PSI 2025 Conference
9th June 2025

WHEN TO SCHEDULE THE INTERIM ANALYSIS IN THE PRESENCE OF MISSING DATA?

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[1] University of Bath, [2] Roche UK, [3] University College London

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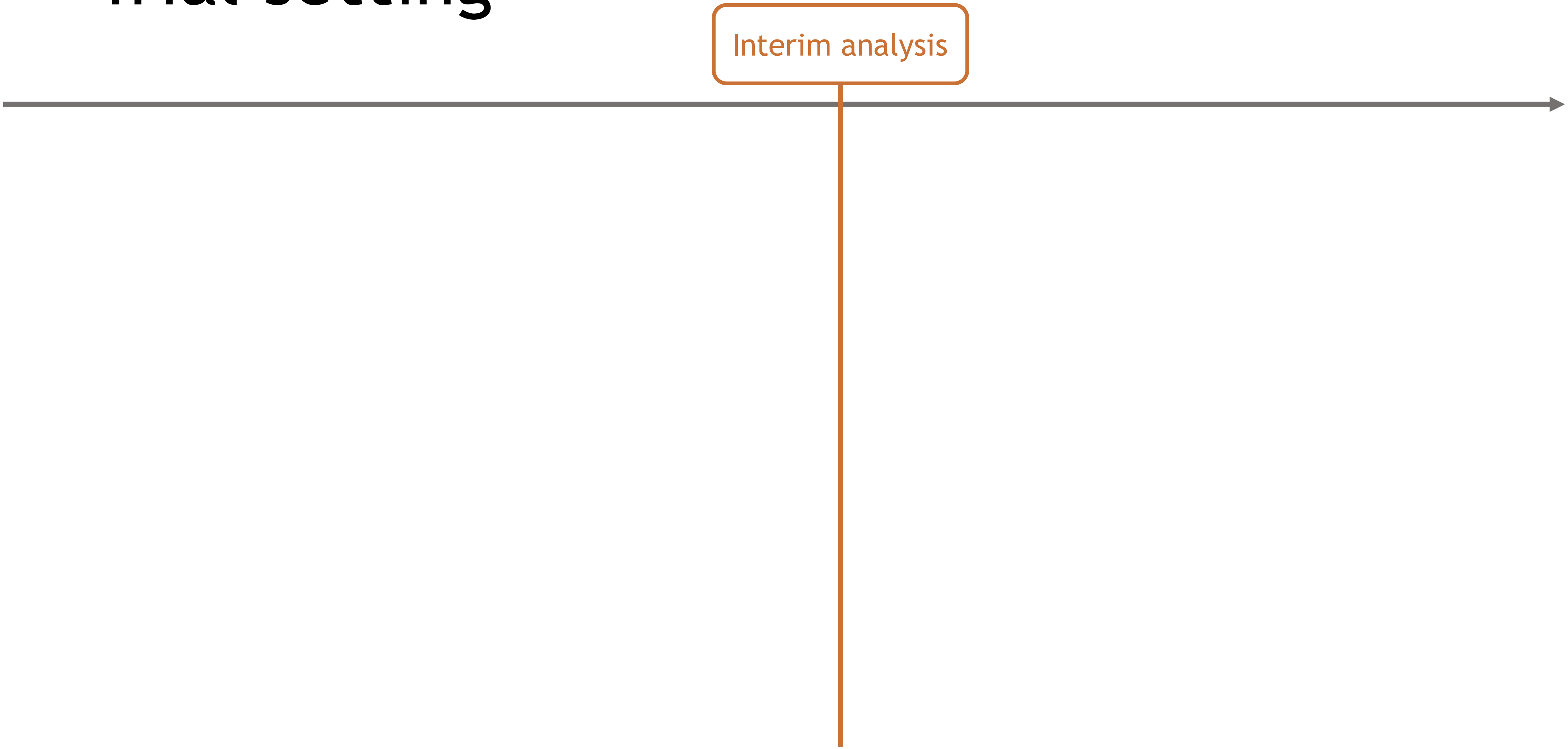
Trial setting

Trial setting



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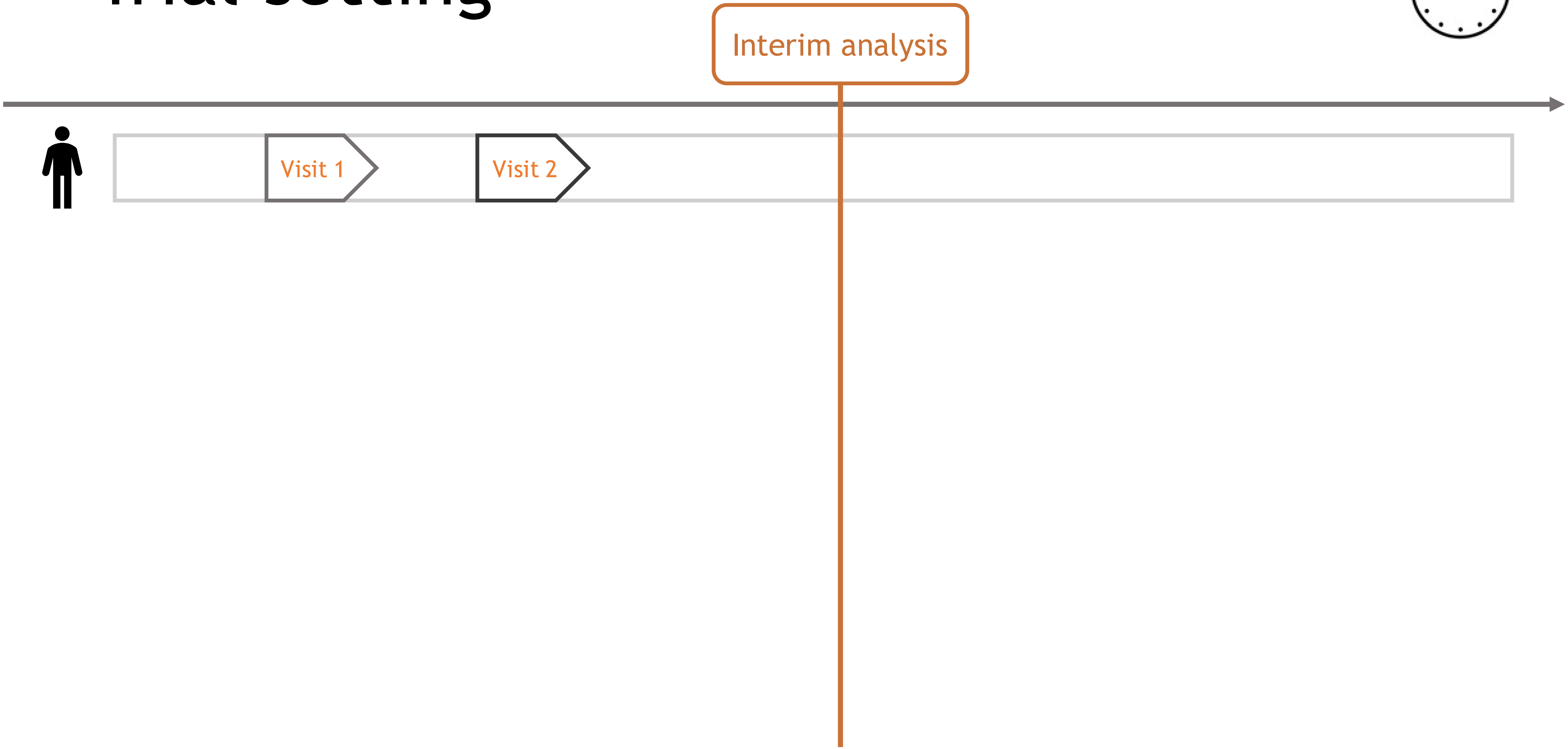

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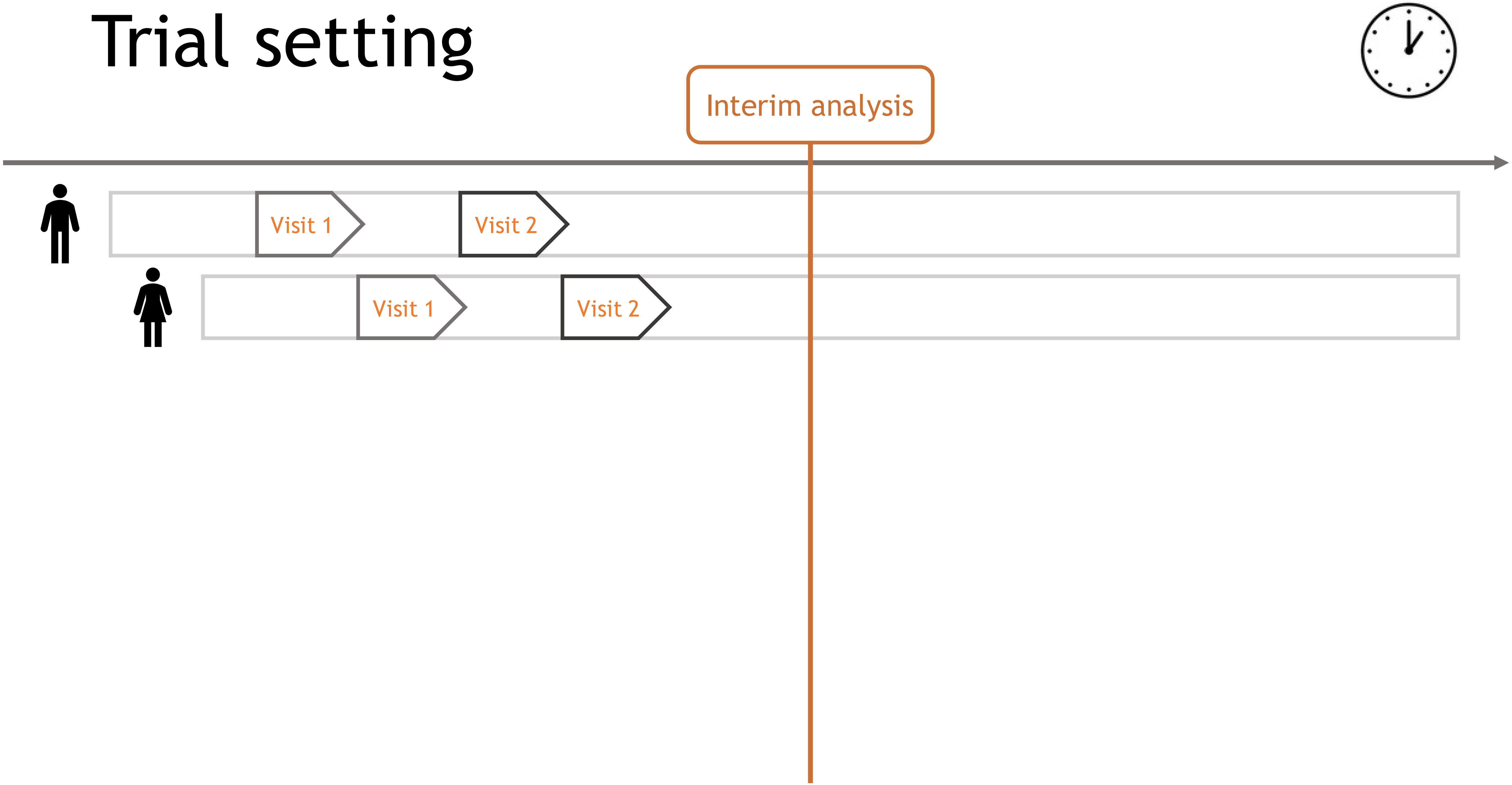

