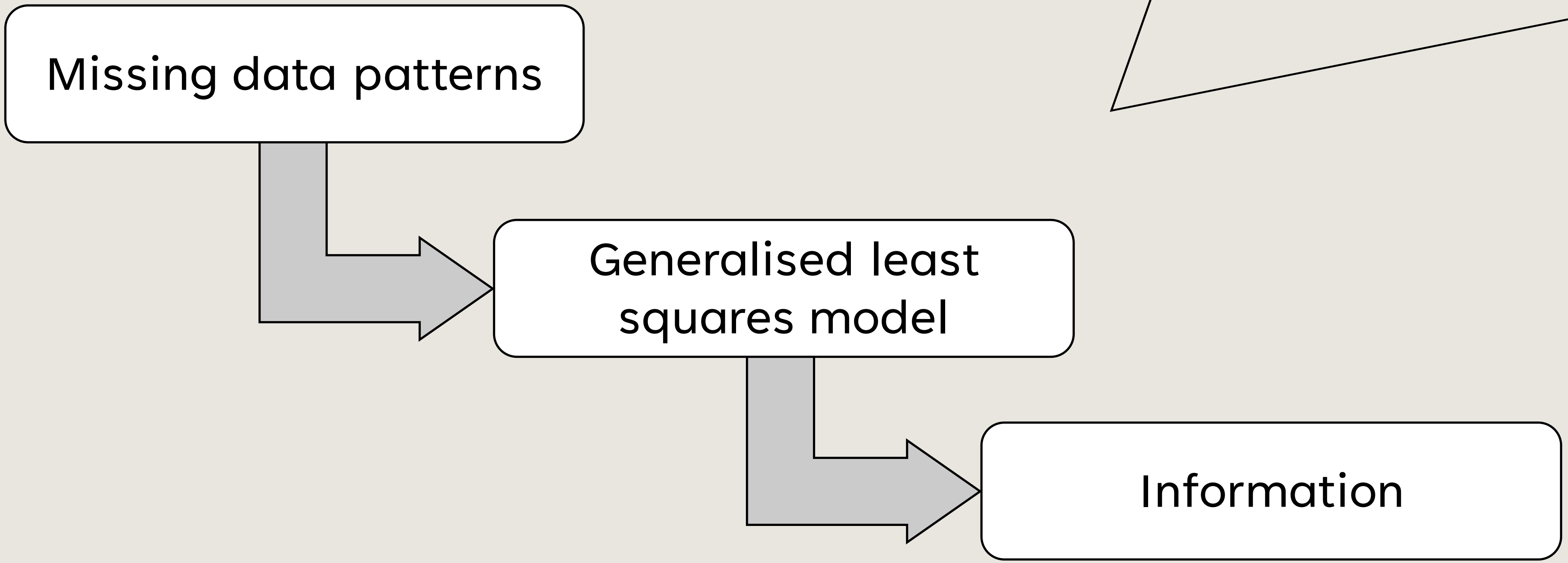
$$\bar{X}_{22} \sim N\left(\mu_2, \frac{\sigma^2}{n_2}\right)$$

$$\bar{X}_{31} \sim N\left(\mu_1, \frac{\sigma^2}{n_3}\right)$$

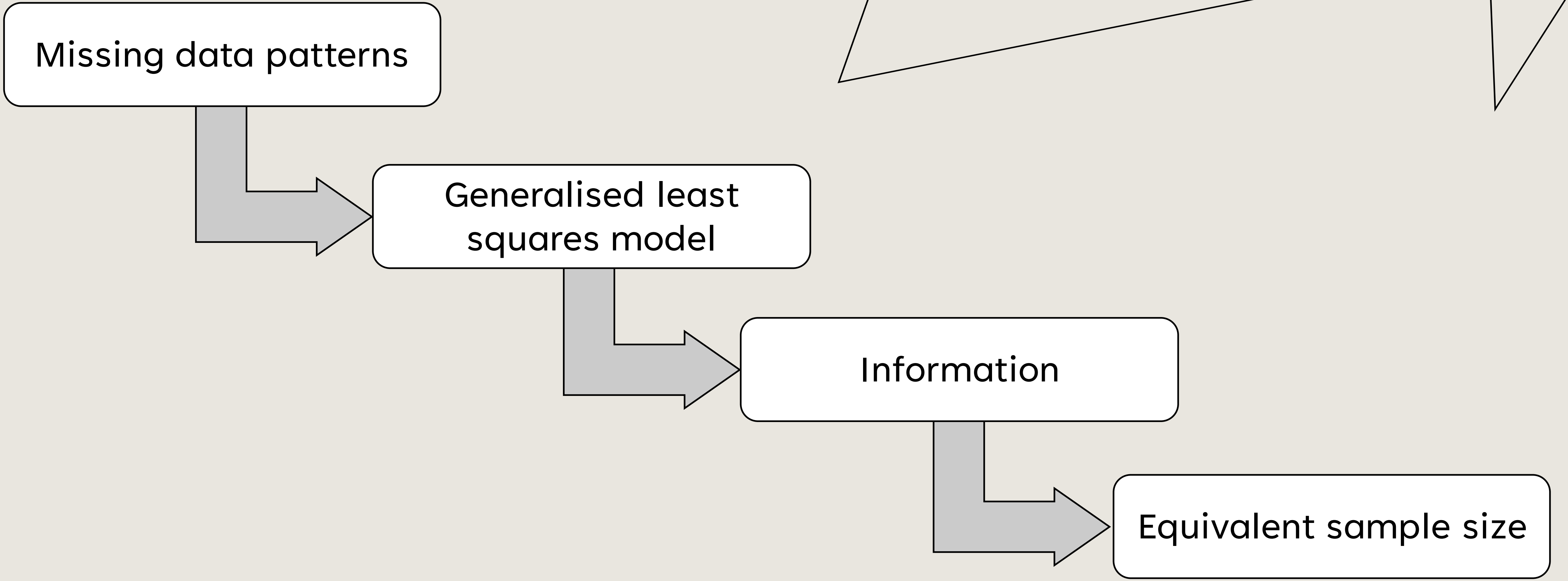
FRAMEWORK



FRAMEWORK


Missing data patterns
Generalised least squares model
Information

FRAMEWORK


Missing data patterns
Generalised least squares model
Information
Equivalent sample size

EQUIVALENT SAMPLE SIZE (EqSS)

Pattern	Visit 1	Visit 2
1	✓	✓
2	✗	✓
3	✓	✗

Complete patients only (Pattern 1):

$$I(\hat{\mu}_2) = \frac{n}{\sigma^2}$$

n ... total sample size

EQUIVALENT SAMPLE SIZE (EqSS)

Pattern	Visit 1	Visit 2
1	✓	✓
2	✗	✓
3	✓	✗

Complete patients only (Pattern 1):

$$I(\hat{\mu}_2) = \frac{n}{\sigma^2}$$

n ... total sample size

EQUIVALENT SAMPLE SIZE (EqSS)

Pattern	Visit 1	Visit 2
1	✓	✓
2	✗	✓
3	✓	✗

Complete patients only (Pattern 1):

$$I(\hat{\mu}_2) = \frac{n}{\sigma^2}$$

n ... total sample size

With partially observed patients:

$$I(\hat{\mu}_2) = \frac{\dfrac{n_1(n_1 + n_2 + n_3) + n_2 n_3 (1 - \rho^2)}{n_1 + n_3(1 - \rho^2)}}{\sigma^2}$$

n_1 ... number of Pattern 1 individuals
n_2 ... number of Pattern 2 individuals
n_3 ... number of Pattern 3 individuals

UNIVERSITY OF BATH

EQUIVALENT SAMPLE SIZE (EqSS)

Pattern	Visit 1	Visit 2
1	✓	✓
2	✗	✓
3	✓	✗

Complete patients only (Pattern 1):

$$I(\hat{\mu}_2) = \frac{n}{\sigma^2}$$

n … total sample size

With partially observed patients:

$$I(\hat{\mu}_2) = \frac{\frac{n_1(n_1 + n_2 + n_3) + n_2 n_3(1 - \rho^2)}{n_1 + n_3(1 - \rho^2)}}{\sigma^2}$$

n_1 … number of Pattern 1 individuals
n_2 … number of Pattern 2 individuals
n_3 … number of Pattern 3 individuals

EQUIVALENT SAMPLE SIZE (EqSS)

Pattern	Visit 1	Visit 2
1	✓	✓
2	✗	✓
3	✓	✗

Complete patients only (Pattern 1):

$$I(\hat{\mu}_2) = \frac{n}{\sigma^2}$$

n ... total sample size

With partially observed patients:

$$I(\hat{\mu}_2) = \frac{\frac{n_1(n_1 + n_2 + n_3) + n_2 n_3 (1 - \rho^2)}{n_1 + n_3(1 - \rho^2)}}{\sigma^2}$$

n_1 ... number of Pattern 1 individuals
n_2 ... number of Pattern 2 individuals
n_3 ... number of Pattern 3 individuals

How many fully observed individuals are the partially observed individuals equivalent to?

UNIVERSITY OF BATH

EQUIVALENT SAMPLE SIZE (EqSS)

Pattern	Visit 1	Visit 2
1	✓	✓
2	✗	✓
3	✓	✗

Complete patients only (Pattern 1):

$$I(\hat{\mu}_2) = \frac{n}{\sigma^2}$$

n ... total sample size

With partially observed patients:

$$I(\hat{\mu}_2) = \frac{\frac{n_1(n_1 + n_2 + n_3) + n_2 n_3 (1-\rho^2)}{n_1 + n_3(1-\rho^2)}}{\sigma^2}$$

n_1 ... number of Pattern 1 individuals

n_2 ... number of Pattern 2 individuals

n_3 ... number of Pattern 3 individuals

How many fully observed individuals are the partially observed individuals equivalent to?

Approximation as $n_1 \gg n_3$:

$$\frac{n_1(n_1 + n_2 + n_3) + n_2 n_3 (1-\rho^2)}{n_1 + n_3(1-\rho^2)} \approx n_1 + n_2 + \rho^2 n_3$$

TIMING OF THE INTERIM ANALYSIS

- Based on information fraction (IF), determined by equivalent sample size (EqSS)

$$\boldsymbol{IF} = \frac{interim\ information}{final\ information} = \frac{\frac{interim\ EqSS}{\sigma^2}}{\frac{final\ EqSS}{\sigma^2}} = \frac{\boldsymbol{interim\ EqSS}}{\boldsymbol{final\ EqSS}}$$

EQUIVALENT SAMPLE SIZE

UNIVERSITY OF BATH

EQUIVALENT SAMPLE SIZE

NUMBER OF PATIENTS WITH EACH MISSING DATA PATTERN

EQUIVALENT SAMPLE SIZE

NUMBER OF PATIENTS WITH

EACH MISSING DATA PATTERN

+

ESTIMATE CORRELATION

EQUIVALENT SAMPLE SIZE

NUMBER OF PATIENTS WITH

EACH MISSING DATA PATTERN

+

ESTIMATE CORRELATION

↓

USE THE FRAMEWORK

ROLE OF BLINDING

NUMBER OF PATIENTS WITH
EACH MISSING DATA PATTERN

+

ESTIMATE CORRELATION

↓

USE THE FRAMEWORK

UNIVERSITY OF BATH

NUMBER OF PATIENTS WITH
EACH MISSING DATA PATTERN

+

ESTIMATE CORRELATION

↓

USE THE FRAMEWORK

UNIVERSITY OF BATH

NUMBER OF PATIENTS WITH

EACH MISSING DATA PATTERN

+

ESTIMATE CORRELATION ?

