PEX MVD

MÉTHODOLOGIE ET VALORISATION DES DONNÉES

ENSAI

École nationale de la statistique et de l'analyse de l'information

EVALUATION OF THE EXCHANGEABILITY NON-EXCHANGEABILITY METHODOLOGY IN PHASE II POC STUDIES

Audrey PUAUD

20nd November 2018

SERVIER

Contents

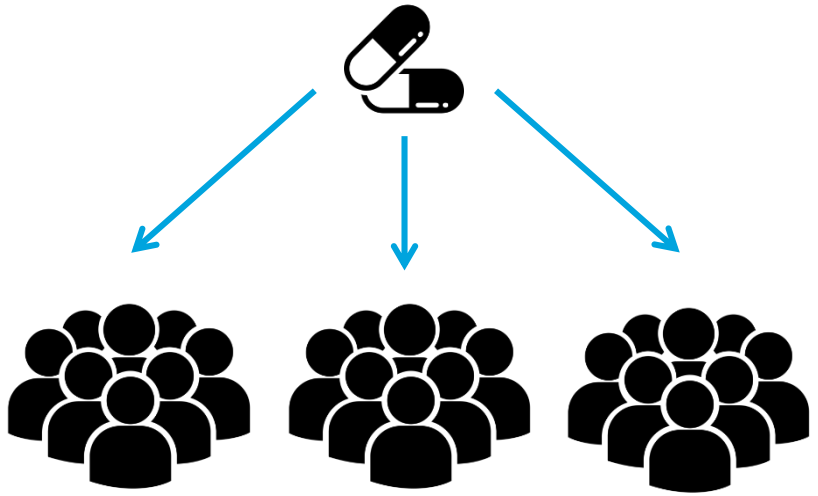
Context

What?

Oncology

Early phases (I/II)

Multiple **subgroups**



Why?

To **identify** interesting strata **earlier**

To **combine information** in a single trial

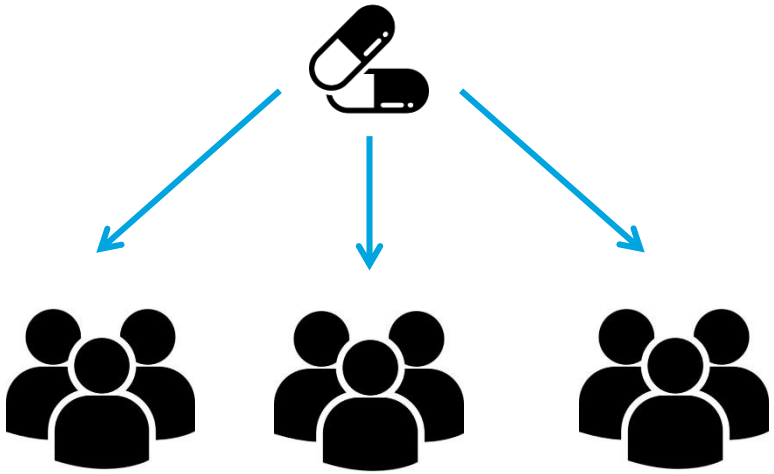
Context

What?

Oncology

Early phases (I/II)

Multiple **subgroups**



Why?

To **identify** interesting strata **earlier**

To **combine information** in a single trial

Context

- **Phase II Proof-of-Concept** trials

- **Binary** endpoint: response vs. no response (e.g tumour shrinkage)

True response rate of strata j

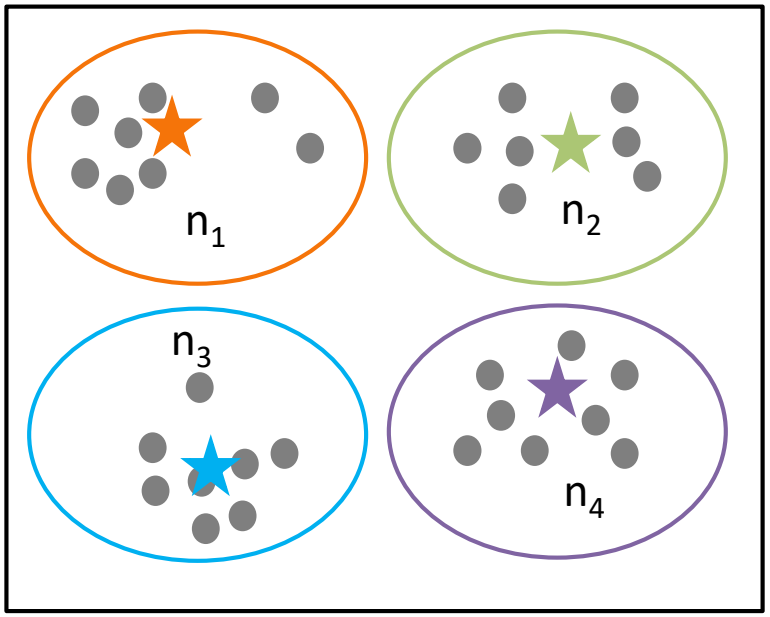
Number of responses of strata j ⇢ $Y_j|\pi_j \sim B(\pi_j, n_j)$ ⇠ *Number of patients of strata j*