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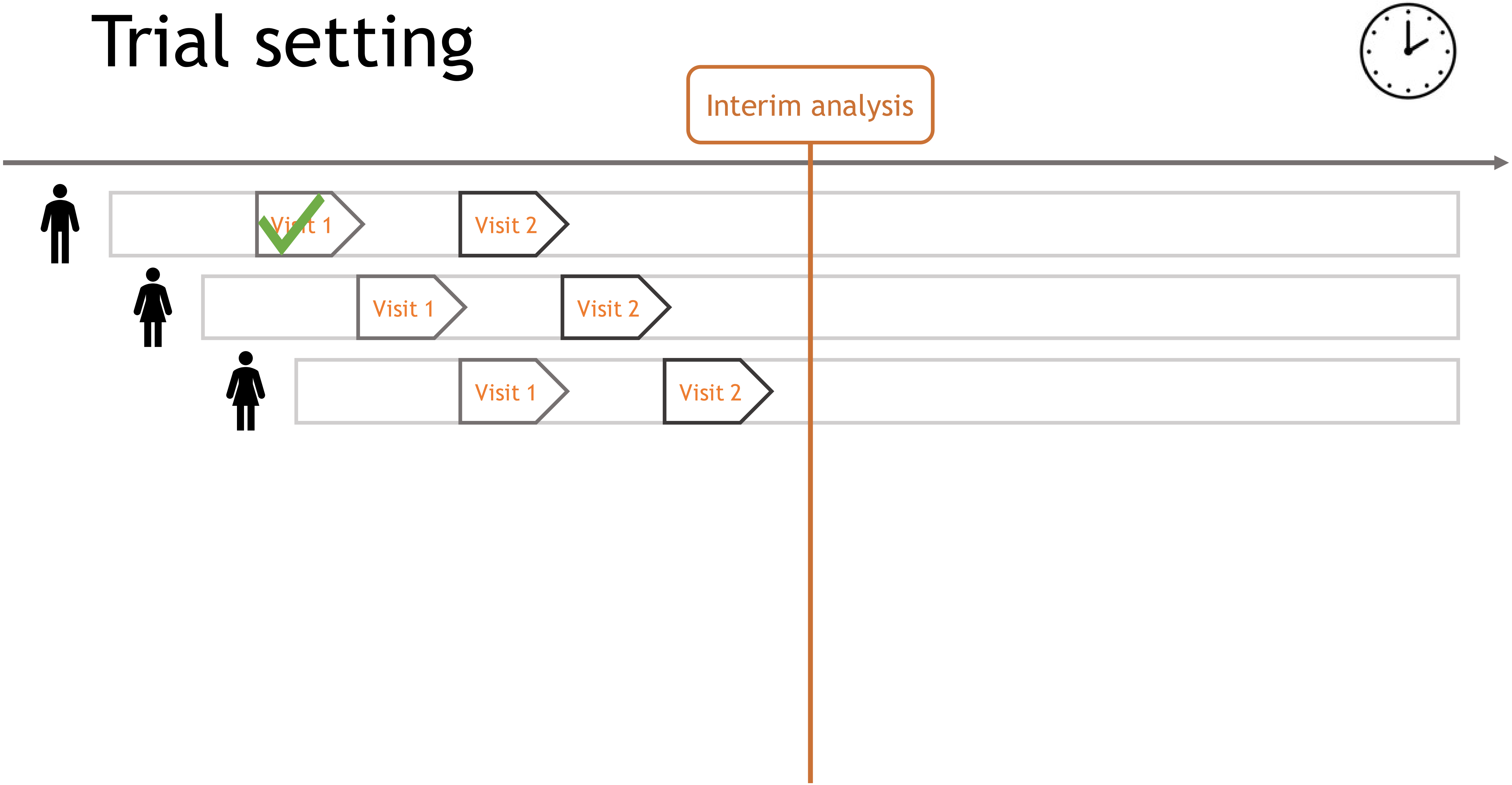
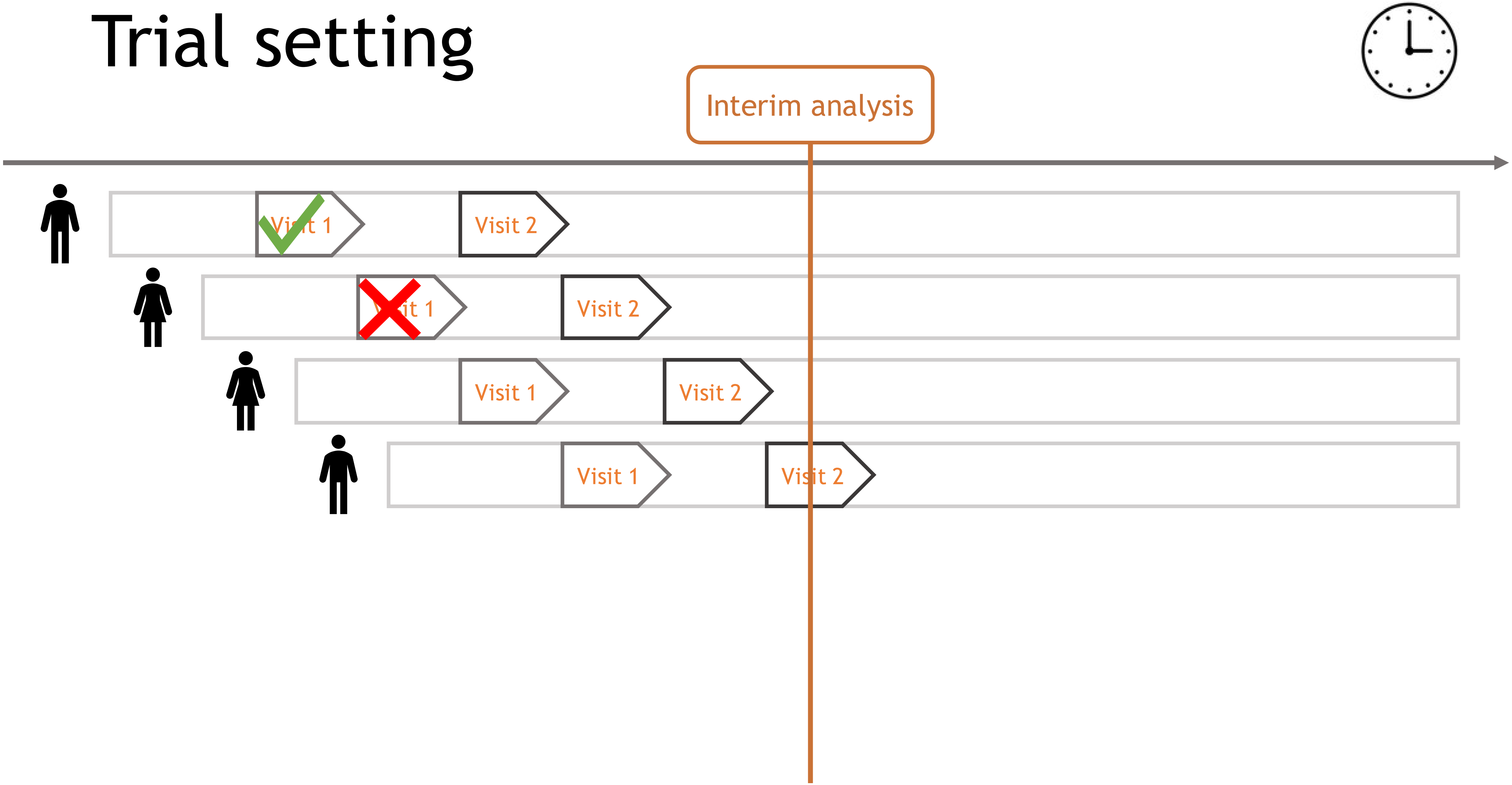


Trial setting



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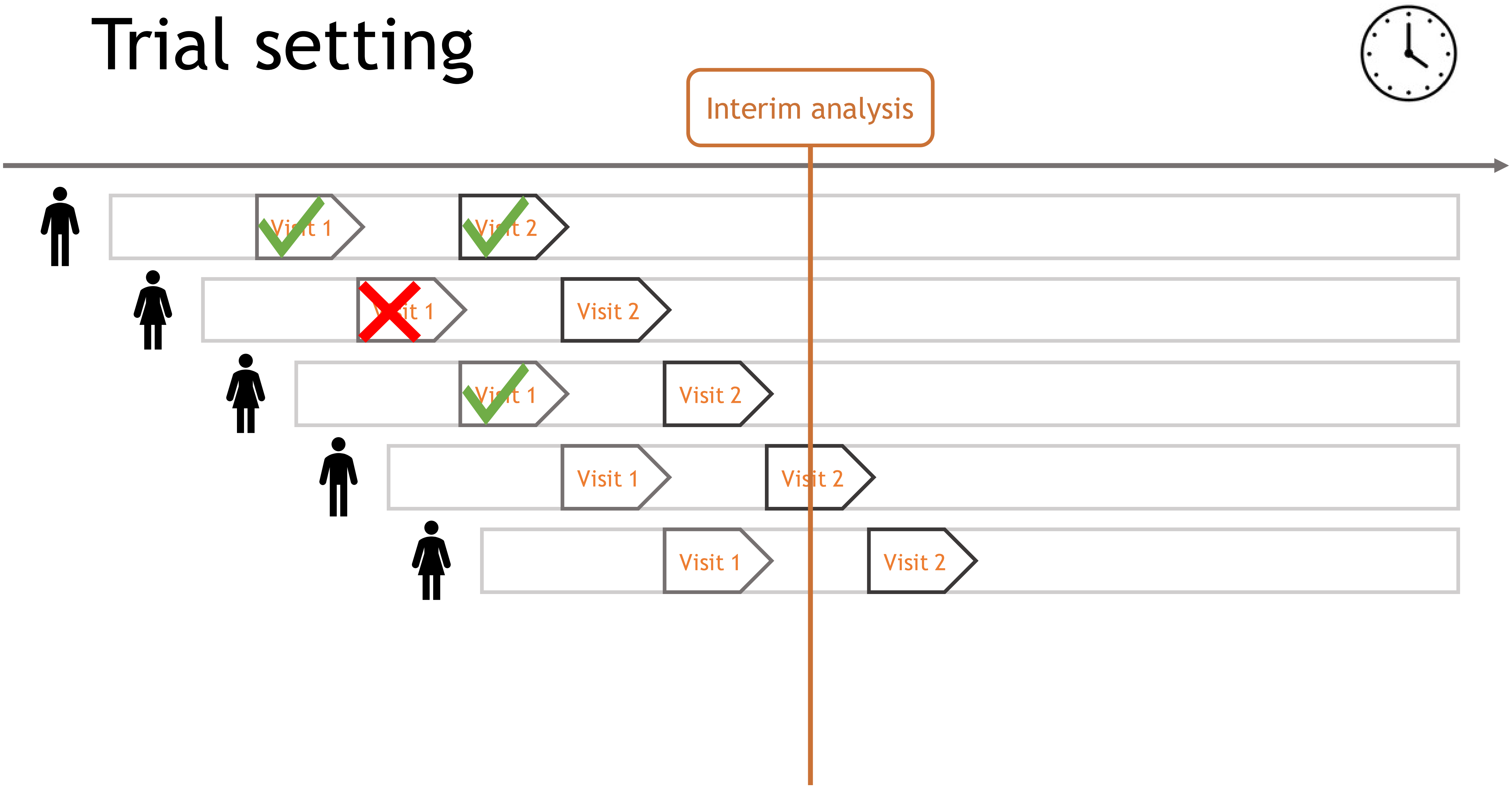

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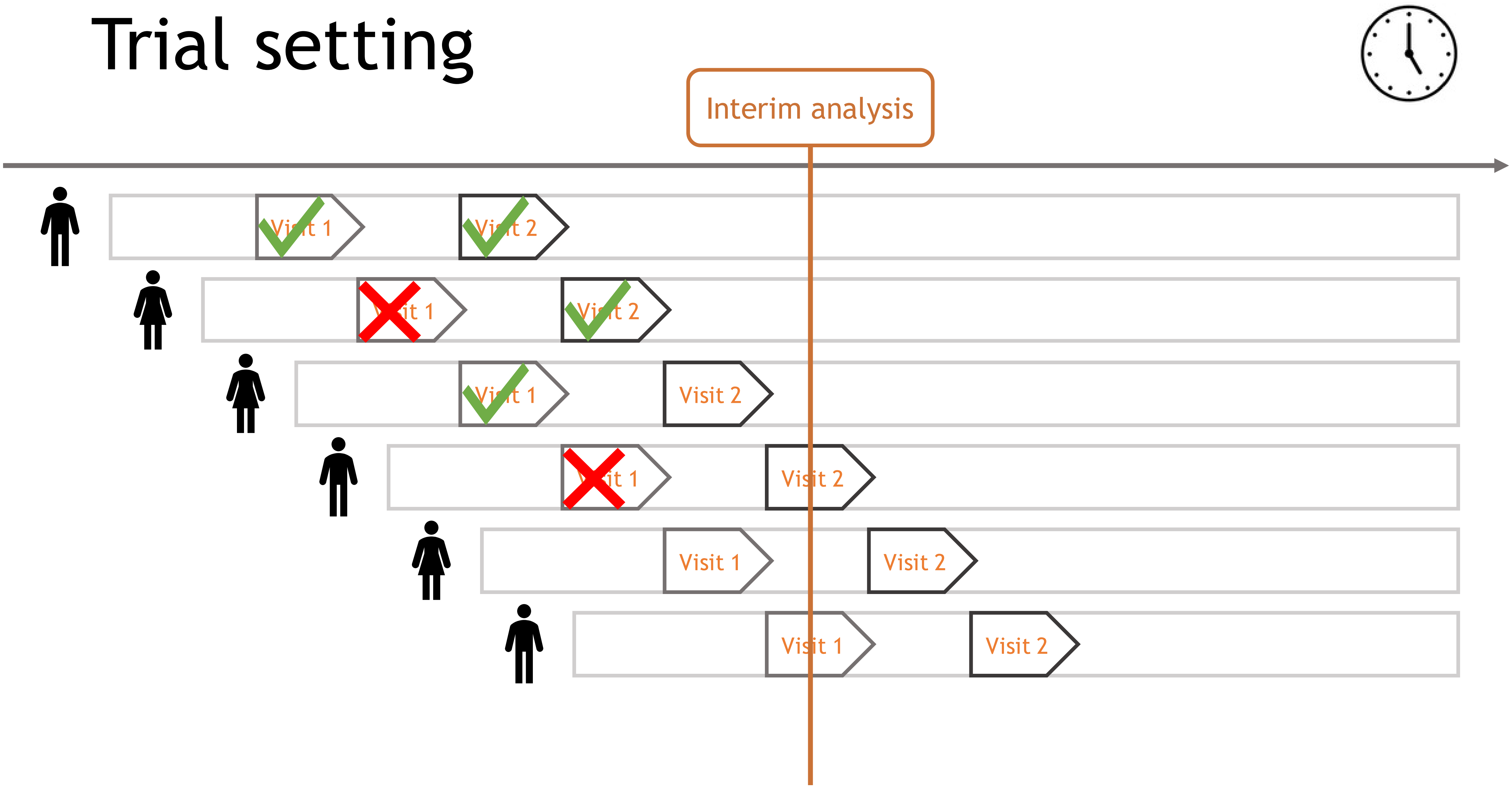