↓

USE THE FRAMEWORK

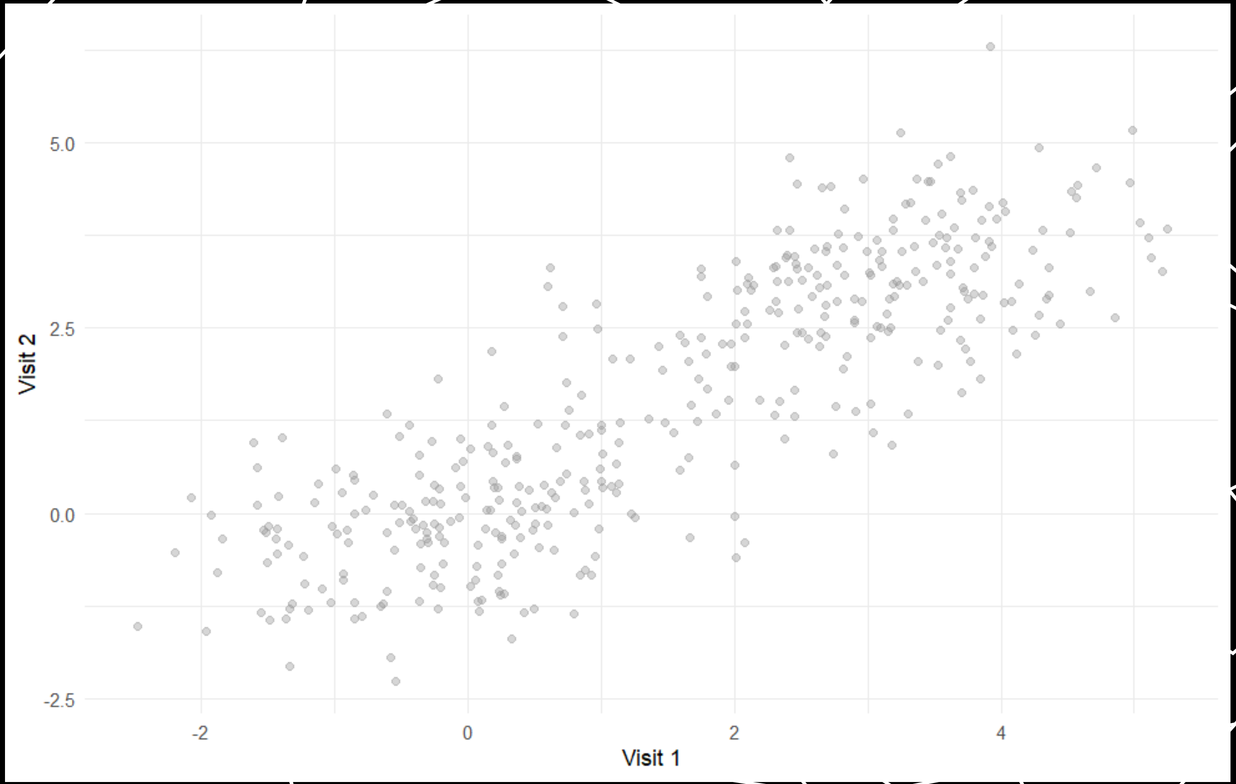
NUMBER OF PATIENTS WITH EACH MISSING DATA PATTERN

+

ESTIMATE CORRELATION ?

↓

USE THE FRAMEWORK



UNIVERSITY OF BATH

UNBLINDED AT INTERIM

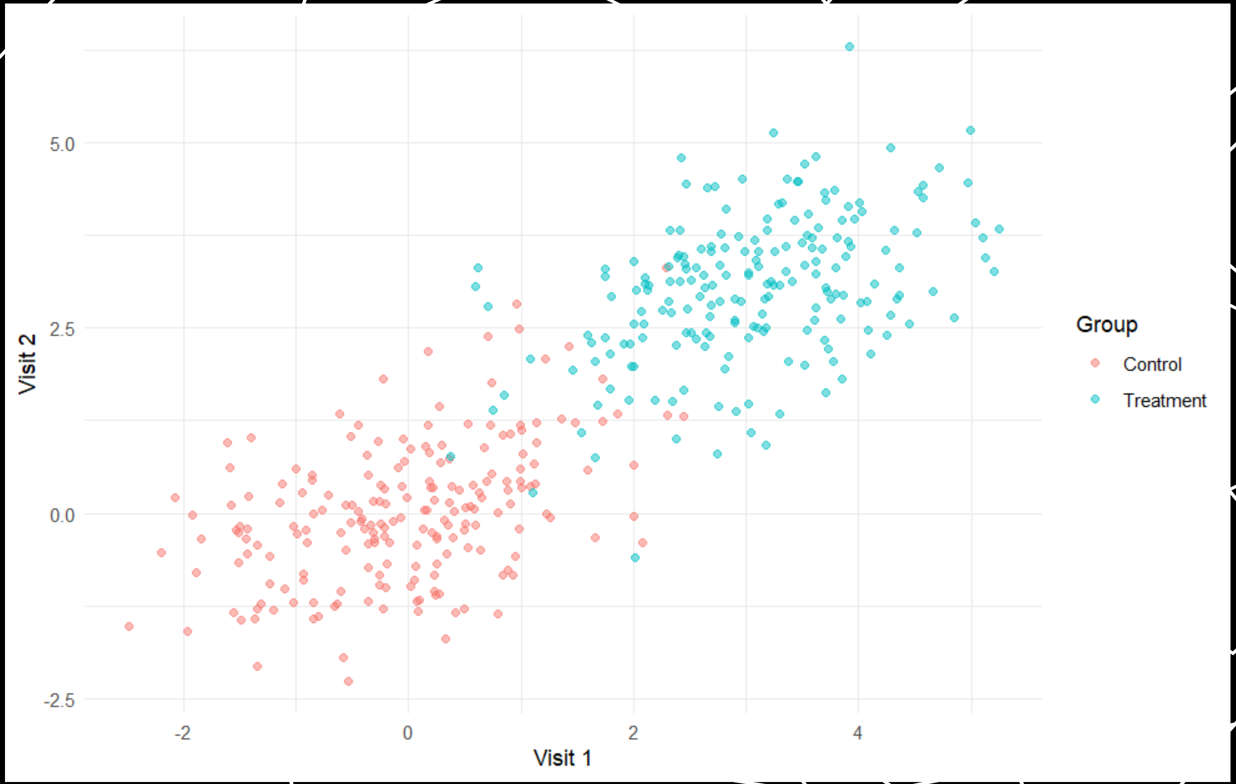
NUMBER OF PATIENTS WITH EACH MISSING DATA PATTERN

+

ESTIMATE CORRELATION ?

↓

USE THE FRAMEWORK



UNIVERSITY OF BATH

UNBLINDED AT INTERIM

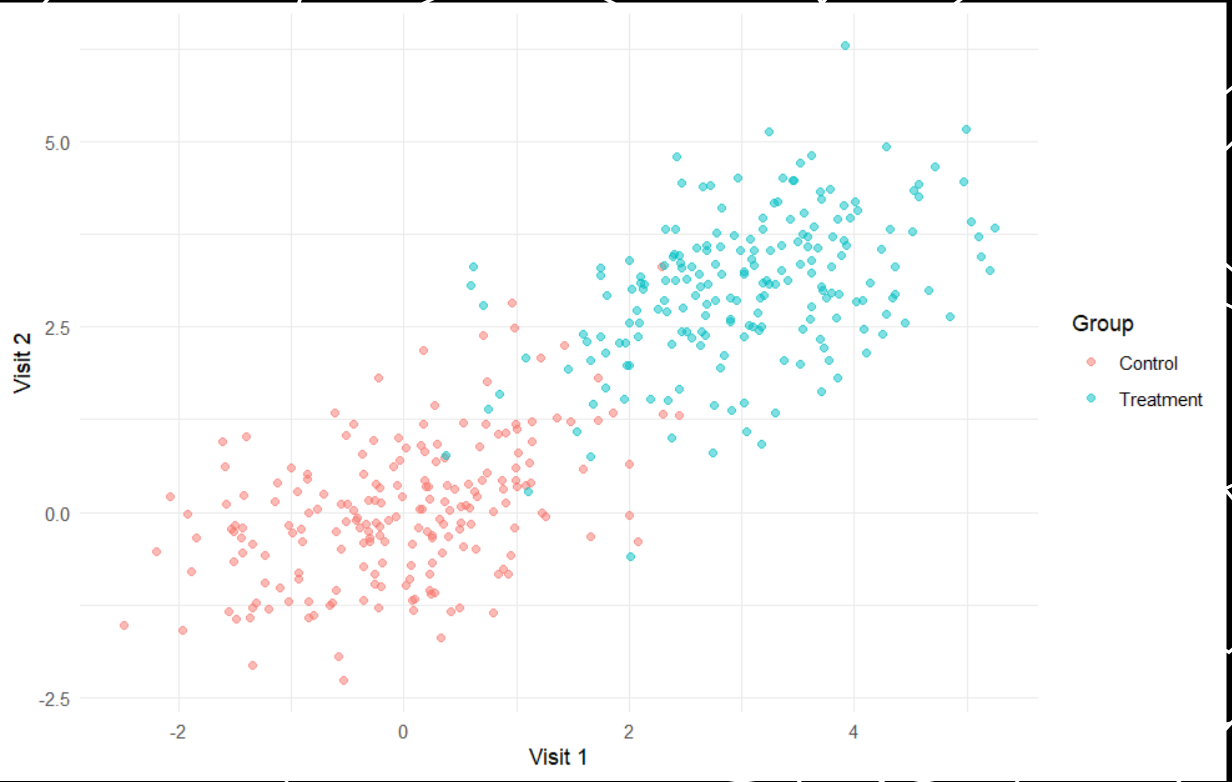
NUMBER OF PATIENTS WITH EACH MISSING DATA PATTERN