Log-odds of the true response rate ⇢ $\theta_j = \log(\frac{\pi_j}{1-\pi_j})$

Standard methods

Stratification modeling

$$\theta_j \sim N(m_j, v_j)$$



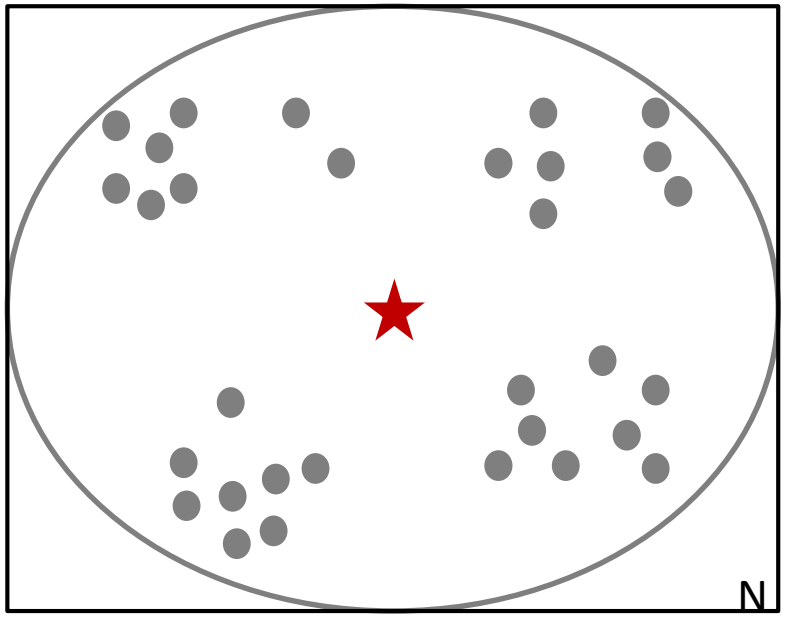
Estimates per group

Reliability?
Over-interpretation?

Standard methods

Pooling

$$\theta \sim N(m, v)$$



Precision

No estimate per group

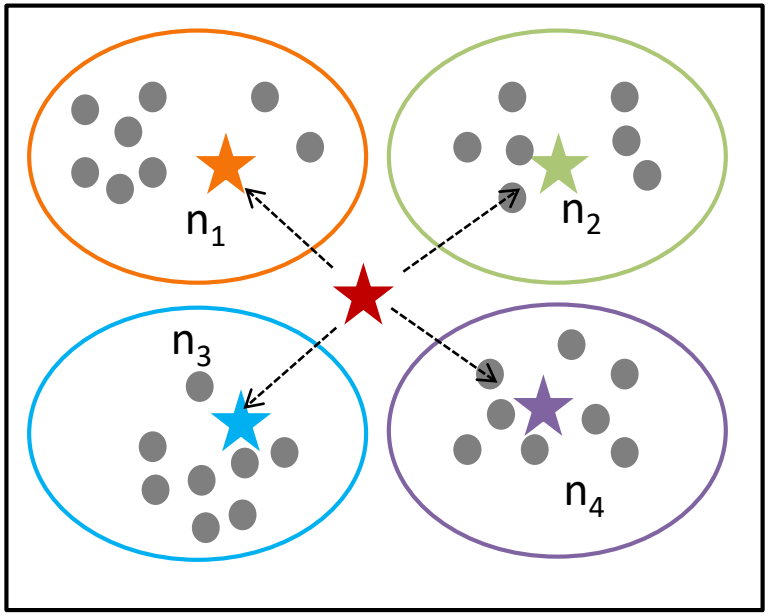
Accuracy?

Standard methods

Hierarchical modeling

$$\theta_j|\mu,\tau \sim N(\mu,\tau^2)$$

$$\mu \sim N(m,v) \quad \tau \sim HN(\sigma^2)$$



Estimates per group

Borrowing information

Exchangeability assumption?

Idea

Neuenschwander, B.,Wandel, S., Roychoudhury, S. & Bailey, S. (2016). Robust exchangeability designs for early phase clinical trials with multiple strata.