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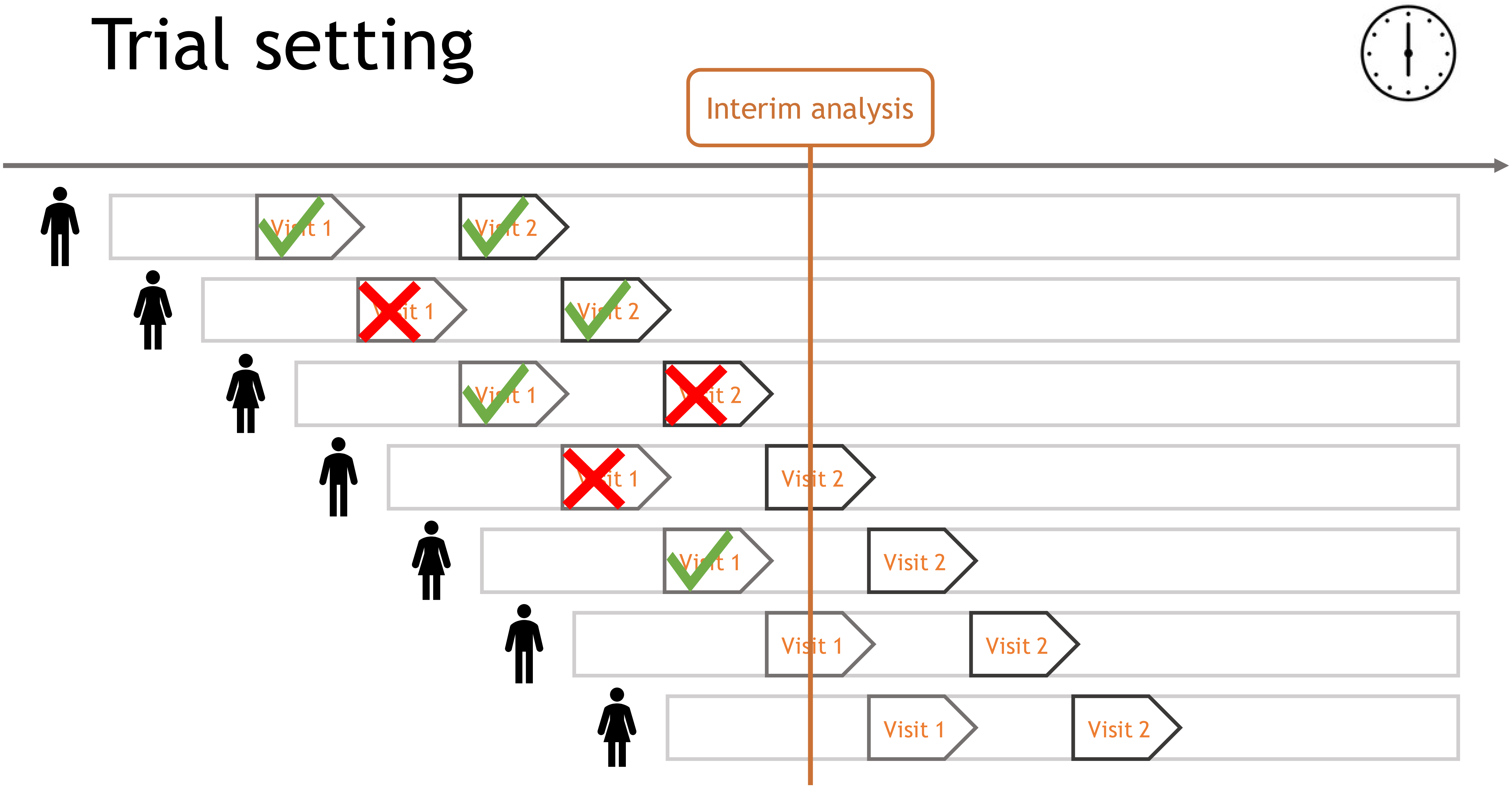

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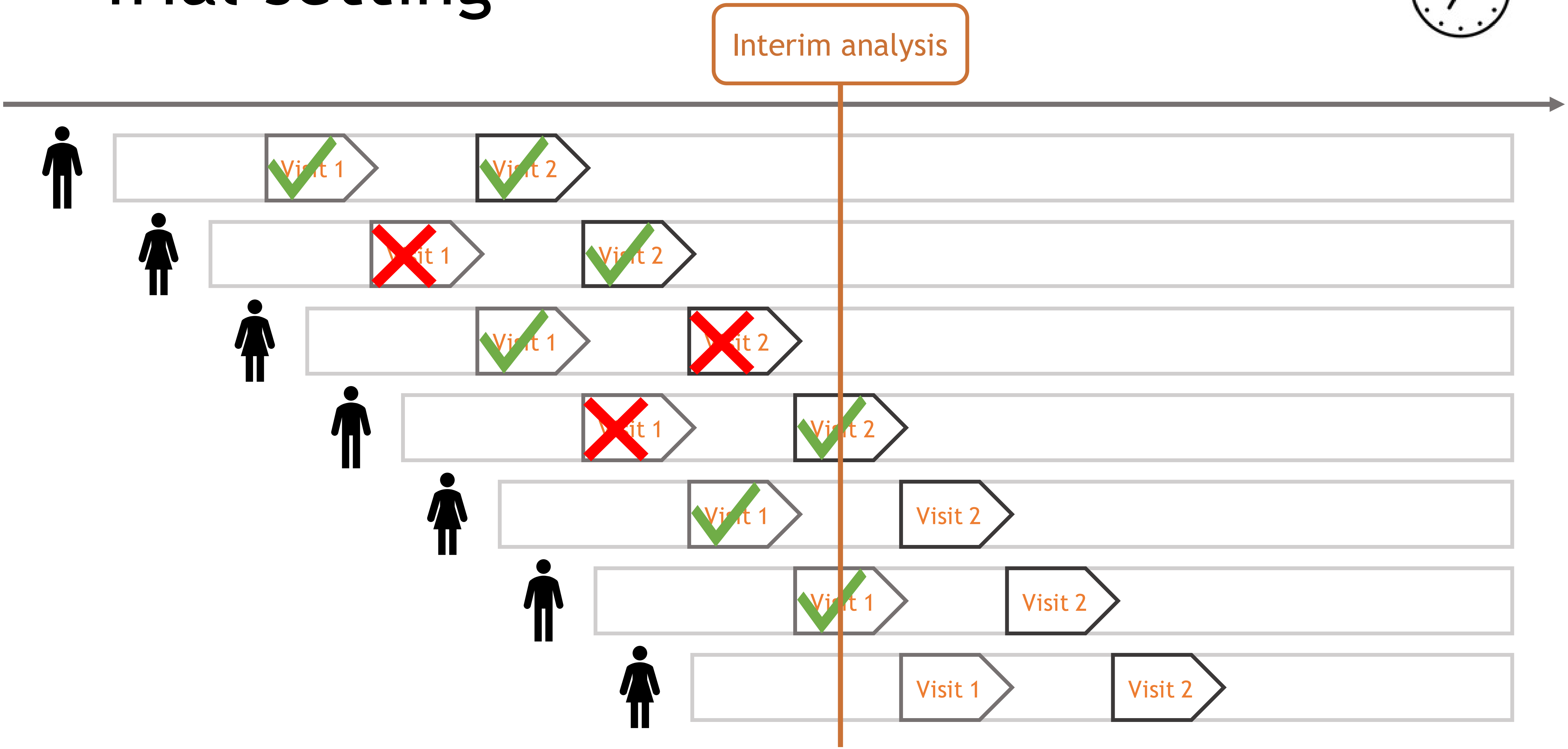

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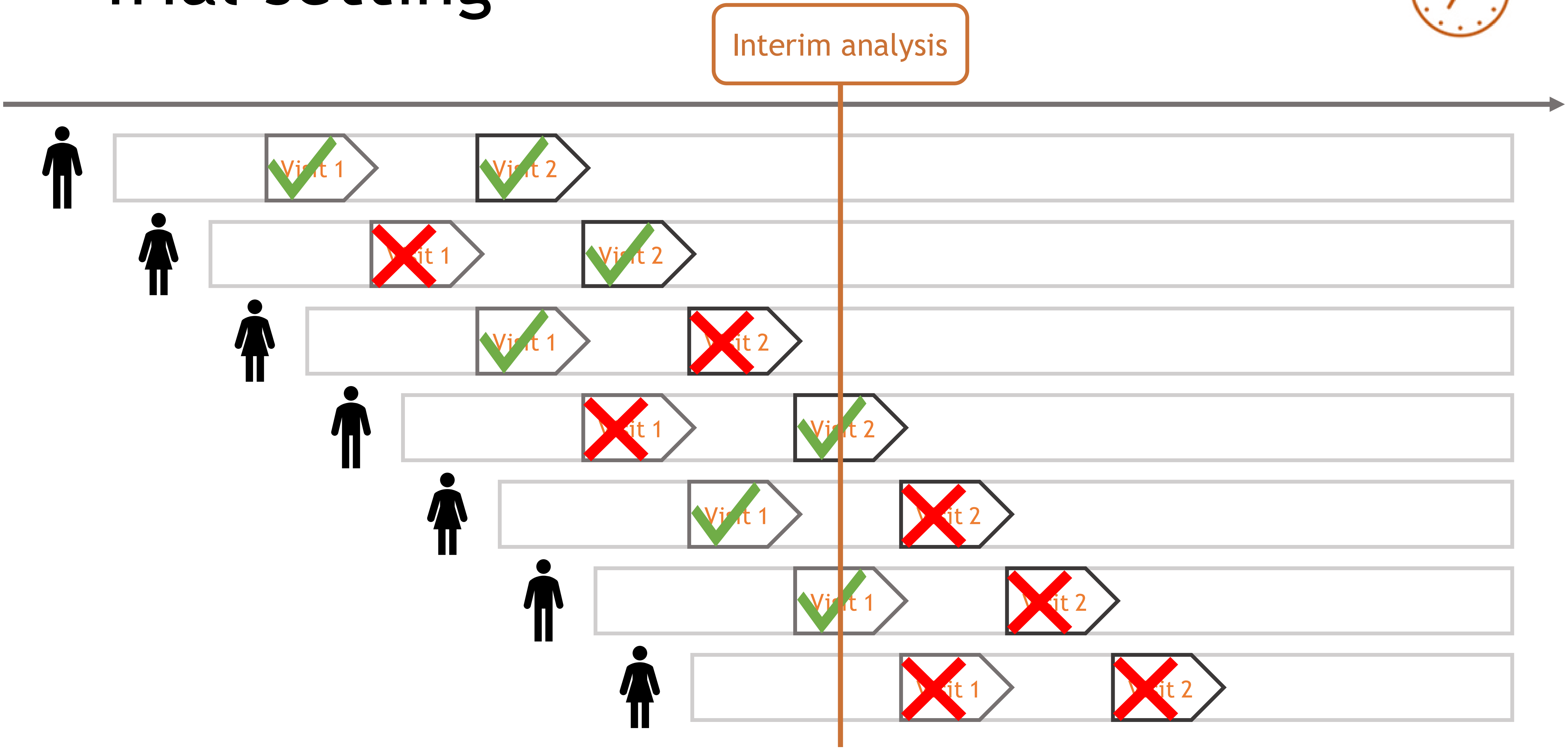

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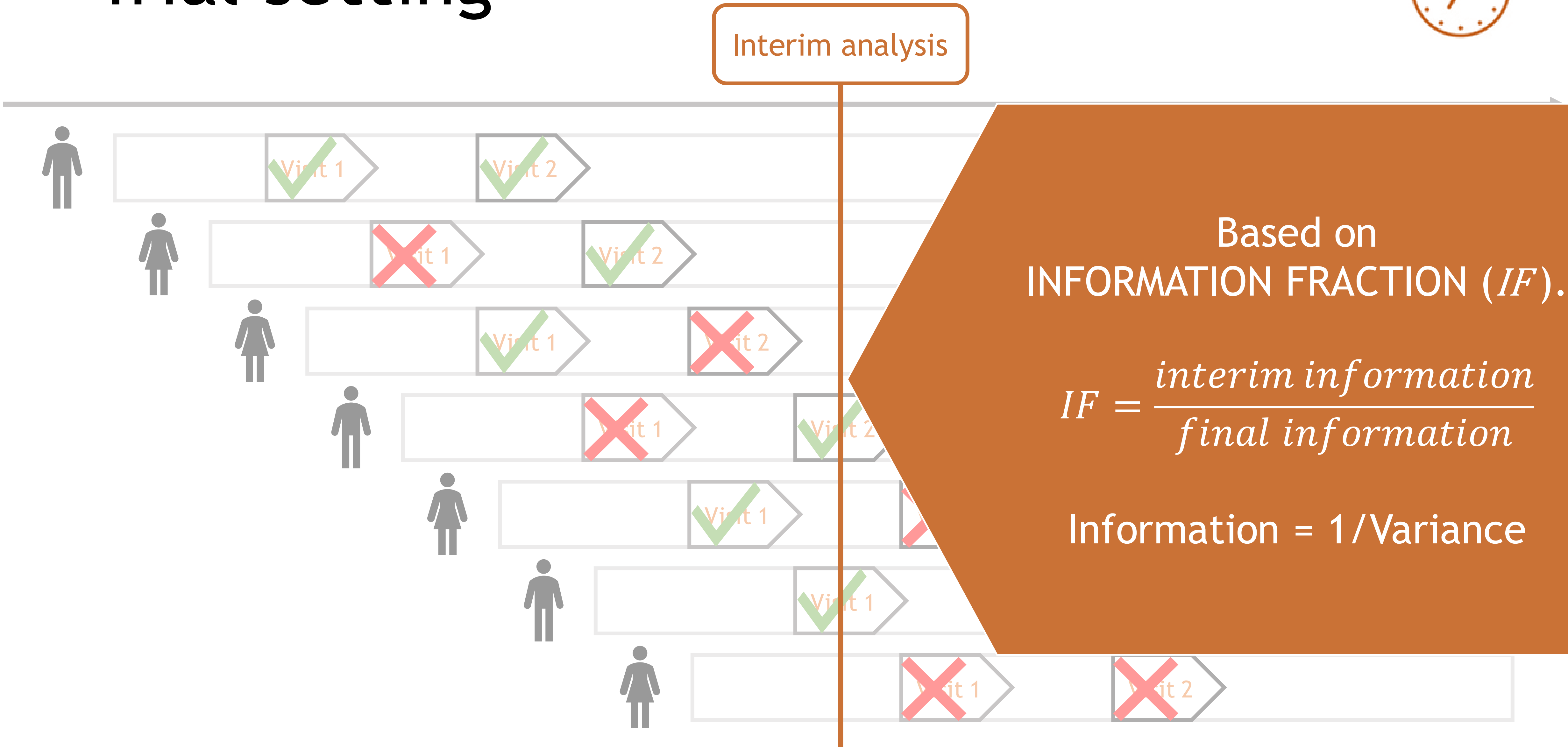