+

ESTIMATE CORRELATION

↓

USE THE FRAMEWORK



UNIVERSITY OF BATH

UNBLINDED AT INTERIM

NUMBER OF PATIENTS WITH

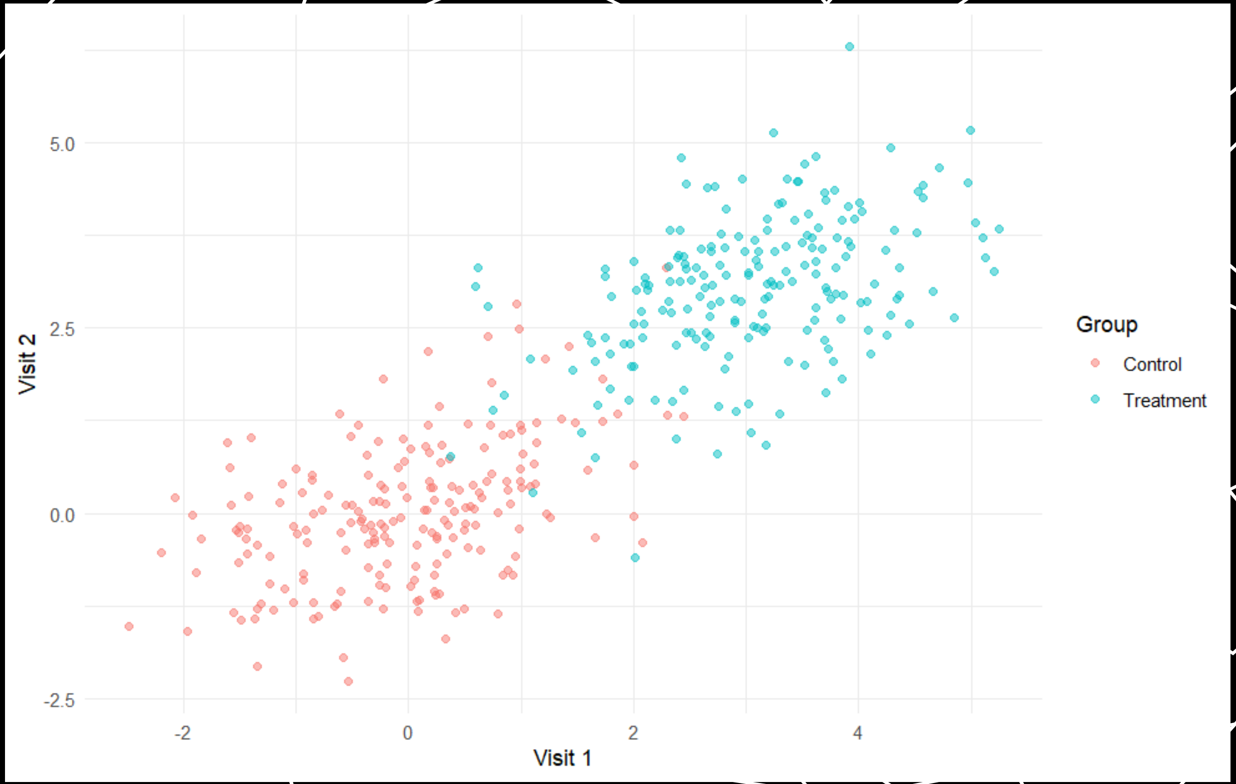
EACH MISSING DATA PATTERN

+

ESTIMATE CORRELATION

↓

USE THE FRAMEWORK



UNIVERSITY OF BATH

BLINDED AT INTERIM

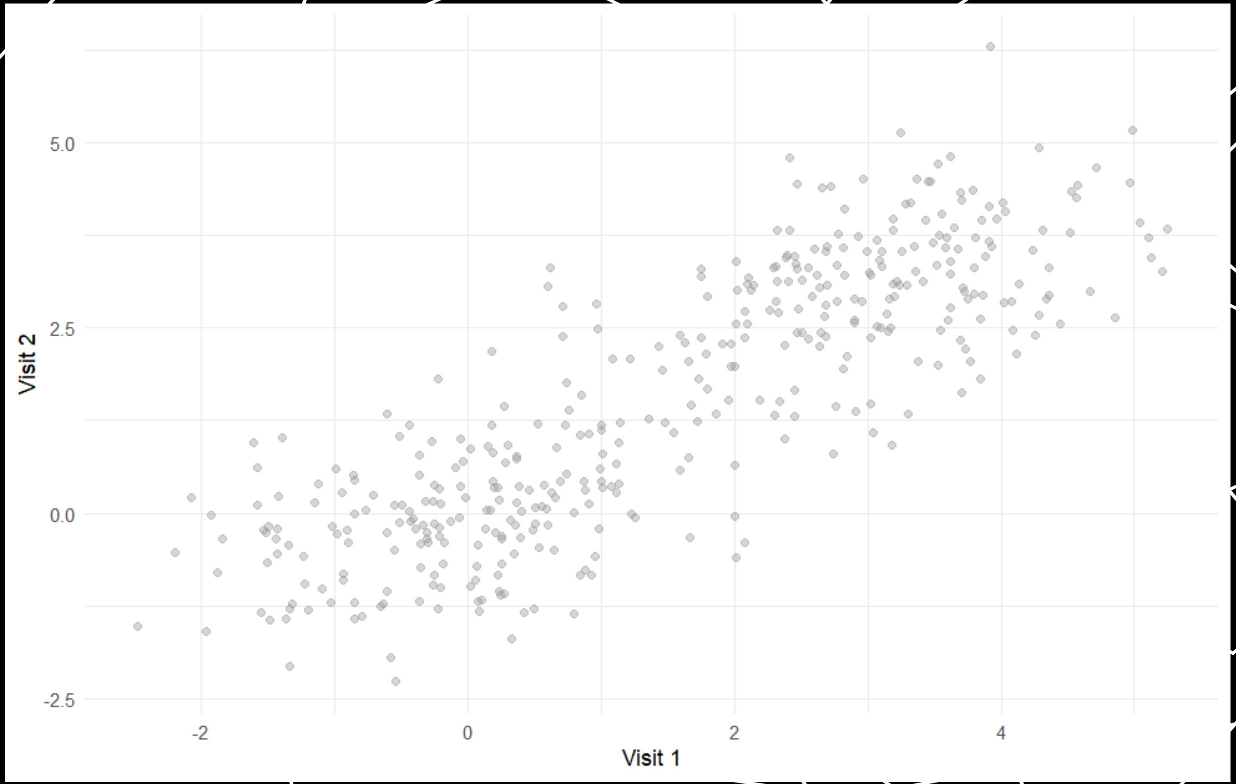
NUMBER OF PATIENTS WITH EACH MISSING DATA PATTERN

+

ESTIMATE CORRELATION

↓

USE THE FRAMEWORK



BLINDED AT INTERIM

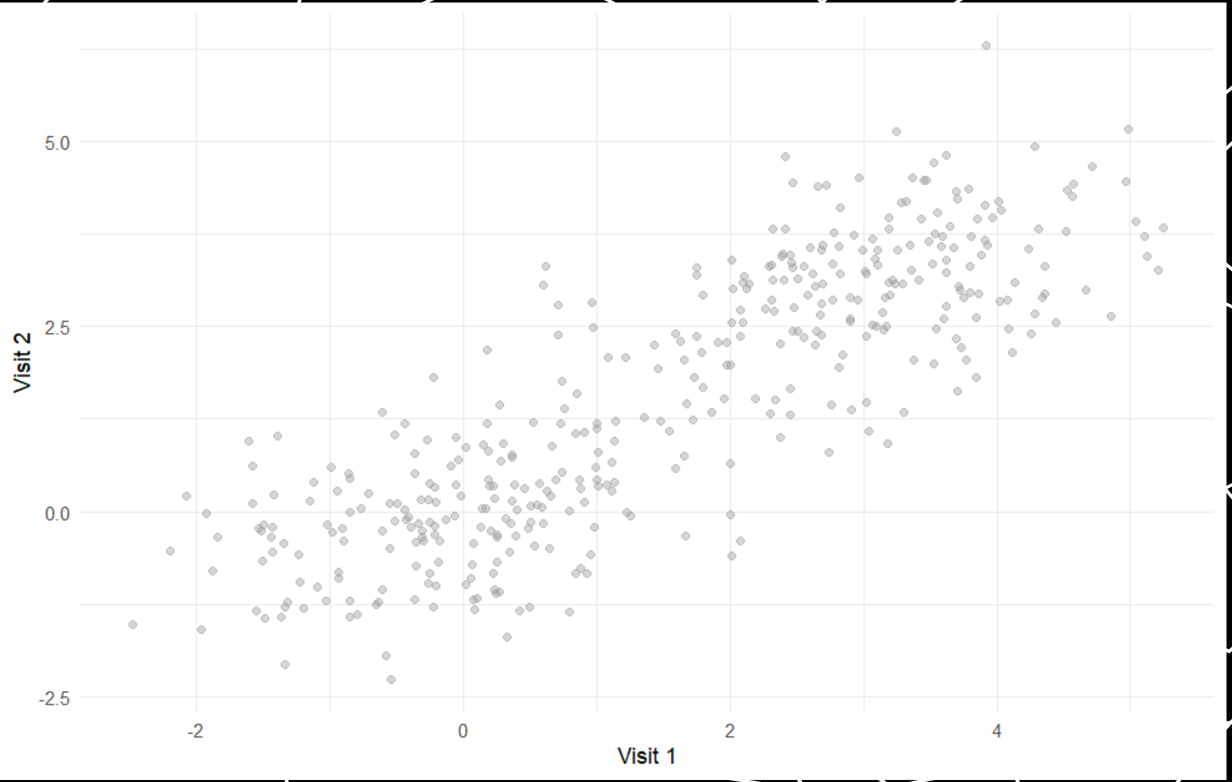
NUMBER OF PATIENTS WITH EACH MISSING DATA PATTERN

+

ESTIMATE CORRELATION

↓

USE THE FRAMEWORK



BLINDED AT INTERIM

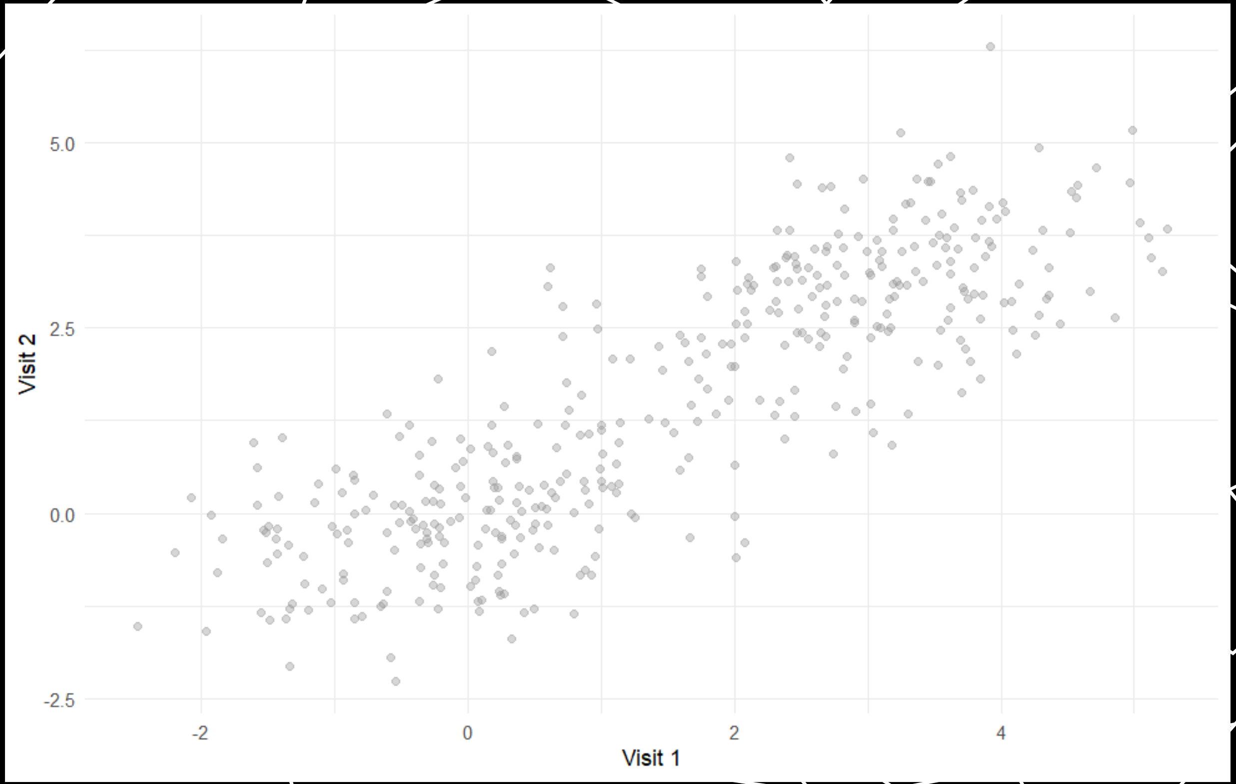
NUMBER OF PATIENTS WITH EACH MISSING DATA PATTERN

+

ESTIMATE CORRELATION ?