Robust mixture extension
of the standard hierarchical approach

EX: Exchangeability across similar strata

+

NEX: Non-exchangeability for extreme strata

⇩

EXNEX

Methodology

EXNEX approach

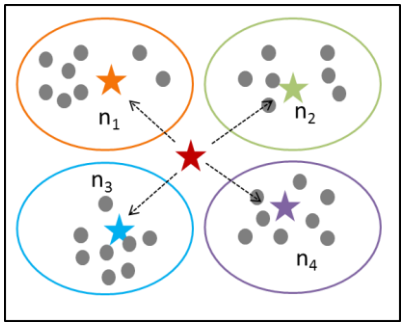
Mixture of hierarchical and stratified modeling method

EXCHANGEABLE (EX)

$$\theta_j|\mu,\tau \sim N(\mu,\tau^2)$$

$$\mu \sim N(m,v)$$

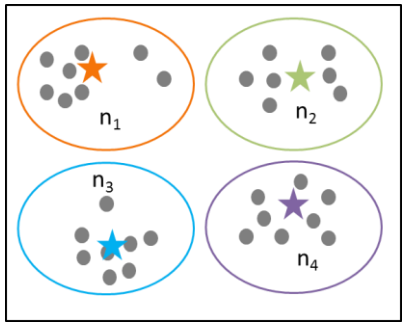
$$\tau \sim HN(\sigma^2)$$



With probability w_j

NON-EXCHANGEABLE (NEX)

$$\theta_j \sim N(m_j, v_j)$$



With probability $1 - w_j$

Methodology

Bayesian inference:

Prior x Likelihood = **Posterior**

Methodology

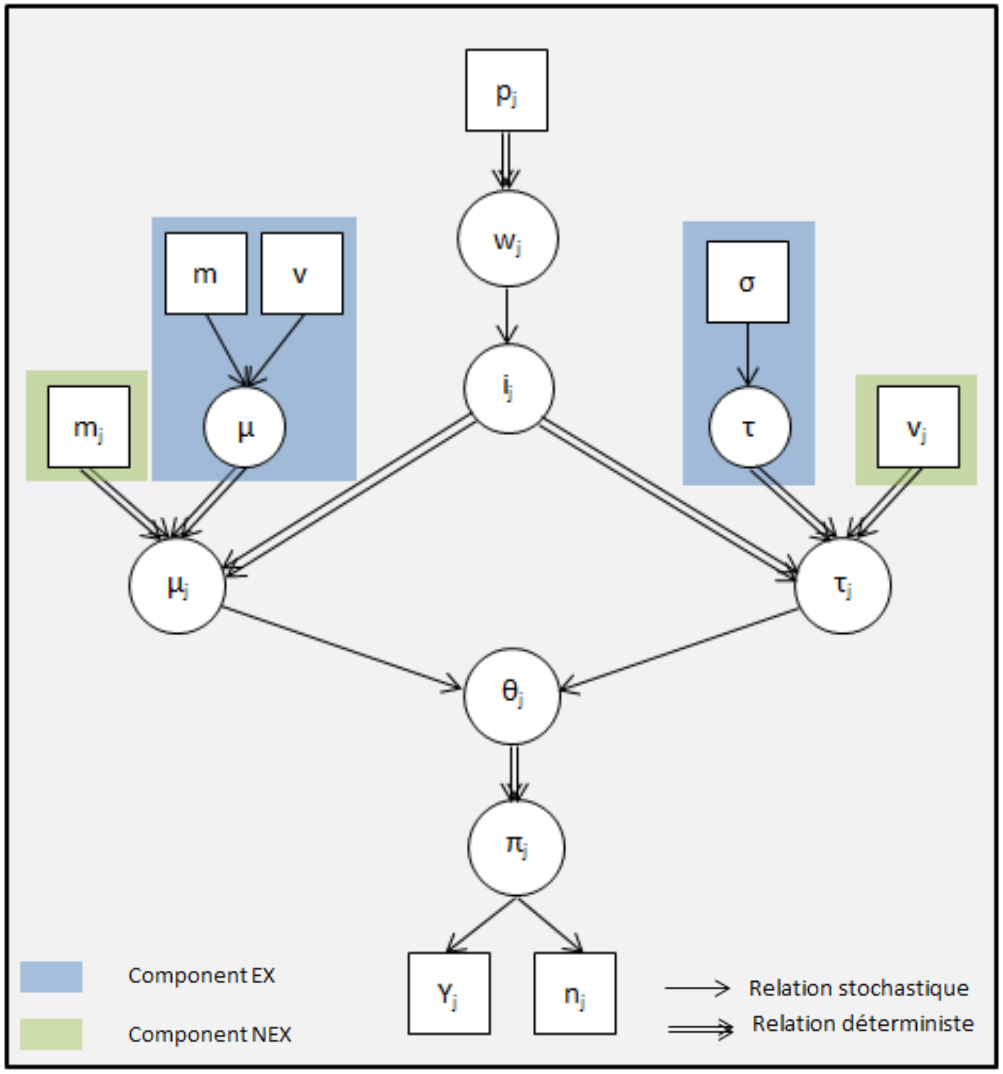
Bayesian inference:

Prior x Likelihood = **Posterior**

Markov chain Monte Carlo (**MCMC**) algorithms

Rjags (**Gibbs** sampler)

Methodology



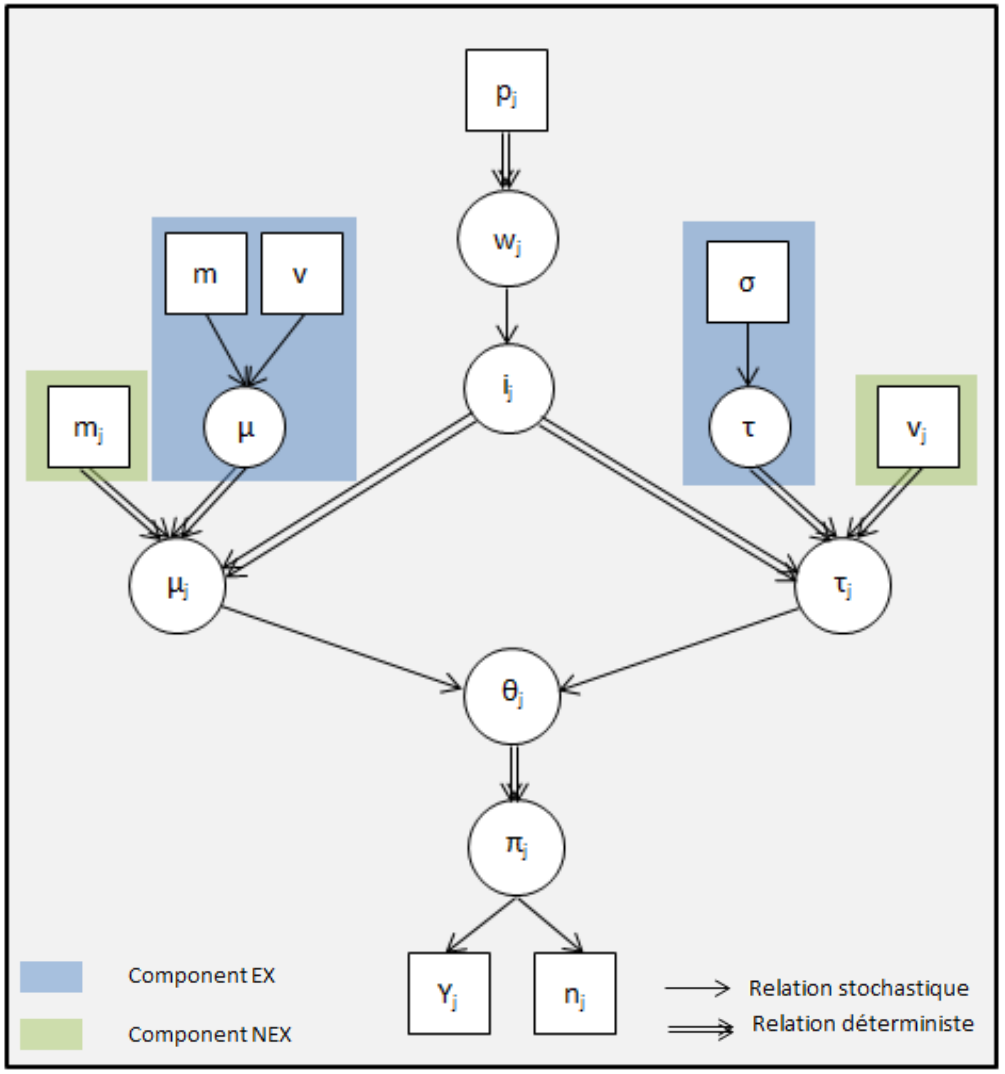
$$\theta_j|\mu_j,\tau_j,i_j \sim N(\mu_j,{\tau_j}^2)$$

$$i_j \sim Cat(w_j)$$

For each MCMC iteration:

$$\begin{cases} \mu_j = \mu \quad \text{et} \quad \tau_j = \tau \quad if \quad i_j = 1 \\ \mu_j = m_j \quad \text{et} \tau_j = \sqrt{v_j} \quad if \quad i_j = 2 \end{cases}$$

Methodology



$$\theta_j|\mu_j,\tau_j,i_j \sim N(\mu_j,{\tau_j}^2)$$

$$i_j \sim Cat(w_j)$$

For each MCMC iteration:

$$\begin{cases} \mu_j = \mu^{(1)} \text{ et } \tau_j = \tau^{(1)} \quad if \quad i_j = 1 \\ \mu_j = \mu^{(2)} \text{ et } \tau_j = \tau^{(2)} \quad if \quad i_j = 2 \\ \mu_j = m_j \quad \text{et } \tau_j = \sqrt{v_j} \quad if \quad i_j = 3 \end{cases}$$