Based on
INFORMATION FRACTION (IF).

$$IF = \frac{interim\ information}{final\ information}$$

Information = 1/Variance

Data patterns

Pattern	Visit 1	Visit 2
1	✓	✓
2	✗	✓
3	✓	✗
0	✗	✗

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Data structure

Pattern	Visit 1	Visit 2	
1	$\bar{X}_{11}$	$\bar{X}_{12}$	n_1
2	NA	$\bar{X}_{22}$	n_2
3	$\bar{X}_{31}$	NA	n_3
0	NA	NA	n_0

Data structure

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

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

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

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

Data modelling

Pattern	Visit 1	Visit 2	
1	$\bar{X}_{11}$	$\bar{X}_{12}$	n_1
2	NA	$\bar{X}_{22}$	n_2
3	$\bar{X}_{31}$	NA	n_3

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

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

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

$$\boldsymbol{Y} = \begin{pmatrix}\bar{X}_{11}\\ \bar{X}_{12}\\ \bar{X}_{22}\\ \bar{X}_{31}\end{pmatrix} \quad E(\boldsymbol{Y}) = \begin{pmatrix}\mu_1\\ \mu_2\\ \mu_2\\ \mu_1\end{pmatrix} = D\boldsymbol{\mu} = \begin{pmatrix}1 & 0\\ 0 & 1\\ 0 & 1\\ 1 & 0\end{pmatrix}\begin{pmatrix}\mu_1\\ \mu_2\end{pmatrix}$$

$$Var(\boldsymbol{Y}) = \sigma^2\begin{pmatrix}\frac{1}{n_1} & \frac{\rho^2}{n_1} & 0 & 0\\ \frac{\rho^2}{n_1} & \frac{1}{n_1} & & \\ 0 & & \frac{1}{n_2} & 0\\ 0 & & 0 & \frac{1}{n_3}\end{pmatrix}$$

Data modelling

Pattern	Visit 1	Visit 2	
1	$\bar{X}_{11}$	$\bar{X}_{12}$	n_1
2	NA	$\bar{X}_{22}$	n_2
3	$\bar{X}_{31}$	NA	n_3

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

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

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

Parameter of interest: μ_2

$$\boldsymbol{Y} = \begin{pmatrix}\bar{X}_{11}\\ \bar{X}_{12}\\ \bar{X}_{22}\\ \bar{X}_{31}\end{pmatrix} \quad E(\boldsymbol{Y}) = \begin{pmatrix}\mu_1\\ \mu_2\\ \mu_2\\ \mu_1\end{pmatrix} = D\boldsymbol{\mu} = \begin{pmatrix}1 & 0\\ 0 & 1\\ 0 & 1\\ 1 & 0\end{pmatrix}\begin{pmatrix}\mu_1\\ \mu_2\end{pmatrix}$$

$$Var(\boldsymbol{Y}) = \sigma^2\begin{pmatrix}\begin{matrix}\frac{1}{n_1} & \frac{\rho^2}{n_1}\\ \frac{\rho^2}{n_1} & \frac{1}{n_1}\end{matrix} & 0 & 0\\ 0 & \frac{1}{n_2} & 0\\ 0 & 0 & \frac{1}{n_3}\end{pmatrix}$$

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Variance of $\hat{\mu}_2$

Pattern	Visit 1	Visit 2	
1	$\bar{X}_{11}$	$\bar{X}_{12}$	n_1
2	NA	$\bar{X}_{22}$	n_2
3	$\bar{X}_{31}$	NA	n_3

$$\boldsymbol{Y} = \begin{pmatrix} \bar{X}_{11} \\ \bar{X}_{12} \\ \bar{X}_{22} \\ \bar{X}_{31} \end{pmatrix} \quad E(\boldsymbol{Y}) = \begin{pmatrix} \mu_1 \\ \mu_2 \\ \mu_2 \\ \mu_1 \end{pmatrix} = D\boldsymbol{\mu} = \begin{pmatrix} 1 & 0 \\ 0 & 1 \\ 0 & 1 \\ 1 & 0 \end{pmatrix} \begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix}$$

$$Var(\boldsymbol{Y}) = \sigma^2 \begin{pmatrix} \begin{matrix} \frac{1}{n_1} & \frac{\rho^2}{n_1} \\ \frac{\rho^2}{n_1} & \frac{1}{n_1} \end{matrix} & 0 & 0 \\ 0 & \frac{1}{n_2} & 0 \\ 0 & 0 & \frac{1}{n_3} \end{pmatrix}$$

$$\hat{\mu}_2 = (0 \quad 1)(D^T Var(\boldsymbol{Y})^{-1} D)^{-1} D^T Var(\boldsymbol{Y})^{-1} \boldsymbol{Y}$$

$$Var(\hat{\mu}_2) = \begin{pmatrix} 0 & 0 \\ 0 & 1 \end{pmatrix} (D^T Var(\boldsymbol{Y})^{-1} D)^{-1}$$

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

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Information of $\hat{\mu}_2$

Pattern	Visit 1	Visit 2	
1	$\bar{X}_{11}$	$\bar{X}_{12}$	n_1
2	NA	$\bar{X}_{22}$	n_2
3	$\bar{X}_{31}$	NA	n_3

$$\boldsymbol{Y} = \begin{pmatrix} \bar{X}_{11} \\ \bar{X}_{12} \\ \bar{X}_{22} \\ \bar{X}_{31} \end{pmatrix} \quad E(\boldsymbol{Y}) = \begin{pmatrix} \mu_1 \\ \mu_2 \\ \mu_2 \\ \mu_1 \end{pmatrix} = D\boldsymbol{\mu} = \begin{pmatrix} 1 & 0 \\ 0 & 1 \\ 0 & 1 \\ 1 & 0 \end{pmatrix} \begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix}$$

$$Var(\boldsymbol{Y}) = \sigma^2 \begin{pmatrix} \begin{matrix} \frac{1}{n_1} & \frac{\rho^2}{n_1} \\ \frac{\rho^2}{n_1} & \frac{1}{n_1} \end{matrix} & 0 & 0 \\ 0 & \frac{1}{n_2} & 0 \\ 0 & 0 & \frac{1}{n_3} \end{pmatrix}$$

$$\hat{\mu}_2 = (0 \quad 1)(D^T Var(\boldsymbol{Y})^{-1} D)^{-1} D^T Var(\boldsymbol{Y})^{-1} \boldsymbol{Y}$$

$$Var(\hat{\mu}_2) = \begin{pmatrix} 0 & 0 \\ 0 & 1 \end{pmatrix} (D^T Var(\boldsymbol{Y})^{-1} D)^{-1}$$

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

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

Equivalent sample size

Pattern	Visit 1	Visit 2	
1	$\bar{X}_{11}$	$\bar{X}_{12}$	n_1
2	NA	$\bar{X}_{22}$	n_2
3	$\bar{X}_{31}$	NA	n_3

<u>Complete patients only (Pattern 1):</u>

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

<u>Partial patients:</u>

$$I(\hat{\mu}_2) = \frac{\boxed{\dfrac{n_1(n_1+n_2+n_3)+n_2n_3(1-\rho^2)}{n_1+n_3(1-\rho^2)}}}{\sigma^2}$$

How many complete patients are the partial patients equivalent to?

$$n \equiv \frac{n_1(n_1+n_2+n_3)+n_2n_3(1-\rho^2)}{n_1+n_3(1-\rho^2)}$$

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Timing of the interim analysis

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

$$\boldsymbol{IF} = \frac{\text{interim information}}{\text{final information}} = \frac{\frac{\text{interim equivalent sample size}}{\sigma^2}}{\frac{\text{final equivalent sample size}}{\sigma^2}} = \boldsymbol{\frac{\textbf{interim equivalent sample size}}{\textbf{final equivalent sample size}}}$$

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WHEN WILL WE REACH 50% OF THE FINAL INFORMATION?

PRACTICAL EXAMPLE

Pattern	Visit 1	Visit 2	
1	$\bar{X}_{11}$	$\bar{X}_{12}$	n_1

1. Design stage

Assumptions

- Visit 1: 6 months
- Visit 2: 12 months
- Enrolment rate: 7/month
- Final equivalent sample size = 190
- Correlation between visits $\rho = 0.8$
- No missing data (Pattern 1 only)

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Pattern	Visit 1	Visit 2	
1	$\bar{X}_{11}$	$\bar{X}_{12}$	n_1

1. Design stage

Assumptions

- Visit 1: 6 months
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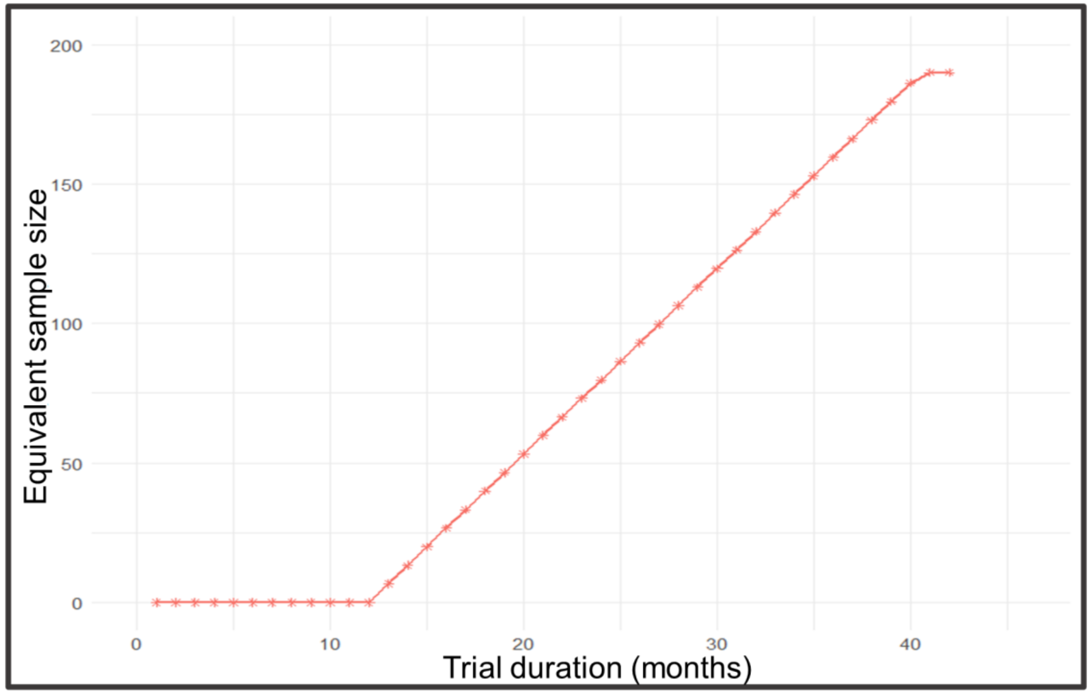

Pattern	Visit 1	Visit 2
1	$\bar{X}_{11}$	$\bar{X}_{12}$

n_1

1. Design stage

Assumptions

- Visit 1: 6 months
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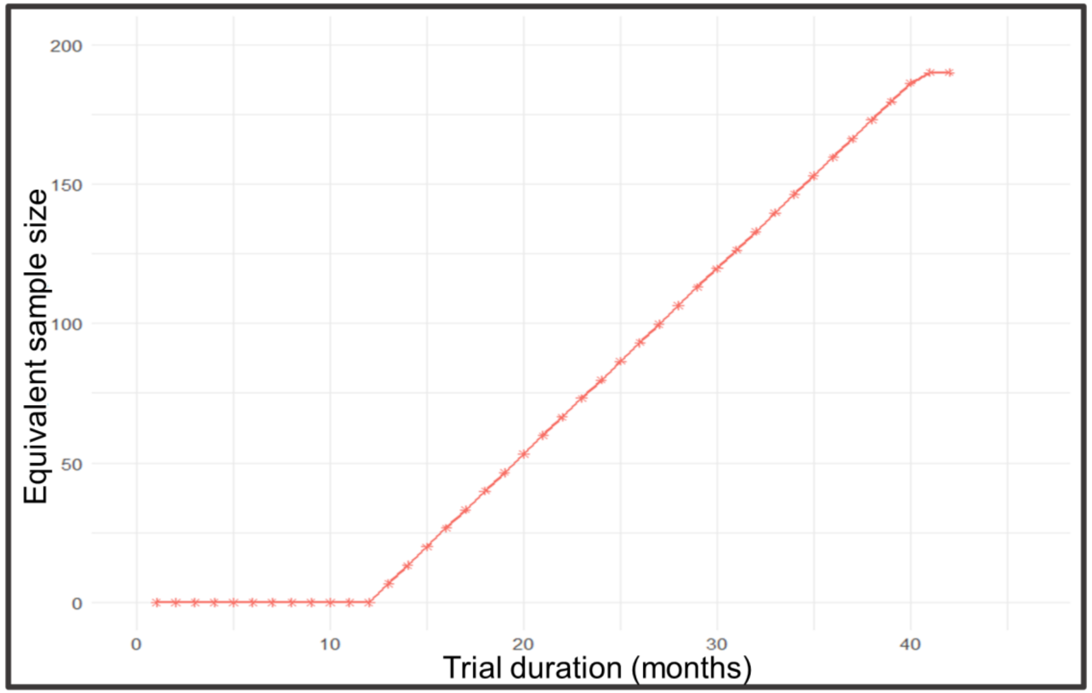
WHEN WILL WE REACH 50% OF THE FINAL INFORMATION?