↓

USE THE FRAMEWORK



BLINDED AT INTERIM

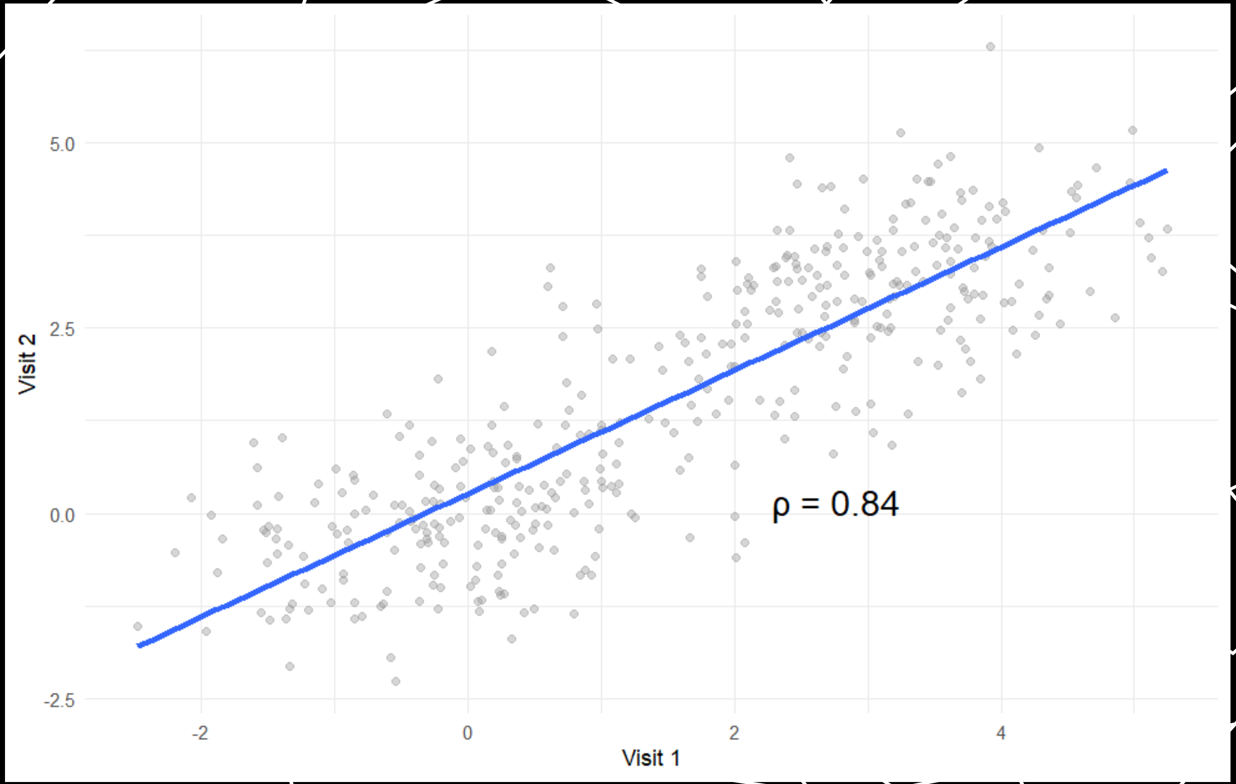
NUMBER OF PATIENTS WITH EACH MISSING DATA PATTERN

+

ESTIMATE CORRELATION ?

↓

USE THE FRAMEWORK



BLINDED AT INTERIM

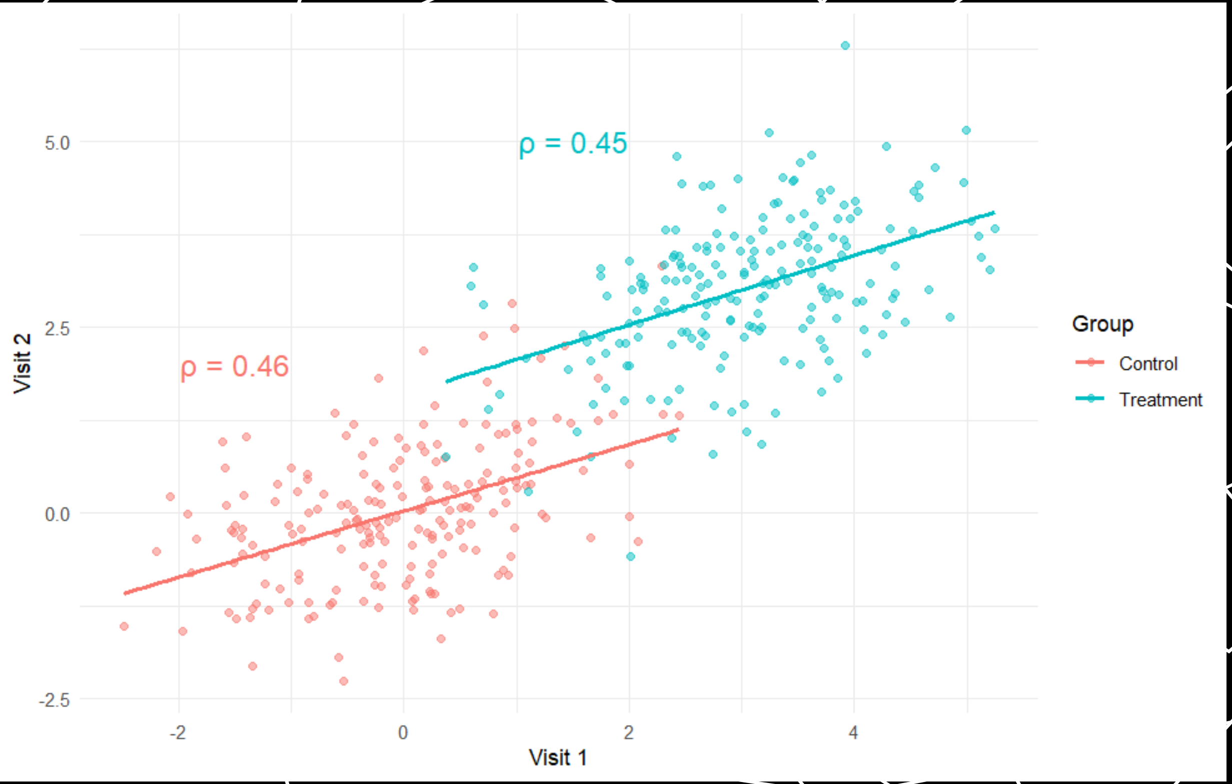
NUMBER OF PATIENTS WITH EACH MISSING DATA PATTERN

+

ESTIMATE CORRELATION ?

↓

USE THE FRAMEWORK



UNIVERSITY OF BATH

BLINDED AT INTERIM

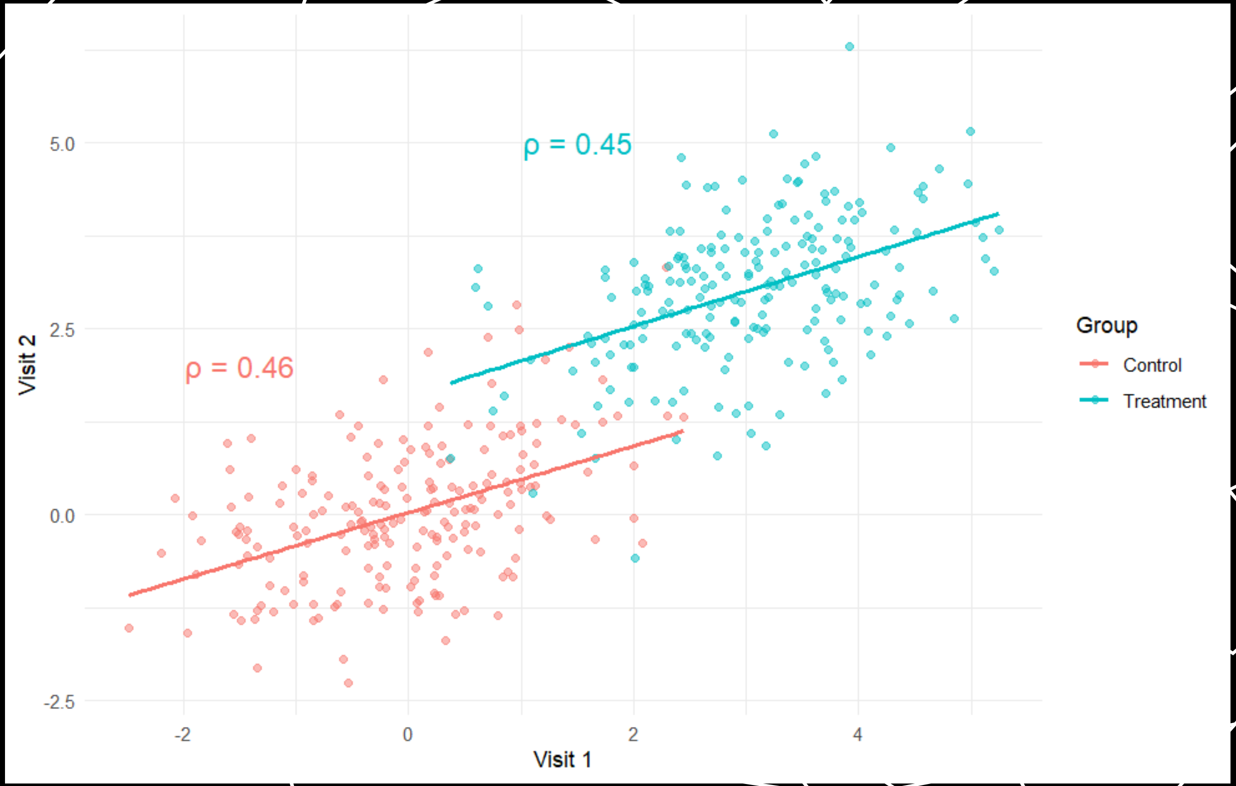
NUMBER OF PATIENTS WITH EACH MISSING DATA PATTERN

+

ESTIMATE CORRELATION ?

↓

USE THE FRAMEWORK



→ BLINDED CORRELATION ESTIMATE IS INFLATED !

UNIVERSITY OF BATH

BLINDED AT INTERIM

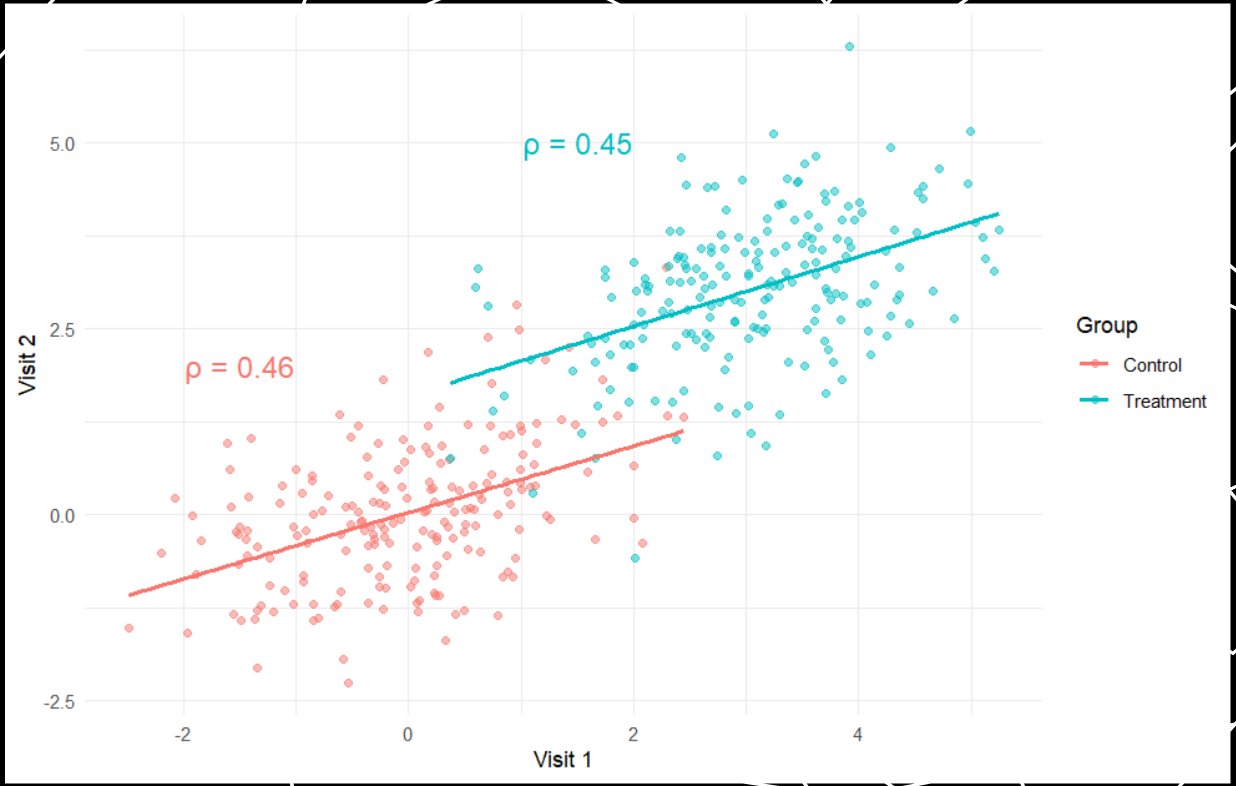
NUMBER OF PATIENTS WITH EACH MISSING DATA PATTERN

+

ESTIMATE CORRELATION ?