Methodology

For each MCMC iteration

EXCHANGEABLE

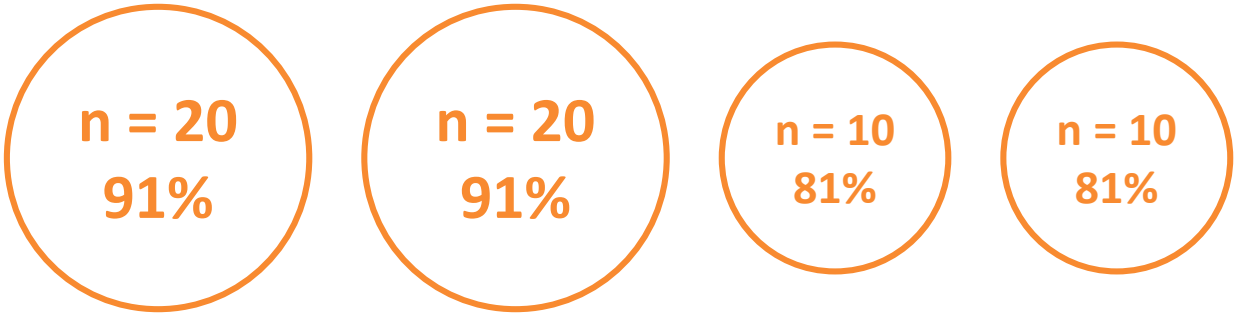
- Follows one of the **common** EX distribution(s)
- **Shares information** with the other exchangeable subgroups of this iteration

NON-EXCHANGEABLE

- Follows its **own** NEX distribution
- **No sharing** of information with the other subgroups