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1	$\bar{X}_{11}$	$\bar{X}_{12}$	n_1

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- Enrolment rate: 7/month
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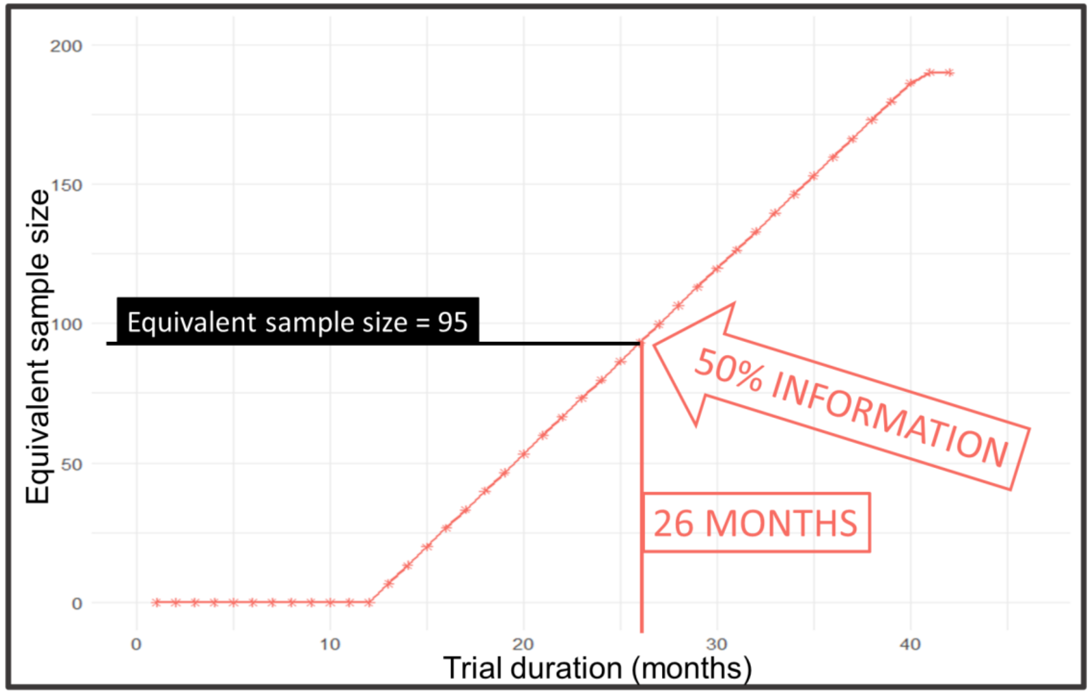
- No missing data (Pattern 1 only)

WHEN WILL WE REACH 50% OF THE FINAL INFORMATION? AT 26 MONTHS



Pattern	Visit 1	Visit 2	
1	$\bar{X}_{11}$	$\bar{X}_{12}$	n_1
3	$\bar{X}_{31}$	NA	n_3
0	NA	NA	n_0

1. Design stage

Assumptions

- Visit 1: 6 months
- Visit 2: 12 months
- Enrolment rate: 7/month
- Final equivalent sample size = 190
- Correlation between visits $\rho = 0.8$
- Missing data from staggered entry and dropout ($P(dropout) = 0.05$)

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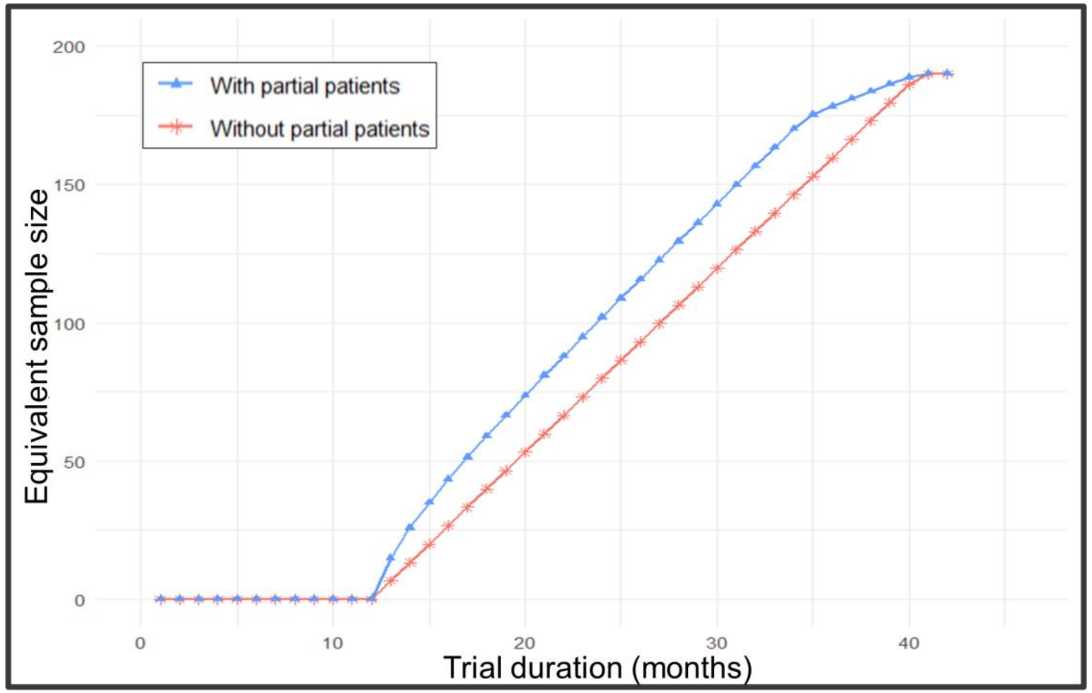
Pattern	Visit 1	Visit 2	
1	$\bar{X}_{11}$	$\bar{X}_{12}$	n_1
3	$\bar{X}_{31}$	NA	n_3
0	NA	NA	n_0

1. Design stage

Assumptions

- Visit 1: 6 months
- Visit 2: 12 months
- Enrolment rate: 7/month
- Final equivalent sample size = 190
- Correlation between visits $\rho = 0.8$
- Missing data from staggered entry and dropout ($P(dropout) = 0.05$)



Pattern	Visit 1	Visit 2	
1	$\bar{X}_{11}$	$\bar{X}_{12}$	n_1
3	$\bar{X}_{31}$	NA	n_3
0	NA	NA	n_0

1. Design stage

Assumptions

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- Final equivalent sample size = 190
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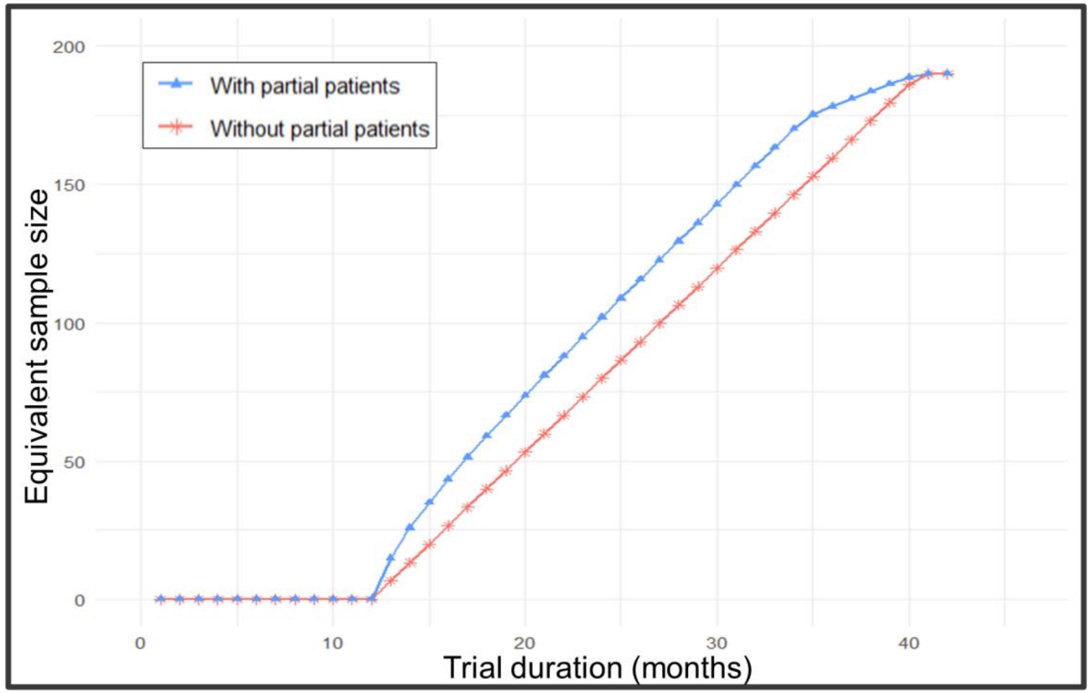
WHEN WILL WE REACH 50% OF THE FINAL INFORMATION?



1. Design stage

Pattern	Visit 1	Visit 2	
1	$\bar{X}_{11}$	$\bar{X}_{12}$	n_1
3	$\bar{X}_{31}$	NA	n_3
0	NA	NA	n_0

Assumptions

- Visit 1: 6 months
- Visit 2: 12 months
- Enrolment rate: 7/month
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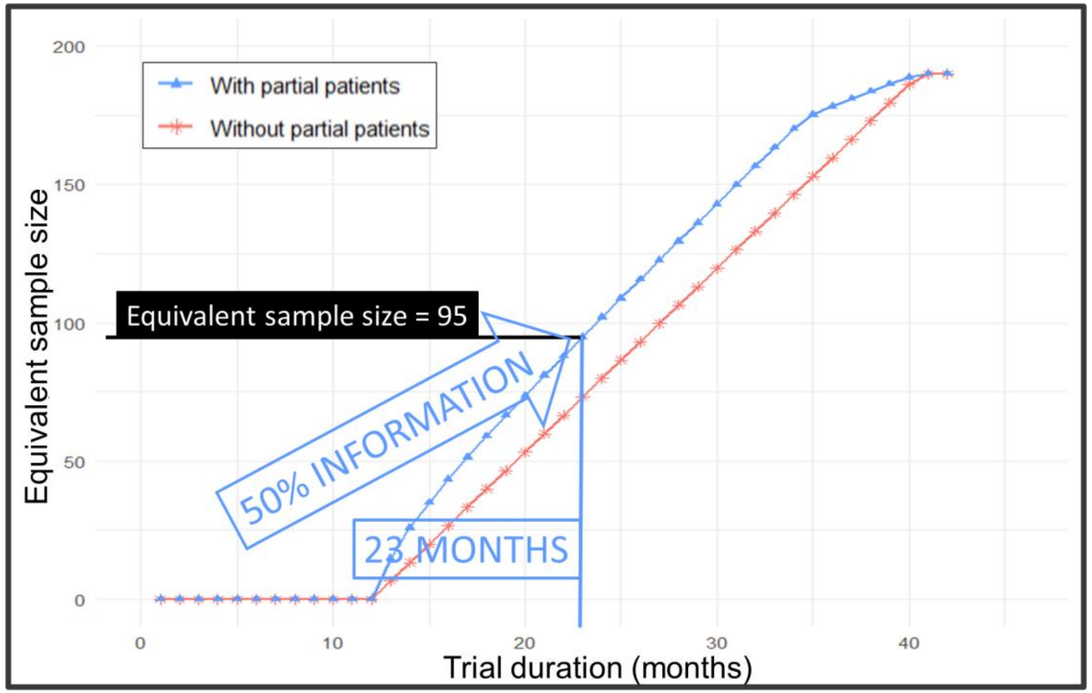
WHEN WILL WE REACH 50% OF THE FINAL INFORMATION? AT 23 MONTHS



1. Design stage

Pattern	Visit 1	Visit 2	
1	$\bar{X}_{11}$	$\bar{X}_{12}$	n_1
3	$\bar{X}_{31}$	NA	n_3
0	NA	NA	n_0