↓

USE THE FRAMEWORK



→ MIXTURE DISTRIBUTION !

BLINDED AT INTERIM

NUMBER OF PATIENTS WITH EACH MISSING DATA PATTERN

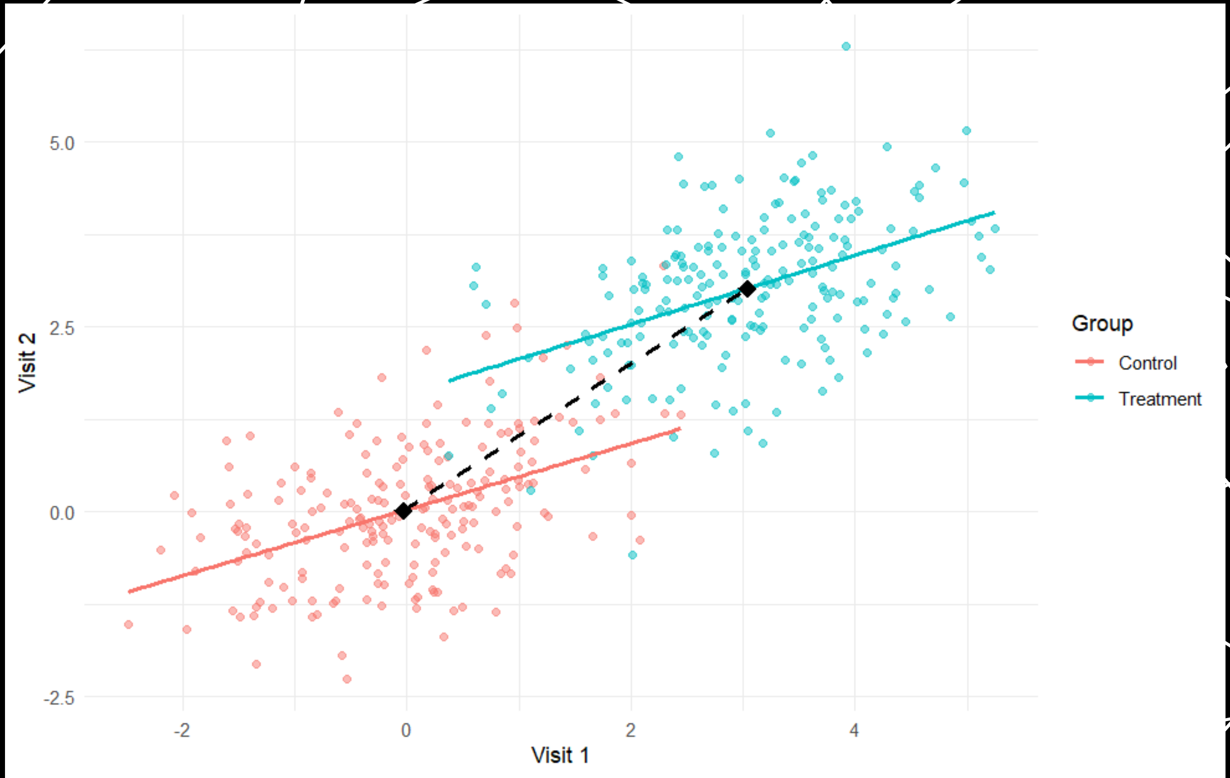
+

ESTIMATE CORRELATION ?

↓

USE THE FRAMEWORK

DIFFERENCES IN TREATMENT ARMS ACROSS VISITS



WITHIN-ARM + BETWEEN-ARM

BLINDED AT INTERIM

NUMBER OF PATIENTS WITH EACH MISSING DATA PATTERN

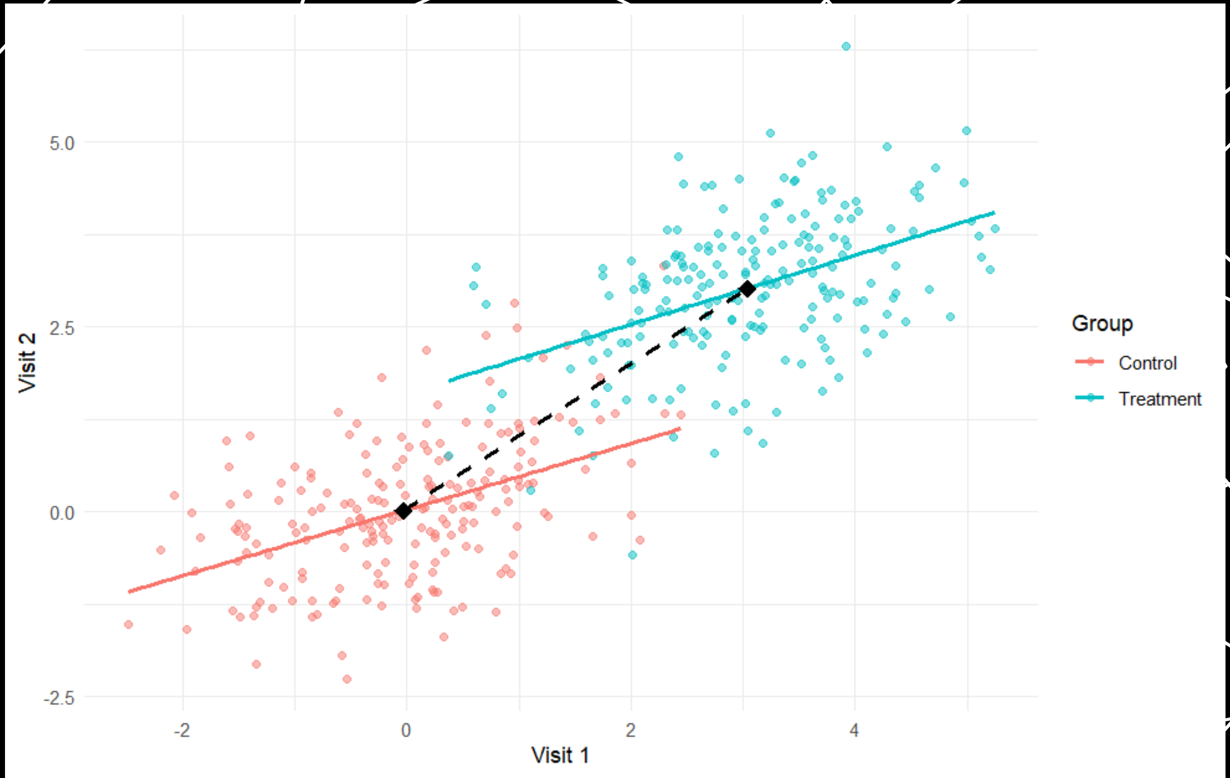
+

ESTIMATE CORRELATION ?

↓

USE THE FRAMEWORK ?

DIFFERENCES IN TREATMENT ARMS ACROSS VISITS



WITHIN-ARM + BETWEEN-ARM

UNIVERSITY OF BATH

POOLED CORRELATION

POOLED CORRELATION BETWEEN VISITS

$$\tilde{\rho}_{12} = \frac{\rho_{12} + p_C p_T s_1 s_2}{\sqrt{(1 + p_C p_T s_1^2)(1 + p_C p_T s_2^2)}}$$

POOLED CORRELATION BETWEEN VISITS

$$\tilde{\rho}_{12} = \frac{\rho_{12} + p_C p_T s_1 s_2}{\sqrt{(1 + p_C p_T s_1^2)(1 + p_C p_T s_2^2)}}$$

$\tilde{\rho}_{12}$ ... pooled correlation between Visit 1 and Visit 2

ρ_{12} ... within-arm correlation between Visit 1 and Visit 2

POOLED CORRELATION BETWEEN VISITS

$$\tilde{\rho}_{12} = \frac{\rho_{12} + p_C p_T s_1 s_2}{\sqrt{(1 + p_C p_T s_1^2)(1 + p_C p_T s_2^2)}}$$

$\tilde{\rho}_{12}$ ... pooled correlation between Visit 1 and Visit 2
ρ_{12} ... within-arm correlation between Visit 1 and Visit 2
p_C ... proportion of individuals on the control arm
p_T ... proportion of individuals on the treatment arm

POOLED CORRELATION BETWEEN VISITS

$$\tilde{\rho}_{12} = \frac{\rho_{12} + p_C p_T s_1 s_2}{\sqrt{(1 + p_C p_T s_1^2)(1 + p_C p_T s_2^2)}}$$

$\tilde{\rho}_{12}$ ... pooled correlation between Visit 1 and Visit 2
ρ_{12} ... within-arm correlation between Visit 1 and Visit 2
p_C ... proportion of individuals on the control arm
p_T ... proportion of individuals on the treatment arm
s_1 ... standardised treatment difference at Visit 1
s_2 ... standardised treatment difference at Visit 2

POOLED CORRELATION BETWEEN VISITS

$$\tilde{\rho}_{12} = \frac{\rho_{12} + p_C p_T s_1 s_2}{\sqrt{(1 + p_C p_T s_1^2)(1 + p_C p_T s_2^2)}}$$

$\tilde{\rho}_{12}$ ... pooled correlation between Visit 1 and Visit 2
ρ_{12} ... within-arm correlation between Visit 1 and Visit 2
p_C ... proportion of individuals on the control arm
p_T ... proportion of individuals on the treatment arm
s_1 ... standardised treatment difference at Visit 1
s_2 ... standardised treatment difference at Visit 2

DIFFERENCE BETWEEN $\tilde{\rho}_{12}$ AND ρ_{12}:

UNIVERSITY OF BATH

POOLED CORRELATION BETWEEN VISITS

$$\tilde{\rho}_{12} = \frac{\rho_{12} + p_C p_T s_1 s_2}{\sqrt{(1 + p_C p_T s_1^2)(1 + p_C p_T s_2^2)}}$$

$\tilde{\rho}_{12}$ … pooled correlation between Visit 1 and Visit 2
ρ_{12} … within-arm correlation between Visit 1 and Visit 2
p_C … proportion of individuals on the control arm
p_T … proportion of individuals on the treatment arm
s_1 … standardised treatment difference at Visit 1
s_2 … standardised treatment difference at Visit 2

DIFFERENCE BETWEEN $\tilde{\rho}_{12}$ AND ρ_{12}: $|\tilde{\rho}_{12} - \rho_{12}|$

POOLED CORRELATION BETWEEN VISITS

$$\tilde{\rho}_{12} = \frac{\rho_{12} + p_C p_T s_1 s_2}{\sqrt{(1 + p_C p_T s_1^2)(1 + p_C p_T s_2^2)}}$$