Application: phase II POC

- **Phase II POC study** (binary endpoint) with **4 subgroups:**

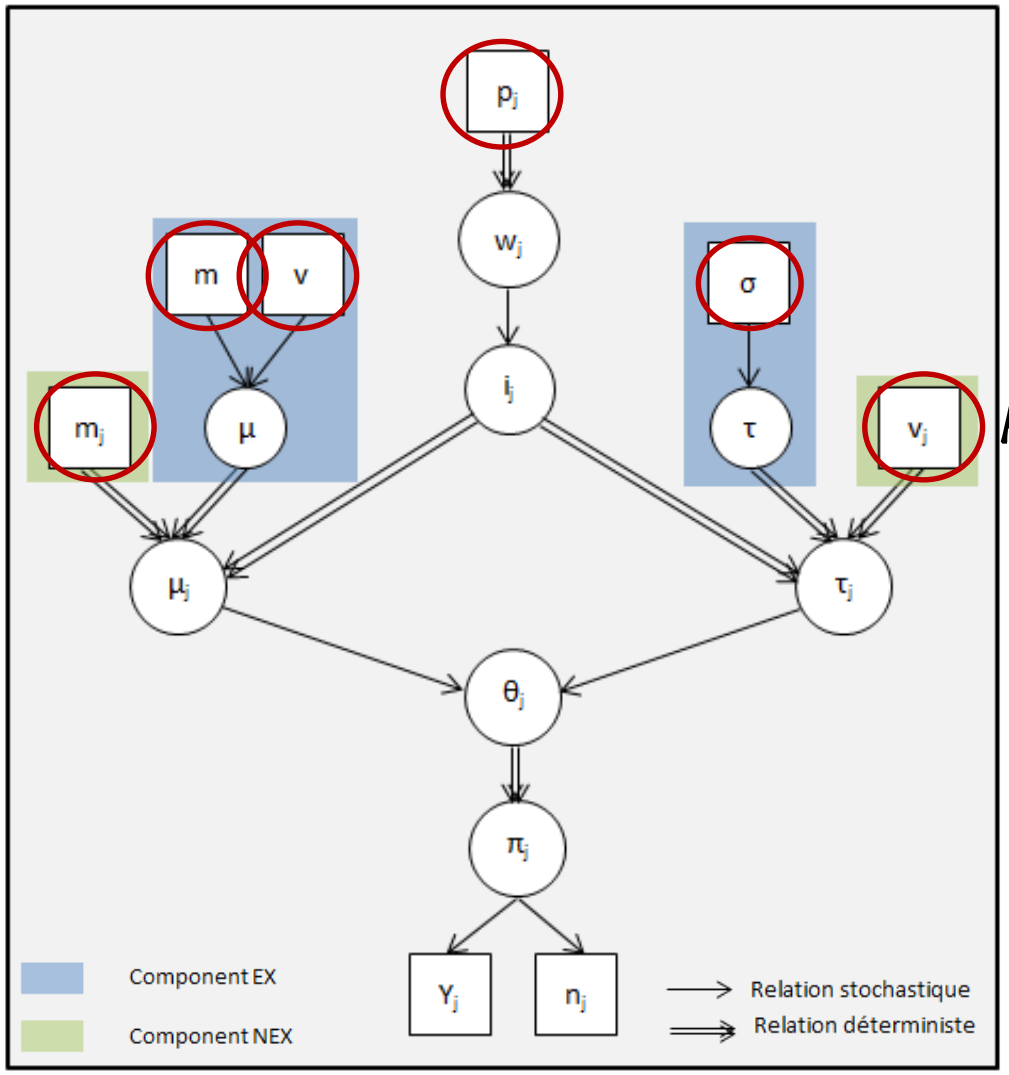


- **Success criteria for each strata:**

$$\hat{\pi} \geq 20\% \ \& \ P(\pi > 10\%) \geq 81\% \ or \ 91\%$$

- Comparison of **hierarchical, stratified** and **EXNEX** modeling methods

Prior specifications



EXNEX model:

$$w_j = p_j = (0.25, 0.25, 0.50)$$

EX component:

$$\mu^{(1)} \sim N(m = logit(0.1), v = 10.1)$$

$$\tau^{(1)} \sim HN(\sigma^2 = 1^2)$$

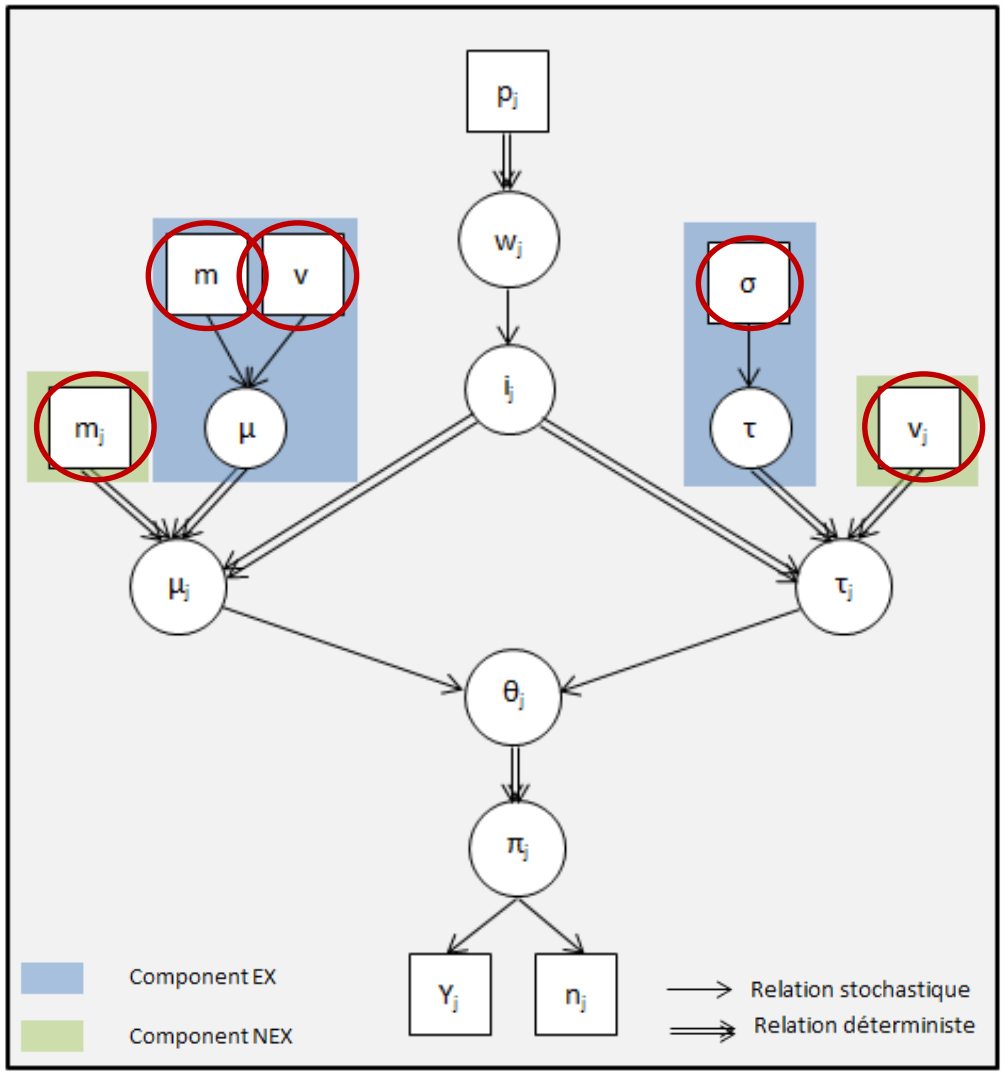
$$\mu^{(2)} \sim N(m = logit(0.3), v = 3.8)$$