Assumptions

- Visit 1: 6 months
- Visit 2: 12 months
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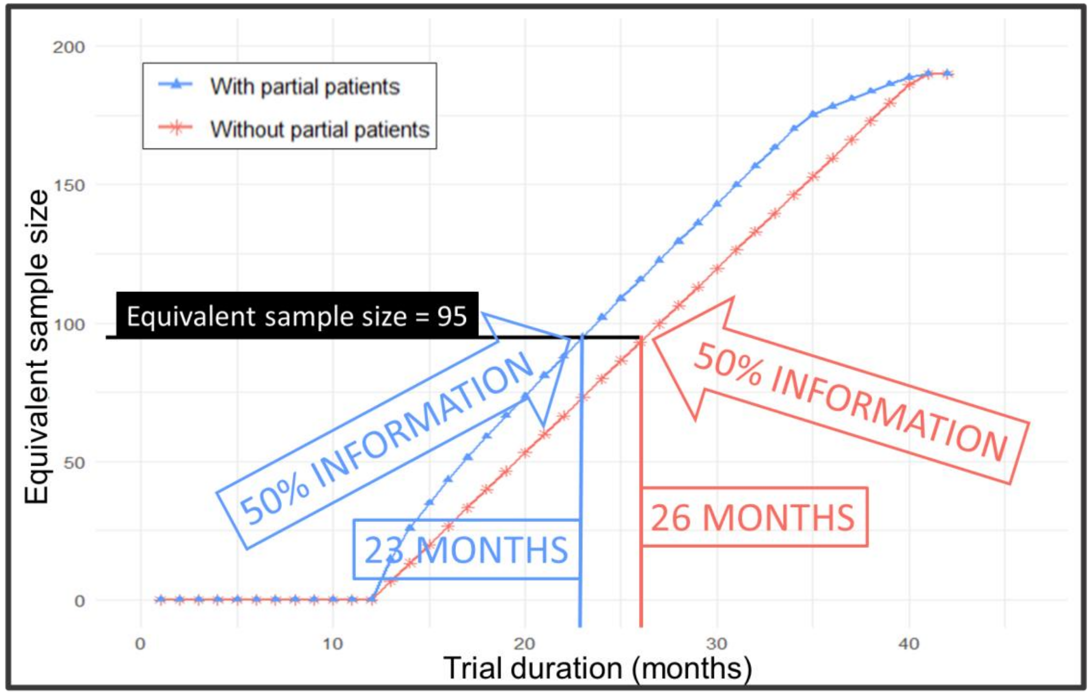

Pattern	Visit 1	Visit 2	
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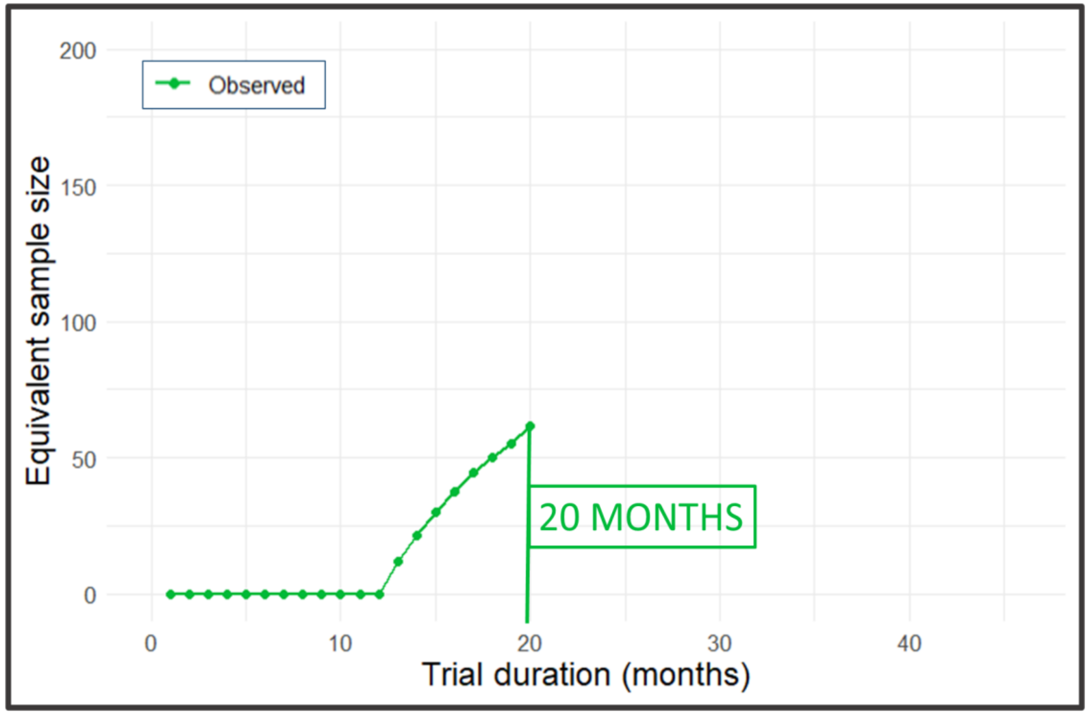
2	NA	$\bar{X}_{22}$	n_2
3	$\bar{X}_{31}$	NA	n_3
0	NA	NA	n_0

2. After observing some data

Observations at 20 months

- Lower enrolment rate (6/month)
- Unforeseen missingness $P(miss\ Visit\ 1) = 0.11, P(miss\ Visit\ 2) = 0.02$
- $n_1 = 42, n_2 = 5, n_3 = 33$



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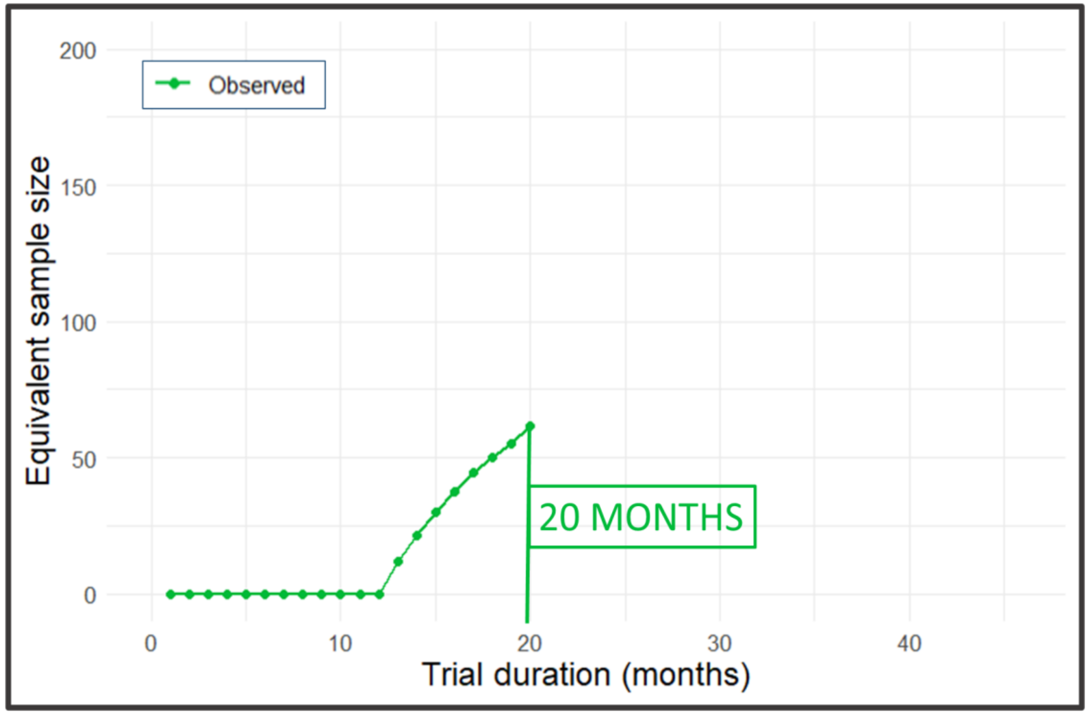

Assess current information level

2. After observing some data

Pattern	Visit 1	Visit 2	
1	$\bar{X}_{11}$	$\bar{X}_{12}$	n_1
2	NA	$\bar{X}_{22}$	n_2
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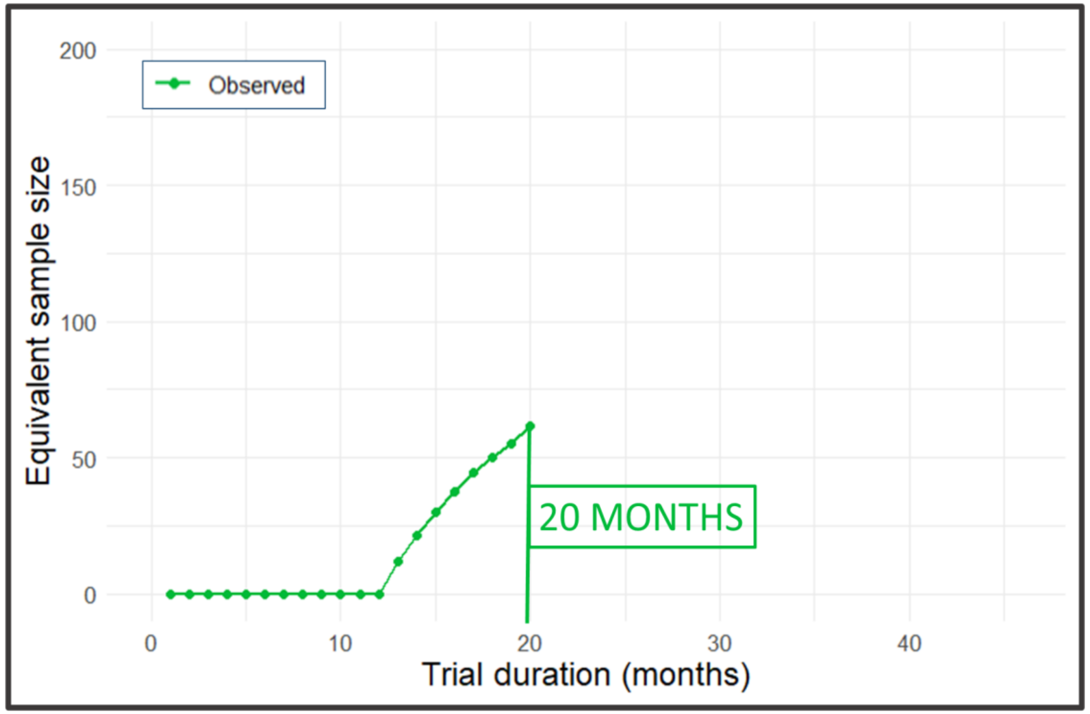

Assess current information level

→ incorporate prior belief

→ obtain updated probabilities

2. After observing some data

Pattern	Visit 1	Visit 2	
1	$\bar{X}_{11}$	$\bar{X}_{12}$	n_1
2	NA	$\bar{X}_{22}$	n_2
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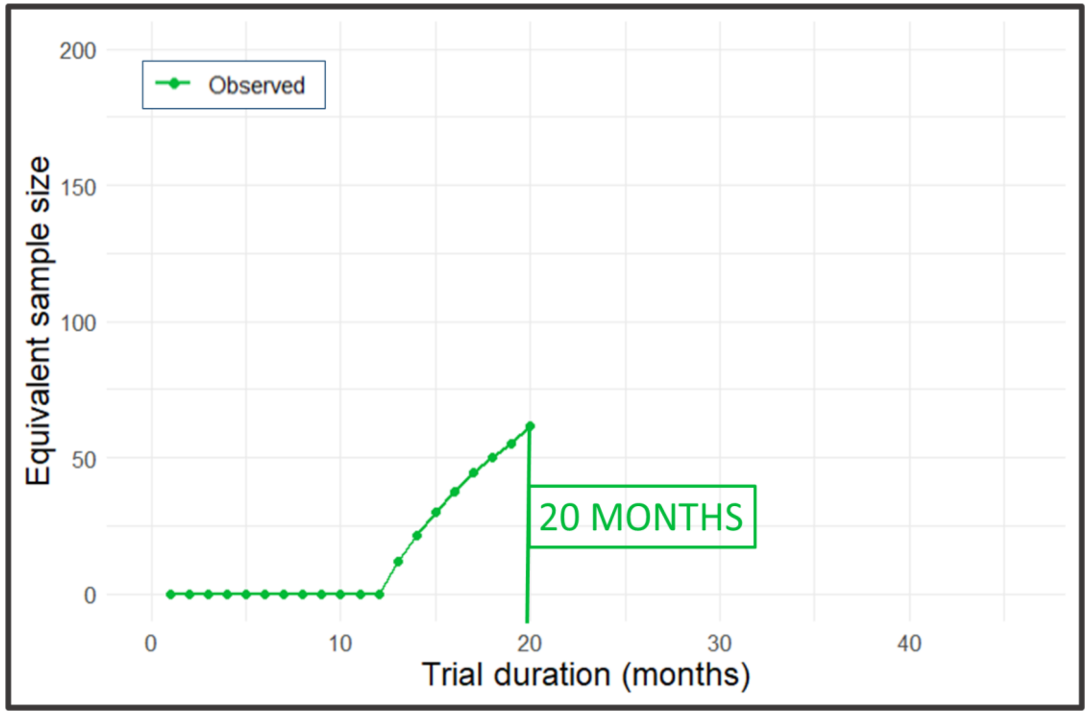

Assess current information level

→ incorporate prior belief

→ obtain updated probabilities

→ Calculate:

- current equivalent sample size = 62
- projected final equivalent sample size = 188

2. After observing some data

Pattern	Visit 1	Visit 2	
1	$\bar{X}_{11}$	$\bar{X}_{12}$	n_1
2	NA	$\bar{X}_{22}$	n_2
3	$\bar{X}_{31}$	NA	n_3
0	NA	NA	n_0