$\tilde{\rho}_{12}$ ... pooled correlation between Visit 1 and Visit 2
ρ_{12} ... within-arm correlation between Visit 1 and Visit 2
p_C ... proportion of individuals on the control arm
p_T ... proportion of individuals on the treatment arm
s_1 ... standardised treatment difference at Visit 1
s_2 ... standardised treatment difference at Visit 2

DIFFERENCE BETWEEN $\tilde{\rho}_{12}$ AND ρ_{12}: $|\tilde{\rho}_{12} - \rho_{12}| \leq \frac{s_1^2 + s_2^2}{8}$

UNIVERSITY OF BATH

POOLED CORRELATION BETWEEN VISITS

$$\tilde{\rho}_{12} = \frac{\rho_{12} + p_C p_T s_1 s_2}{\sqrt{(1 + p_C p_T s_1^2)(1 + p_C p_T s_2^2)}}$$

$\tilde{\rho}_{12}$ … pooled correlation between Visit 1 and Visit 2
ρ_{12} … within-arm correlation between Visit 1 and Visit 2
p_C … proportion of individuals on the control arm
p_T … proportion of individuals on the treatment arm
s_1 … standardised treatment difference at Visit 1
s_2 … standardised treatment difference at Visit 2

DIFFERENCE BETWEEN $\tilde{\rho}_{12}$ AND ρ_{12}:

$$|\tilde{\rho}_{12} - \rho_{12}| \leq \frac{s_1^2 + s_2^2}{8}$$

Depends only on the standardised treatment differences s_1 and s_2

MAGNITUDE OF s_1, s_2 AND $|\tilde{\rho}_{12} - \rho_{12}|$

MAGNITUDE OF s_1, s_2 AND $|\tilde{\rho}_{12} - \rho_{12}|$

s_1 and s_2 obtained from standard power calculations used in trial design

MAGNITUDE OF s_1, s_2 AND $|\tilde{\rho}_{12} - \rho_{12}|$

s_1 and s_2 obtained from standard power calculations used in trial design

- Typical Phase III trial sample sizes: $n = 150 - 400$ per arm

MAGNITUDE OF s_1, s_2 AND $|\tilde{\rho}_{12} - \rho_{12}|$

s_1 and s_2 obtained from standard power calculations used in trial design

- Typical Phase III trial sample sizes: $n = 150 - 400$ per arm
- Commonly used power levels: 80% and 90%

MAGNITUDE OF s_1, s_2 AND $|\tilde{\rho}_{12} - \rho_{12}|$

$\boldsymbol{s_1}$ and $\boldsymbol{s_2}$ obtained from standard power calculations used in trial design

- Typical Phase III trial sample sizes: $n = 150 - 400$ per arm
- Commonly used power levels: 80% and 90%
- $\alpha = 0.025$

MAGNITUDE OF s_1, s_2 AND $|\tilde{\rho}_{12} - \rho_{12}|$

s_1 and s_2 obtained from standard power calculations used in trial design

- Typical Phase III trial sample sizes: $n = 150 - 400$ per arm
- Commonly used power levels: 80% and 90%
- $\alpha = 0.025$

n	Power = 80%	Power = 90%
150	0.323	0.374
200	0.280	0.324
250	0.250	0.290
300	0.229	0.265
350	0.212	0.245
400	0.198	0.229

UNIVERSITY OF BATH

MAGNITUDE OF s_1, s_2 AND $|\tilde{\rho}_{12} - \rho_{12}|$

s_1 and s_2 obtained from standard power calculations used in trial design

- Typical Phase III trial sample sizes: $n = 150 - 400$ per arm
- Commonly used power levels: 80% and 90%
- $\alpha = 0.025$

→ s_1 and s_2 normally small and in the range $0.2 - 0.35$

n	Power = 80%	Power = 90%
150	0.323	0.374
200	0.280	0.324
250	0.250	0.290
300	0.229	0.265
350	0.212	0.245
400	0.198	0.229

UNIVERSITY OF BATH

MAGNITUDE OF s_1, s_2 AND $|\tilde{\rho}_{12} - \rho_{12}|$

s_1 and s_2 obtained from standard power calculations used in trial design

- Typical Phase III trial sample sizes: $n = 150 - 400$ per arm
- Commonly used power levels: 80% and 90%
- $\alpha = 0.025$

→ s_1 and s_2 normally small and in the range $0.2 - 0.35$

Example

Suppose $s_1 = 0.15$ and $s_2 = 0.3$.

UNIVERSITY OF BATH

MAGNITUDE OF s_1, s_2 AND $|\tilde{\rho}_{12} - \rho_{12}|$

s_1 and s_2 obtained from standard power calculations used in trial design

- Typical Phase III trial sample sizes: $n = 150 - 400$ per arm
- Commonly used power levels: 80% and 90%
- $\alpha = 0.025$

→ s_1 and s_2 normally small and in the range $0.2 - 0.35$

Example

Suppose $s_1 = 0.15$ and $s_2 = 0.3$.
Then for $\rho_{12} = 0.8$,

$$|\tilde{\rho}_{12} - \rho_{12}| \leq 0.0045,$$

UNIVERSITY OF BATH

MAGNITUDE OF s_1, s_2 AND $|\tilde{\rho}_{12} - \rho_{12}|$

s_1 and s_2 obtained from standard power calculations used in trial design

- Typical Phase III trial sample sizes: $n = 150 - 400$ per arm
- Commonly used power levels: 80% and 90%
- $\alpha = 0.025$

→ s_1 and s_2 normally small and in the range $0.2 - 0.35$

Example

Suppose $s_1 = 0.15$ and $s_2 = 0.3$.
Then for $\rho_{12} = 0.8$,

$$|\tilde{\rho}_{12} - \rho_{12}| \leq 0.0045,$$

or for any ρ_{12}

$$|\tilde{\rho}_{12} - \rho_{12}| \leq 0.014.$$

UNIVERSITY OF BATH

MAGNITUDE OF s_1, s_2 AND $|\tilde{\rho}_{12} - \rho_{12}|$

s_1 and s_2 obtained from standard power calculations used in trial design

- Typical Phase III trial sample sizes: $n = 150 - 400$ per arm
- Commonly used power levels: 80% and 90%
- $\alpha = 0.025$

→ s_1 and s_2 normally small and in the range $0.2 - 0.35$

Example

Suppose $s_1 = 0.15$ and $s_2 = 0.3$.
Then for $\rho_{12} = 0.8$,

$$|\tilde{\rho}_{12} - \rho_{12}| \leq 0.0045,$$

or for any ρ_{12}

$$|\tilde{\rho}_{12} - \rho_{12}| \leq 0.014.$$

POOLED CORRELATION DOES NOT MATERIALLY DIFFER FROM THE WITHIN-ARM CORRELATION.

UNIVERSITY OF BATH

BLINDED AT INTERIM

NUMBER OF PATIENTS WITH EACH MISSING DATA PATTERN

+

ESTIMATE CORRELATION ?

↓

USE THE FRAMEWORK ?

UNIVERSITY OF BATH

BLINDED AT INTERIM

NUMBER OF PATIENTS WITH EACH MISSING DATA PATTERN

+

ESTIMATE CORRELATION ✓

↓

USE THE FRAMEWORK ?

BLINDED AT INTERIM

NUMBER OF PATIENTS WITH
EACH MISSING DATA PATTERN

+

ESTIMATE CORRELATION ✓

↓

USE THE FRAMEWORK ✓

ILLUSTRATIVE TRIAL SETTING

ILLUSTRATIVE TRIAL SETTING

TRIAL DESIGN

- Two-arm trial (Control vs. Treatment)

ILLUSTRATIVE TRIAL SETTING

TRIAL DESIGN

- Two-arm trial (Control vs. Treatment)
- 3 follow-up visits per subject

ILLUSTRATIVE TRIAL SETTING

TRIAL DESIGN

- Two-arm trial (Control vs. Treatment)
- 3 follow-up visits per subject
- Planned final sample size: 300 per arm

ILLUSTRATIVE TRIAL SETTING

TRIAL DESIGN

- Two-arm trial (Control vs. Treatment)
- 3 follow-up visits per subject
- Planned final sample size: 300 per arm
- Interim sample sizes per arm
  $n \in \{20, 30, 40, 60, 80, 100, 125, 150\}$

ILLUSTRATIVE TRIAL SETTING

TRIAL DESIGN

- Two-arm trial (Control vs. Treatment)
- 3 follow-up visits per subject
- Planned final sample size: 300 per arm
- Interim sample sizes per arm
  $n \in \{20,30,40,60,80,100,125,150\}$

DATA GENERATION (MULTIVARIATE NORMAL)

- Mean structure:
  $\mu_C = (0,0,0) \qquad \mu_T = (0.33,0.67,1)$

UNIVERSITY OF BATH

ILLUSTRATIVE TRIAL SETTING

TRIAL DESIGN

- Two-arm trial (Control vs. Treatment)
- 3 follow-up visits per subject
- Planned final sample size: 300 per arm
- Interim sample sizes per arm
  $n \in \{20,30,40,60,80,100,125,150\}$

DATA GENERATION (MULTIVARIATE NORMAL)

- Mean structure:
  $\mu_C = (0,0,0)$ $\mu_T = (0.33,0.67,1)$
- Correlation structure: AR(1), $\rho = 0.8$

ILLUSTRATIVE TRIAL SETTING

TRIAL DESIGN

- Two-arm trial (Control vs. Treatment)
- 3 follow-up visits per subject
- Planned final sample size: 300 per arm
- Interim sample sizes per arm
  $n \in \{20,30,40,60,80,100,125,150\}$

DATA GENERATION (MULTIVARIATE NORMAL)

- Mean structure:
  $\mu_C = (0,0,0) \qquad \mu_T = (0.33,0.67,1)$
- Correlation structure: AR(1), $\rho = 0.8$
- Missingness: $\approx$50% per measurement

ILLUSTRATIVE TRIAL SETTING

TRIAL DESIGN

- Two-arm trial (Control vs. Treatment)
- 3 follow-up visits per subject
- Planned final sample size: 300 per arm
- Interim sample sizes per arm
  $n \in \{20,30,40,60,80,100,125,150\}$

DATA GENERATION (MULTIVARIATE NORMAL)

- Mean structure:
  $\mu_C = (0,0,0)$ $\mu_T = (0.33,0.67,1)$
- Correlation structure: AR(1), $\rho = 0.8$
- Missingness: ≈50% per measurement

→ Assess information fraction at each interim sample size using our framework

UNIVERSITY OF BATH

NUMBER OF PATIENTS WITH
EACH MISSING DATA PATTERN

+

ESTIMATE CORRELATION

↓

USE THE FRAMEWORK

NUMBER OF PATIENTS WITH EACH MISSING DATA PATTERN

+

ESTIMATE CORRELATION

↓

USE THE FRAMEWORK

NUMBER OF PATIENTS WITH EACH MISSING DATA PATTERN

+

ESTIMATE CORRELATION?