Observations at 20 months

- Lower enrolment rate (6/month)
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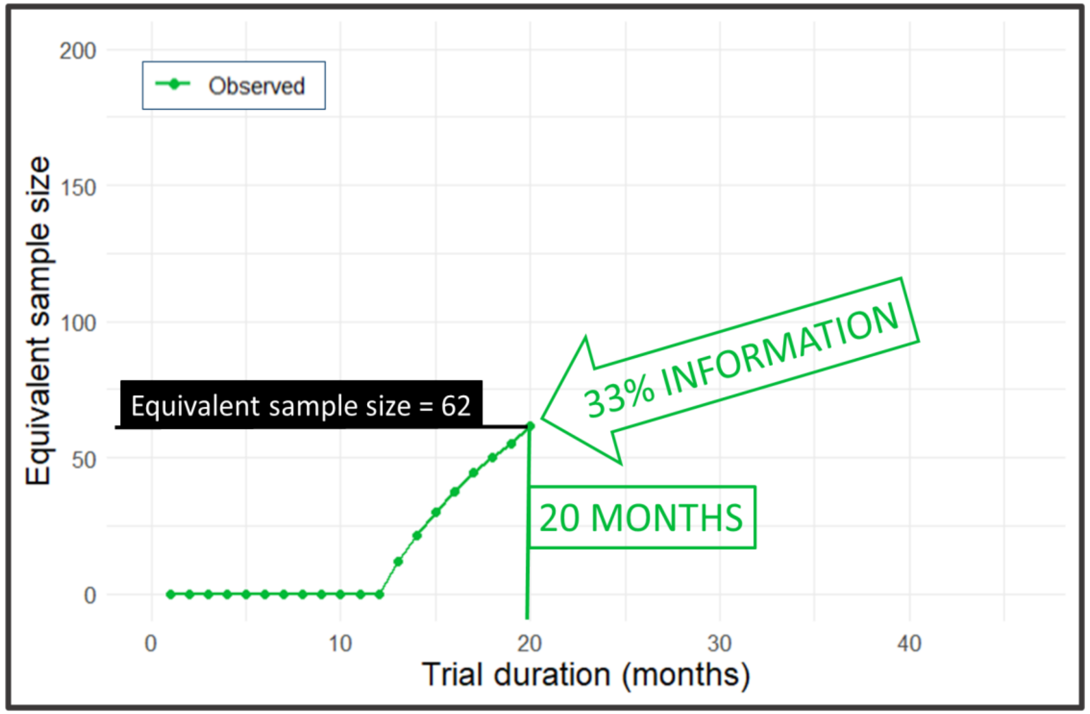


Assess current information level

→ incorporate prior belief

→ obtain updated probabilities

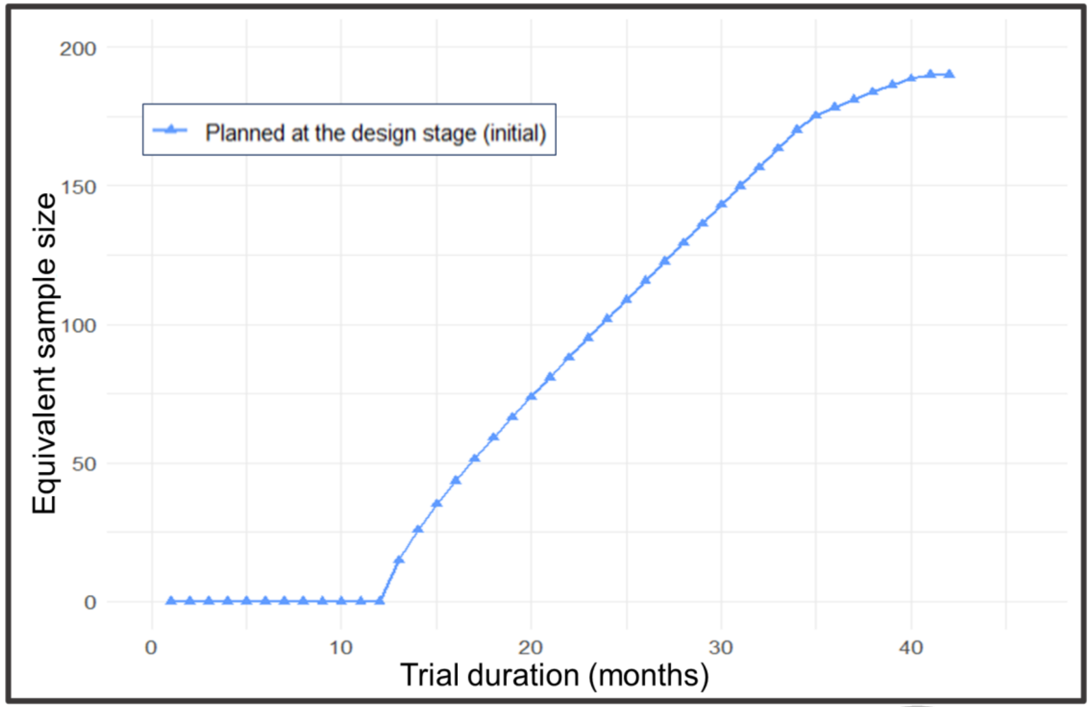
→ Calculate:

- current equivalent sample size = 62
- projected final equivalent sample size = 188

→ 62/188 = 33% information accrued

3. New projection

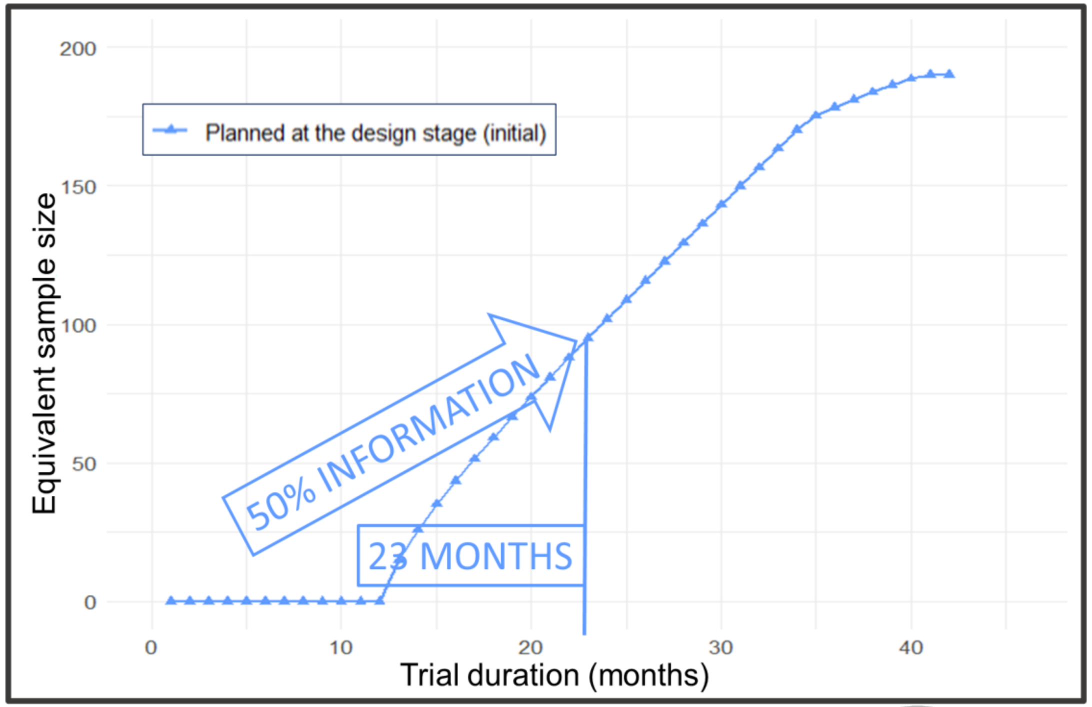
INITIAL PROJECTION



3. New projection

INITIAL PROJECTION

WHEN WILL WE REACH 50% OF THE FINAL INFORMATION? AT 23 MONTHS



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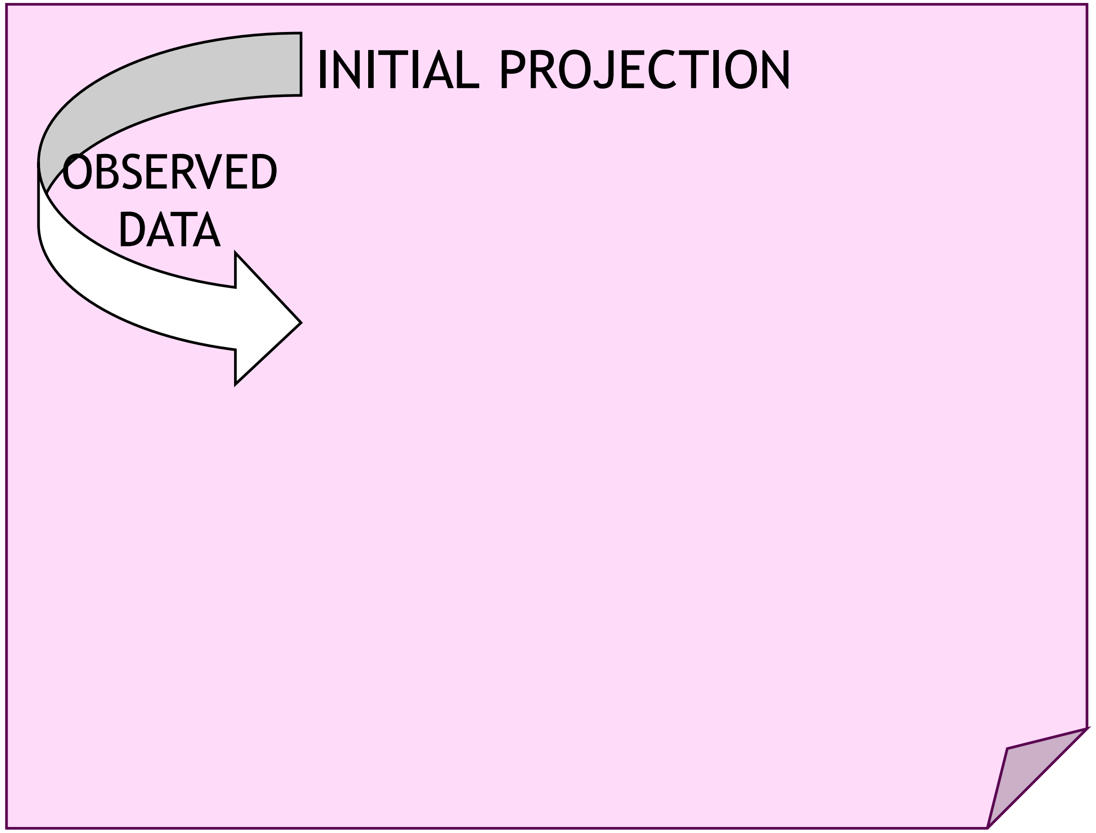