↓

USE THE FRAMEWORK

UNIVERSITY OF BATH

ESTIMATE CORRELATION ACROSS INTERIM SAMPLE SIZES

- Estimated using a MMRM

ESTIMATE CORRELATION ACROSS INTERIM SAMPLE SIZES

- Estimated using a MMRM
- Obtain two estimates:

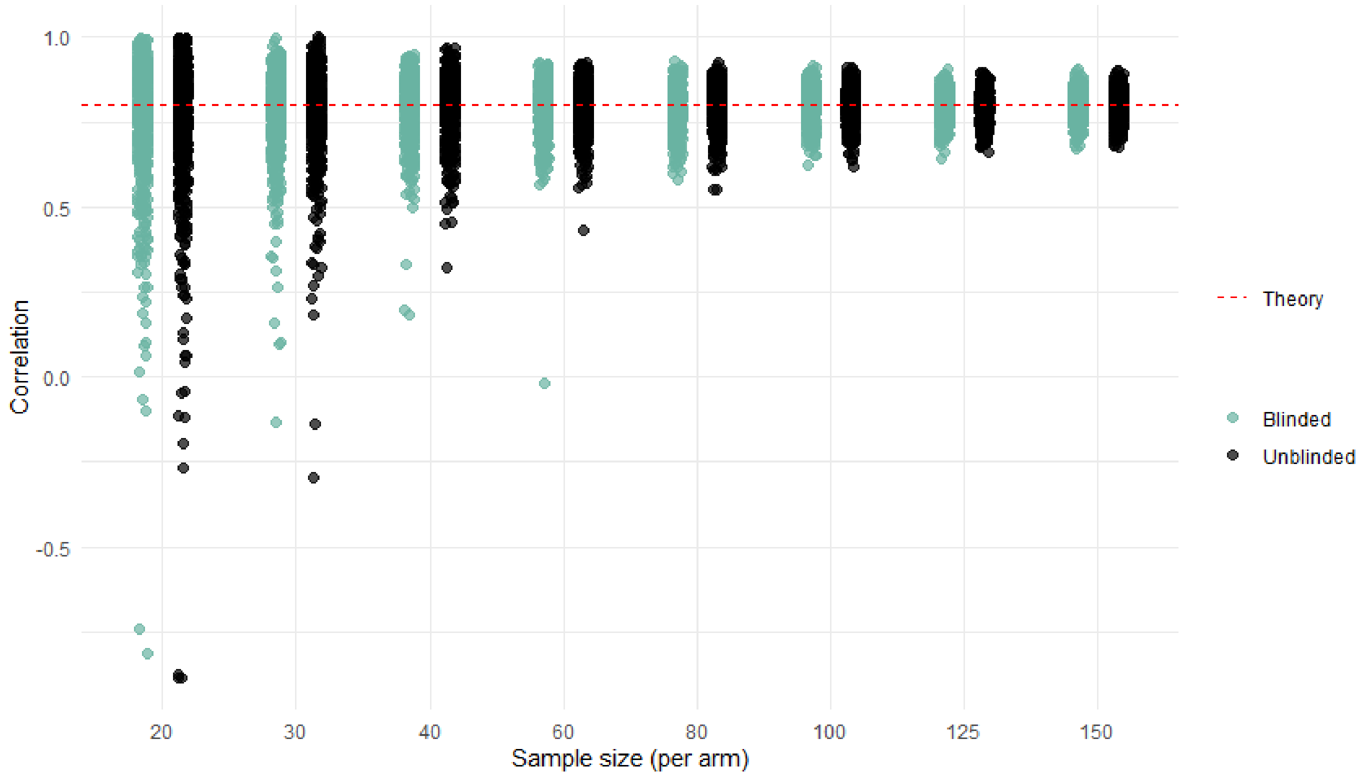
ESTIMATE CORRELATION ACROSS INTERIM SAMPLE SIZES

- Estimated using a MMRM
- Obtain two estimates:
  - Blinded
  - Unblinded

ESTIMATE CORRELATION ACROSS INTERIM SAMPLE SIZES

- Estimated using a MMRM
- Obtain two estimates:
  - Blinded
  - Unblinded

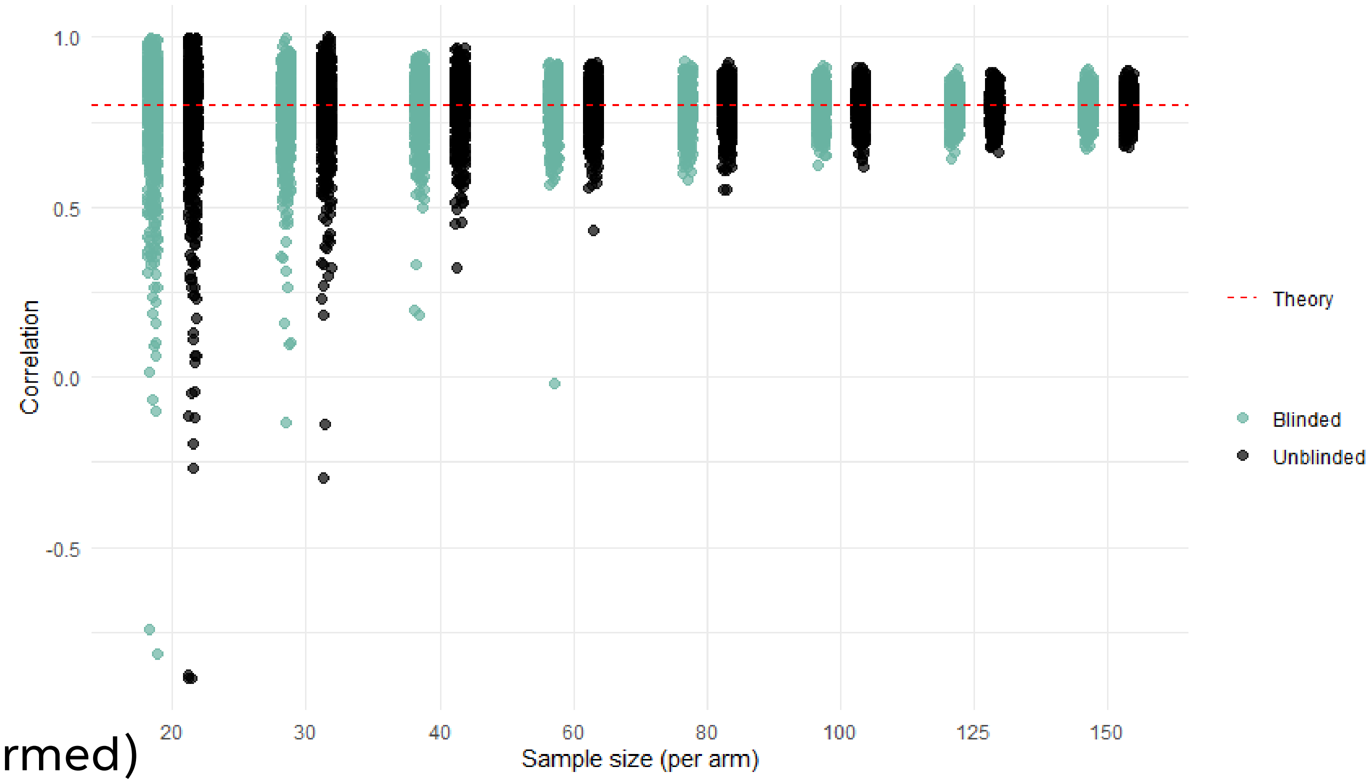
CORRELATION VS. SAMPLE SIZE



ESTIMATE CORRELATION ACROSS INTERIM SAMPLE SIZES

- Estimated using a MMRM
- Obtain two estimates:
  - Blinded
  - Unblinded

CORRELATION VS. SAMPLE SIZE

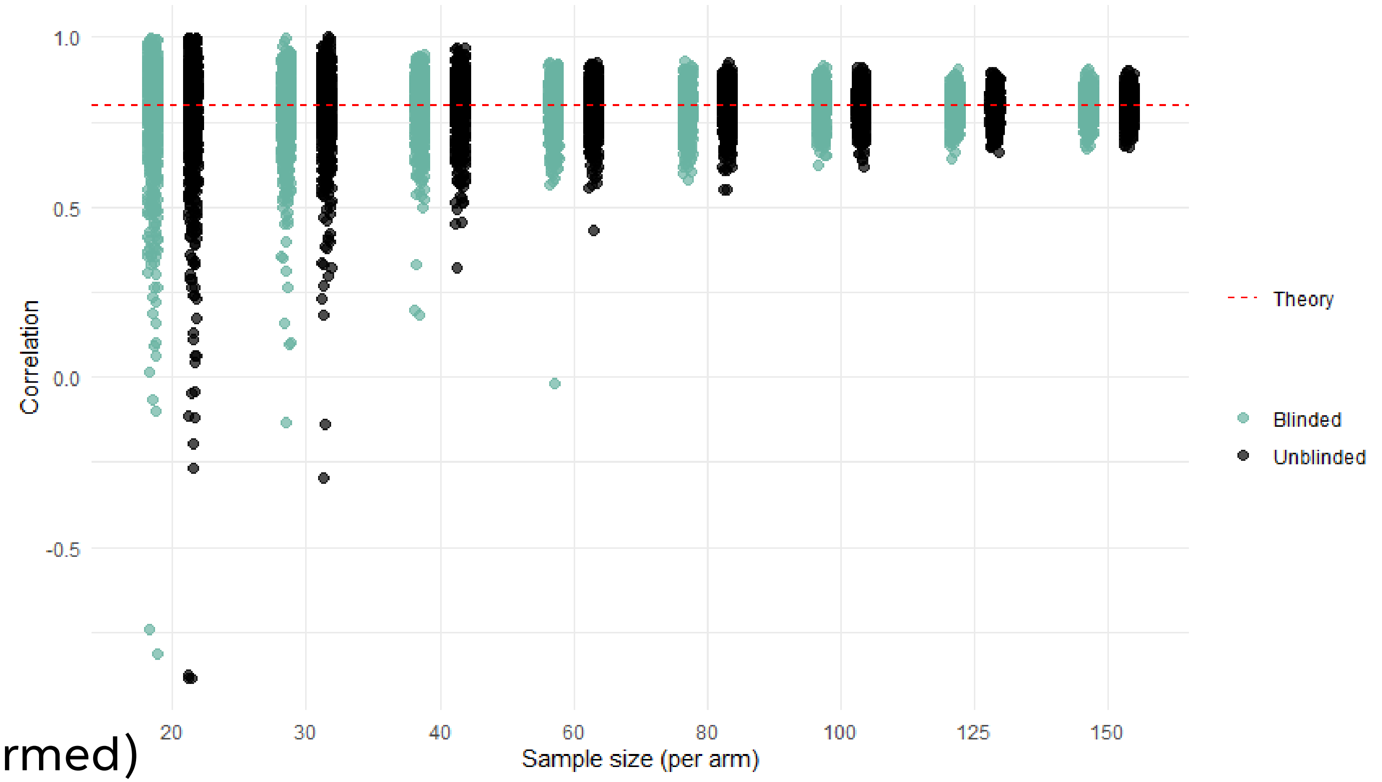


- Blinded ≈ unblinded (theory confirmed)

ESTIMATE CORRELATION ACROSS INTERIM SAMPLE SIZES

- Estimated using a MMRM
- Obtain two estimates:
  - Blinded
  - Unblinded

CORRELATION VS. SAMPLE SIZE



- Blinded ≈ unblinded (theory confirmed)
- Strong small-sample variability

ROLE OF SMALL SAMPLE SIZE

INFORMATION FRACTION ACROSS INTERIM SAMPLE SIZES

- Blinded correlation-based estimate

INFORMATION FRACTION ACROSS INTERIM SAMPLE SIZES

- Blinded correlation-based estimate
- Unblinded correlation-based estimate

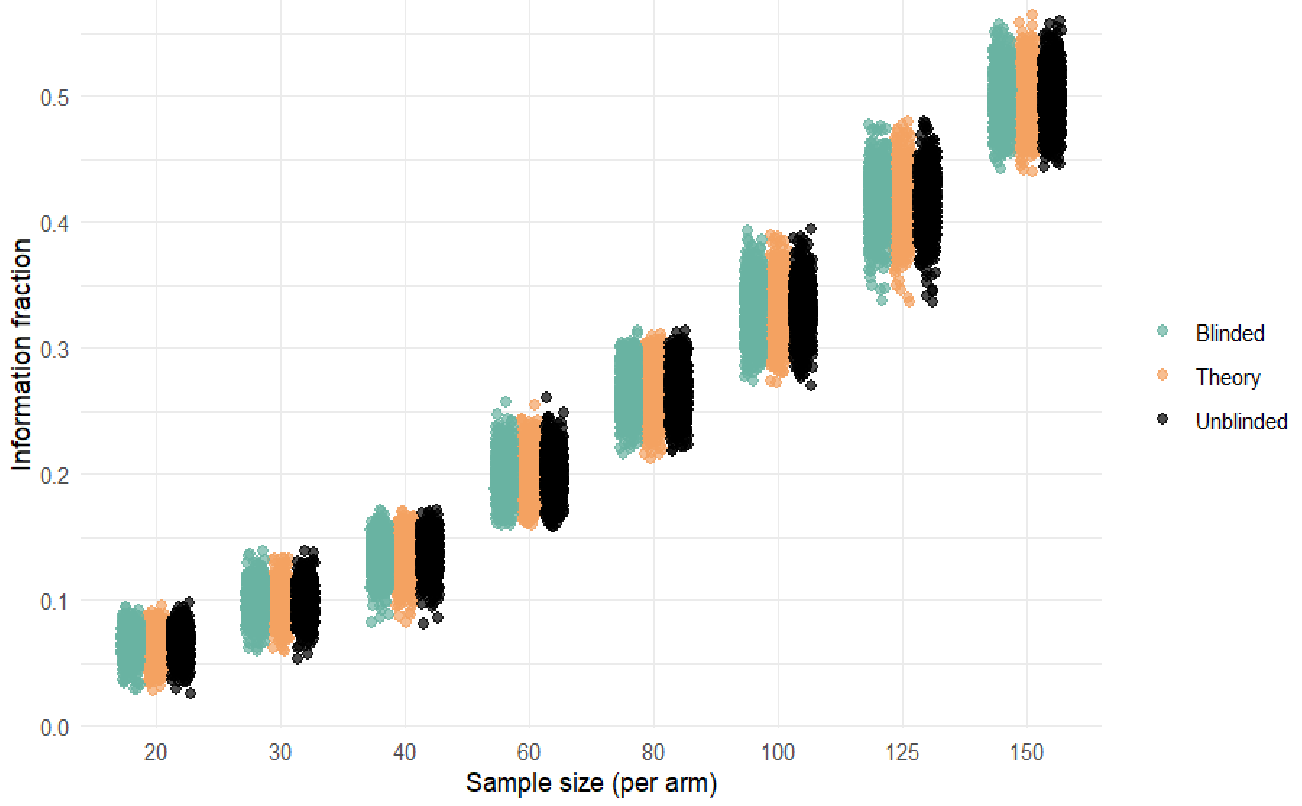
INFORMATION FRACTION ACROSS INTERIM SAMPLE SIZES

- Blinded correlation-based estimate
- Unblinded correlation-based estimate
- Theoretical benchmark

INFORMATION FRACTION ACROSS INTERIM SAMPLE SIZES

- Blinded correlation-based estimate
- Unblinded correlation-based estimate
- Theoretical benchmark

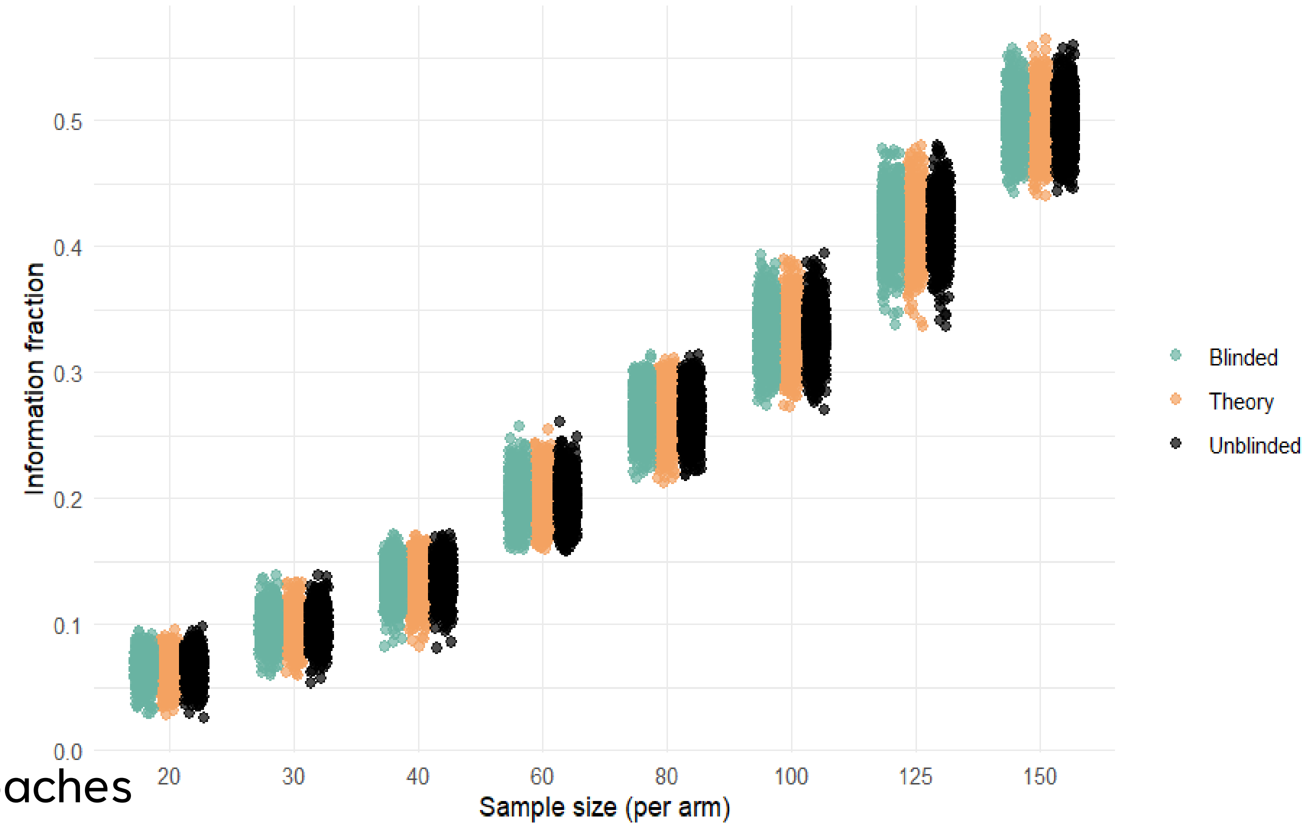
INFORMATION FRACTION VS. SAMPLE SIZE



INFORMATION FRACTION ACROSS INTERIM SAMPLE SIZES

- Blinded correlation-based estimate
- Unblinded correlation-based estimate
- Theoretical benchmark

INFORMATION FRACTION VS. SAMPLE SIZE

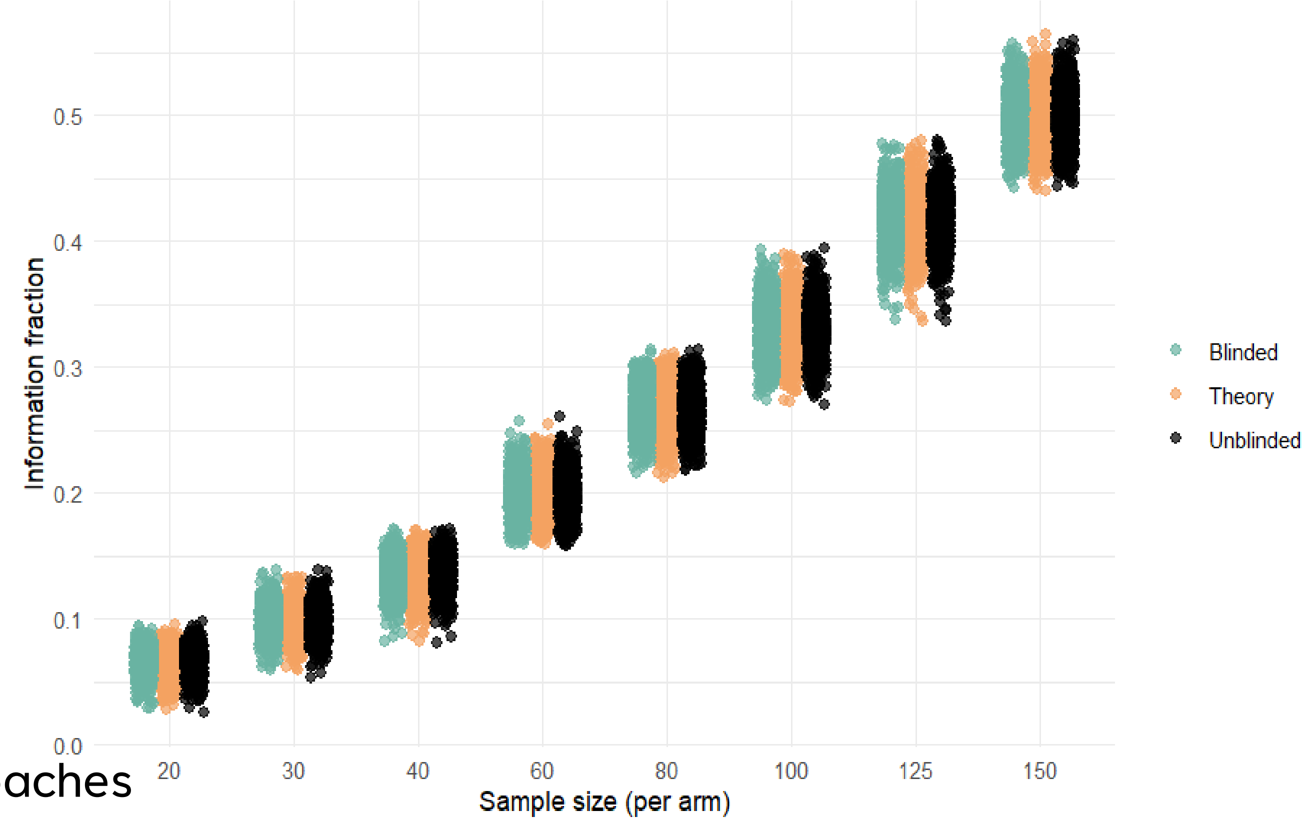


- Information fraction stable across approaches

INFORMATION FRACTION ACROSS INTERIM SAMPLE SIZES

- Blinded correlation-based estimate
- Unblinded correlation-based estimate
- Theoretical benchmark

INFORMATION FRACTION VS. SAMPLE SIZE



- Information fraction stable across approaches
- Slightly higher variability at later stages due to more heterogeneous missing data patterns

CONCLUSIONS

CONCLUSIONS

- Framework: Likelihood-based approach using equivalent sample size to track information in longitudinal trials with missing data

CONCLUSIONS

- Framework: Likelihood-based approach using equivalent sample size to track information in longitudinal trials with missing data
- Blinding: Blinded correlation estimation is sufficient for interim information calculations

CONCLUSIONS

- Framework: Likelihood-based approach using equivalent sample size to track information in longitudinal trials with missing data
- Blinding: Blinded correlation estimation is sufficient for interim information calculations
- Sample size: Information fraction is robust to small-sample variability in correlation

CONCLUSIONS

- Framework: Likelihood-based approach using equivalent sample size to track information in longitudinal trials with missing data
- Blinding: Blinded correlation estimation is sufficient for interim information calculations
- Sample size: Information fraction is robust to small-sample variability in correlation

SCAN ME

Shiny

UNIVERSITY OF BATH

CONCLUSIONS

- Framework: Likelihood-based approach using equivalent sample size to track information in longitudinal trials with missing data
- Blinding: Blinded correlation estimation is sufficient for interim information calculations
- Sample size: Information fraction is robust to small-sample variability in correlation

SCAN ME

SCAN ME

Shiny

UNIVERSITY OF BATH

THANK YOU!

SCAN ME

SCAN ME