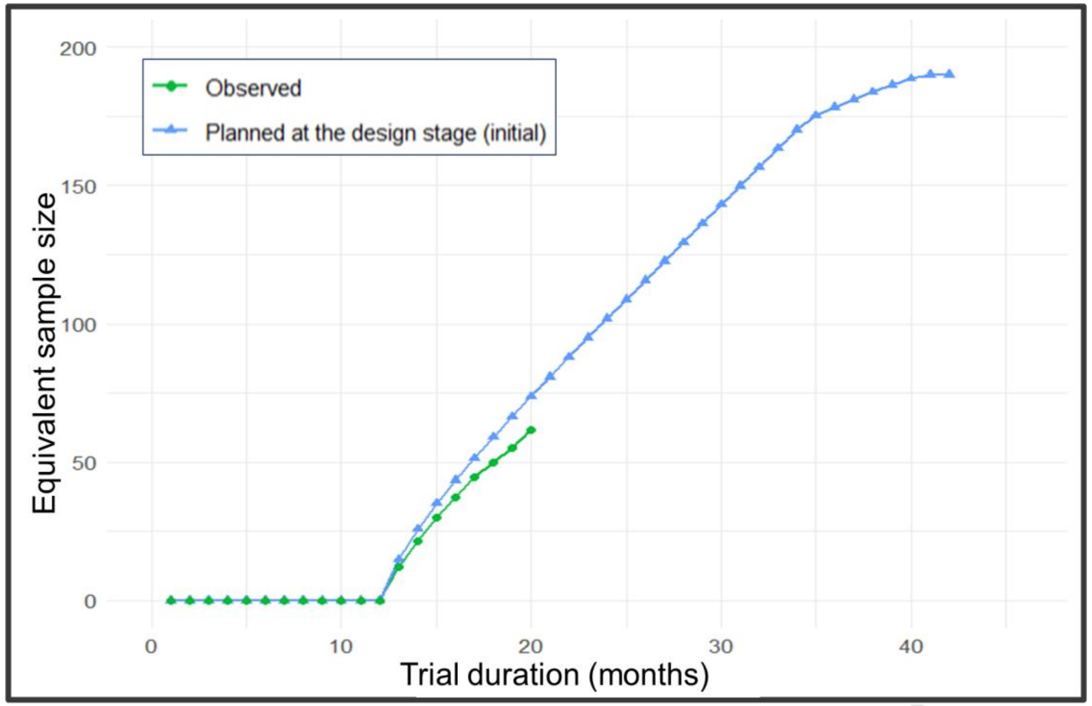

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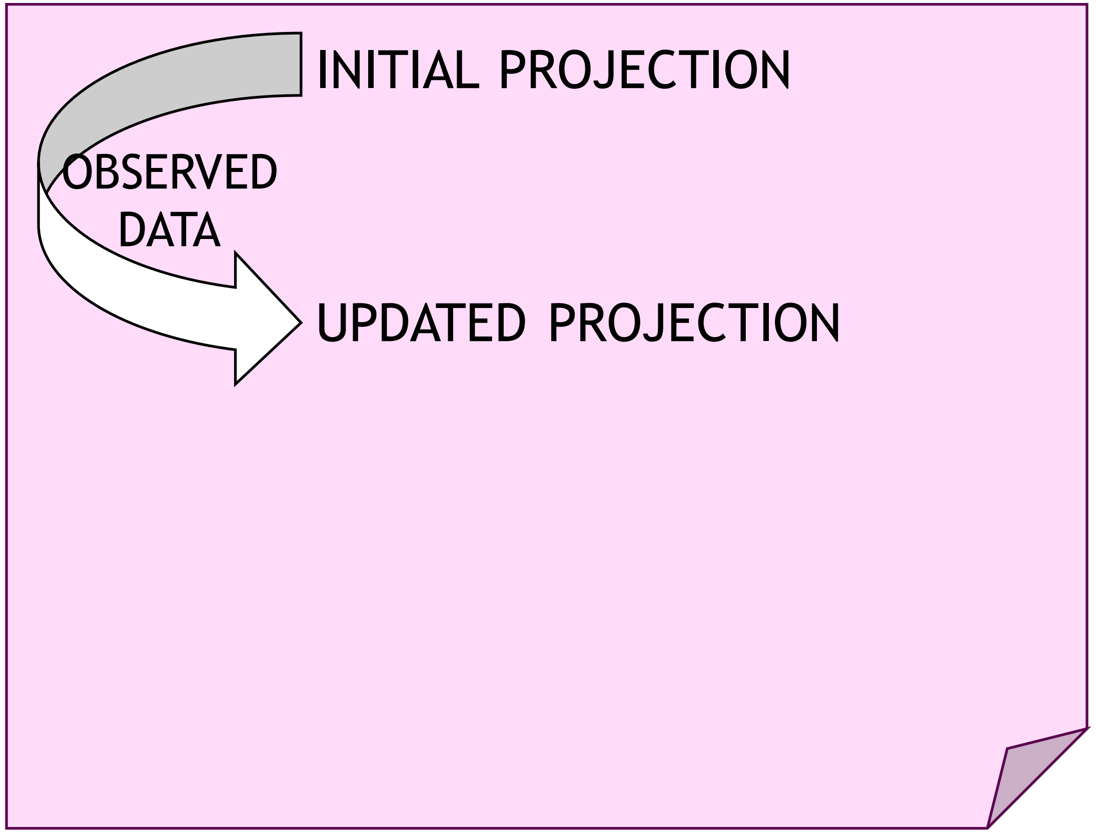
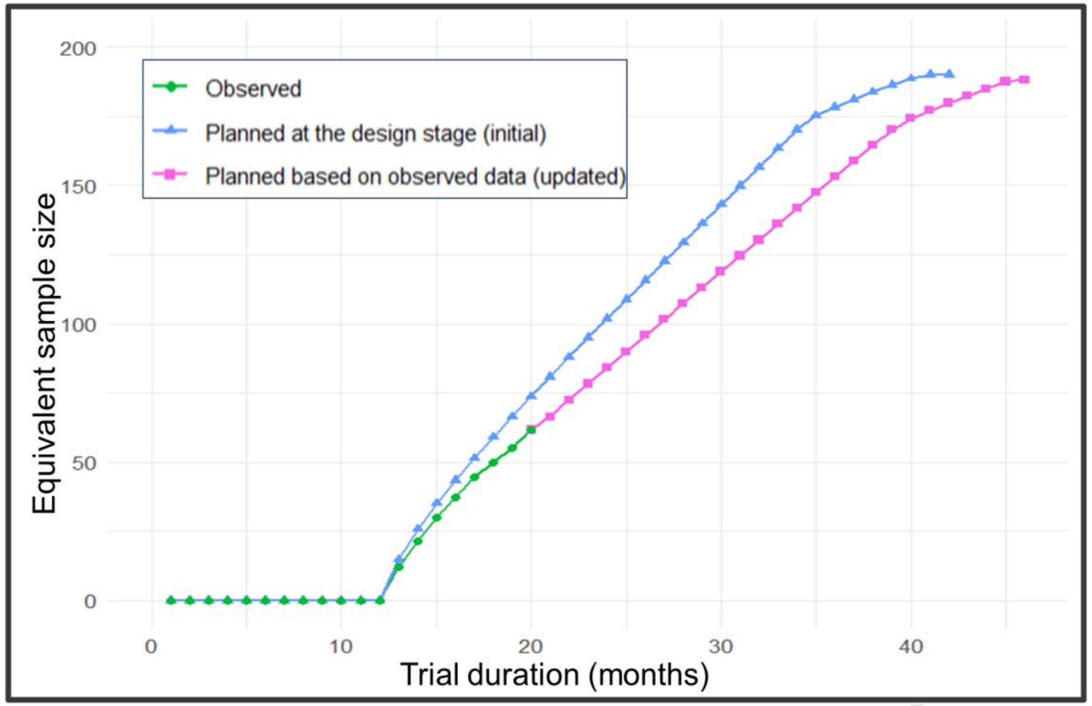




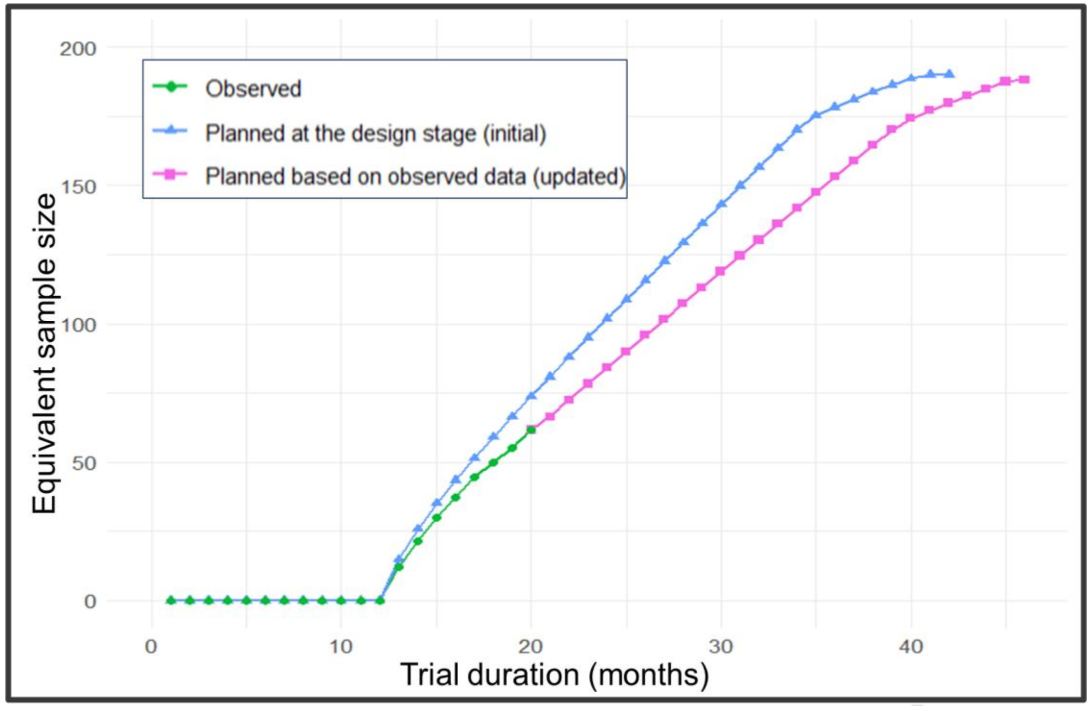
3. New projection

INITIAL PROJECTION

OBSERVED DATA

UPDATED PROJECTION

WHEN WILL WE REACH 50% OF THE FINAL INFORMATION?



3. New projection

INITIAL PROJECTION

OBSERVED DATA

UPDATED PROJECTION

- Projected final equivalent sample size = 188

50% information

⇕

Equivalent sample size = 188/2 = 94

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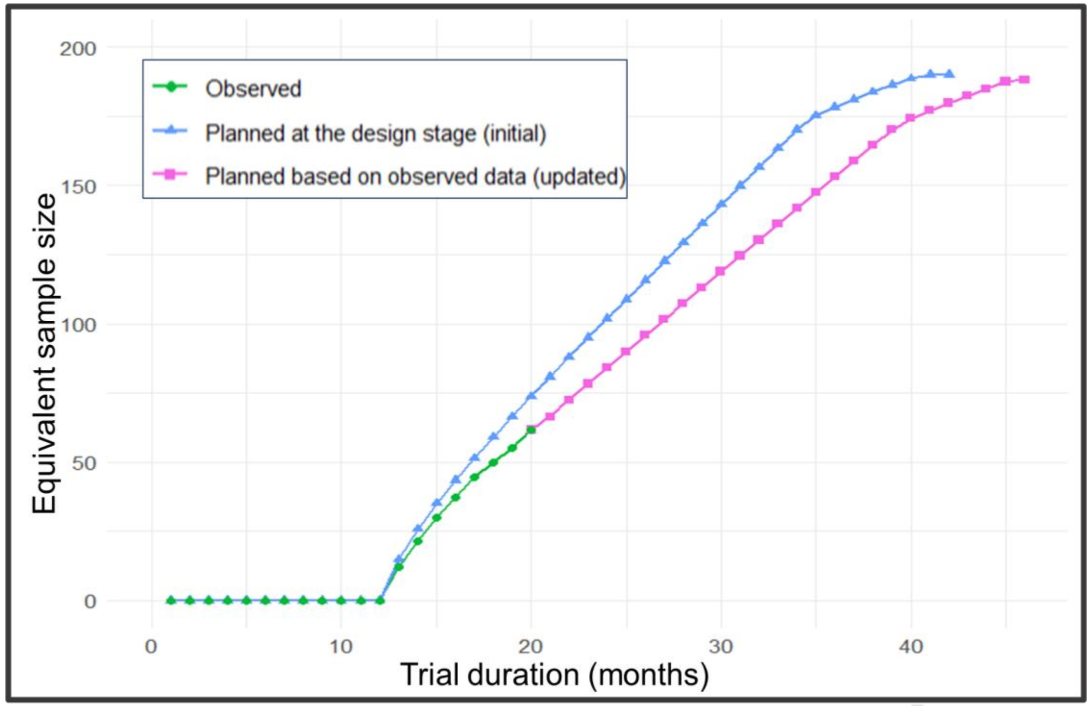
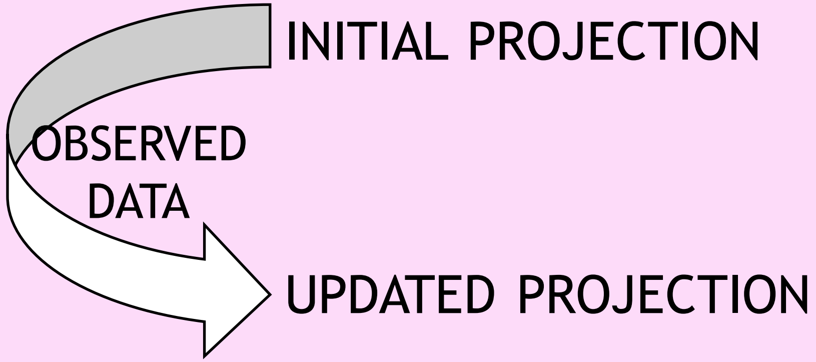


3. New projection



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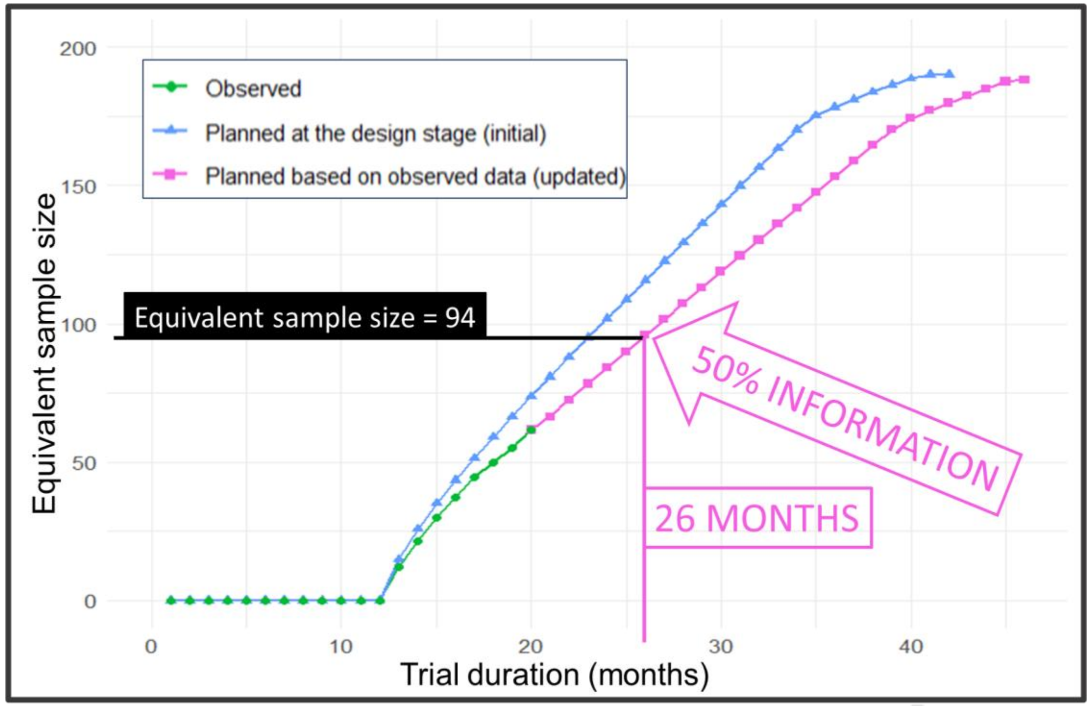
50% information

⇕

Equivalent sample size = 188/2 = 94

WHEN WILL WE REACH 50% OF THE FINAL INFORMATION? AT 26 MONTHS



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Summary

Group individuals with the same missingness patterns and apply the framework to:

- make timeline projections based on assumptions at the design stage
- assess information level during the trial
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Extensions

- more visits → approximation of equivalent sample size
- different target information level with any type of interim analysis
- different assumptions at the design stage (enrolment rate, dropout rate, etc.)
- single-patient contribution to the information level

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THANK YOU!

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