$$\tau^{(2)} \sim HN(\sigma^2 = 1^2)$$

NEX component:

$$\theta_j \sim N\left(m_j = logit(0.2), v_j = 6.3\right)$$

Prior specifications



- **Hierarchical model:**

$$\mu \sim N(m = logit(0.2), v = 5.3)$$

$$\tau \sim HN(\sigma^2 = 1^2)$$

- **Stratified model:**

$$\theta_j \sim N\left(m_j = logit(0.2), v_j = 6.3\right)$$

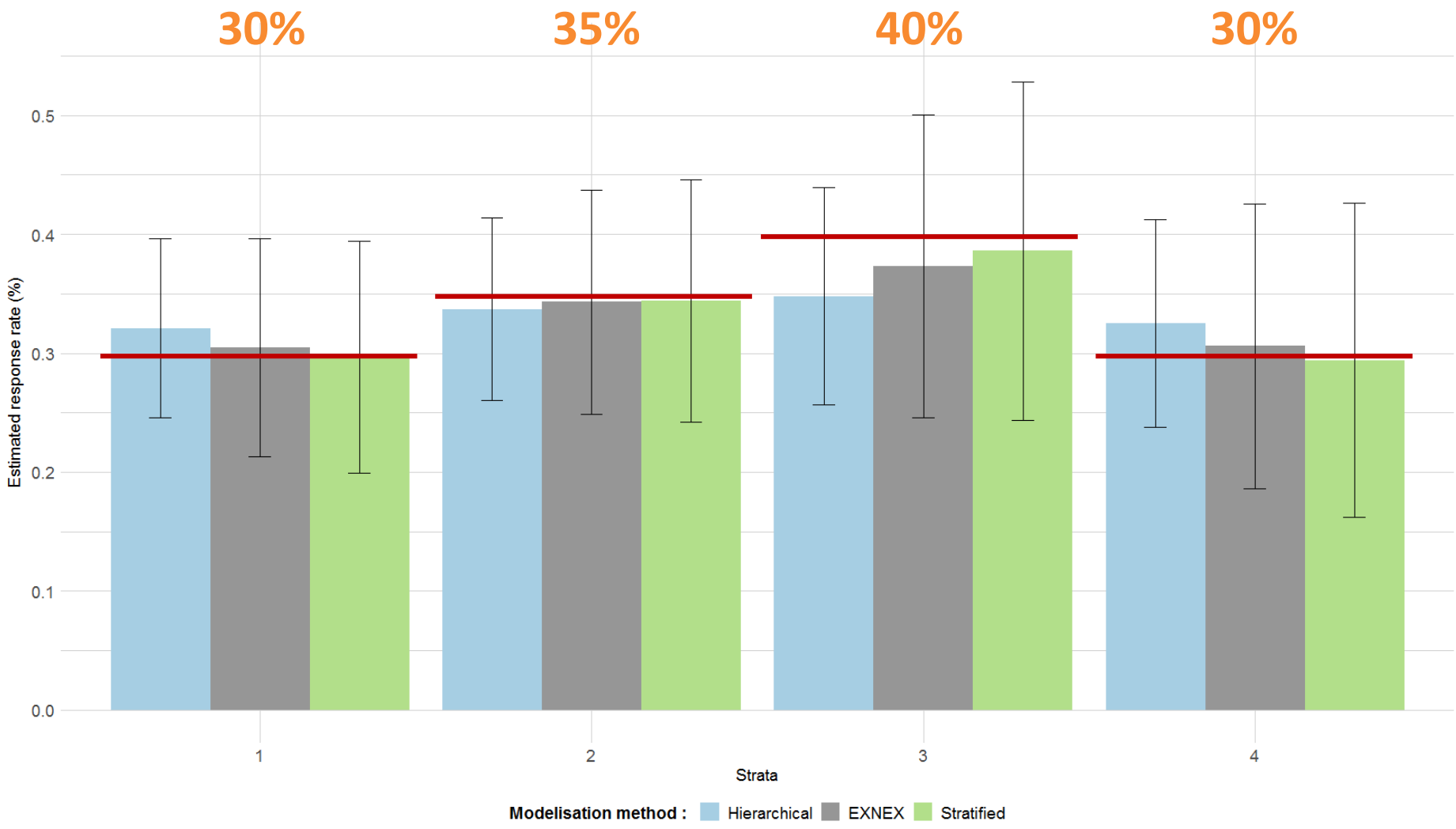
Illustration with 2 scenarii

- 2 scenarii:

Homogeneous

Nugget scenario

Homogeneous situation



Homogeneous situation

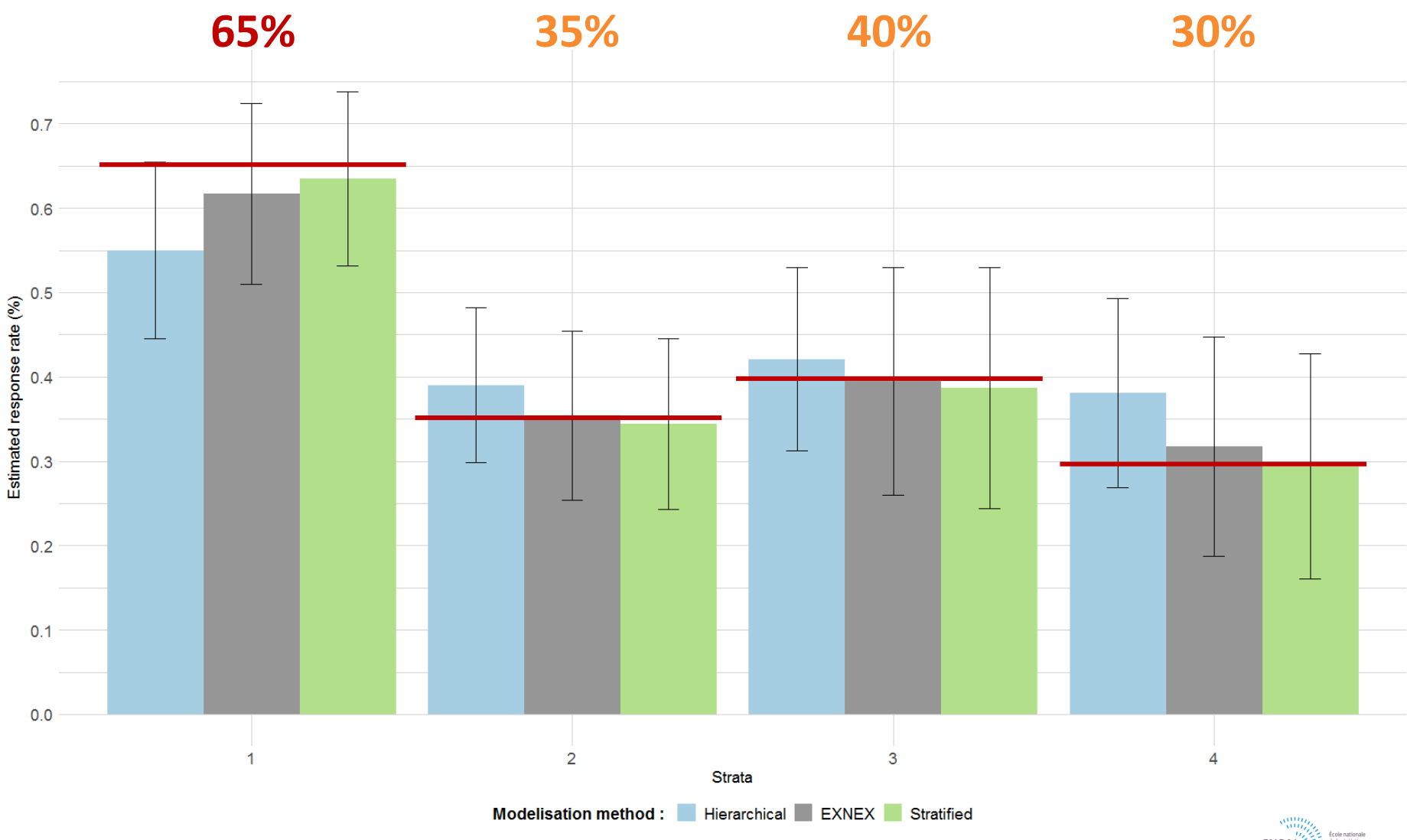
Priors:
$\hat{m}^1$ = logit(0.1)
$\hat{m}^2$ = logit(0.3)
$\hat{m}_j$ = logit(0.2)
$\hat{w}_j$ = (0.25, 0.25, 0.50)

True response rate 30% 35% 40% 30%

Posterior distributions				
Strata	**1**	**2**	**3**	**4**
EX component				
$\hat{m}^1$	logit(0.20)			
$\hat{w}_j^1$	0.27	0.28	0.27	0.27
$\hat{m}^2$	logit(0.32)			
$\hat{w}_j^2$	0.38	0.38	0.37	0.36
NEX component				
$\hat{m}_j$	logit(0.23)	logit(0.24)	logit(0.25)	logit(0.22)
$\hat{w}_j^3$	0.35	0.34	0.37	0.37

Priors:
$\hat{m}^1$ = logit(0.1)
$\hat{m}^2$ = logit(0.3)
$\hat{m}_j$ = logit(0.2)
$\hat{w}_j$ = (0.25, 0.25, 0.50)

Heterogeneous situation



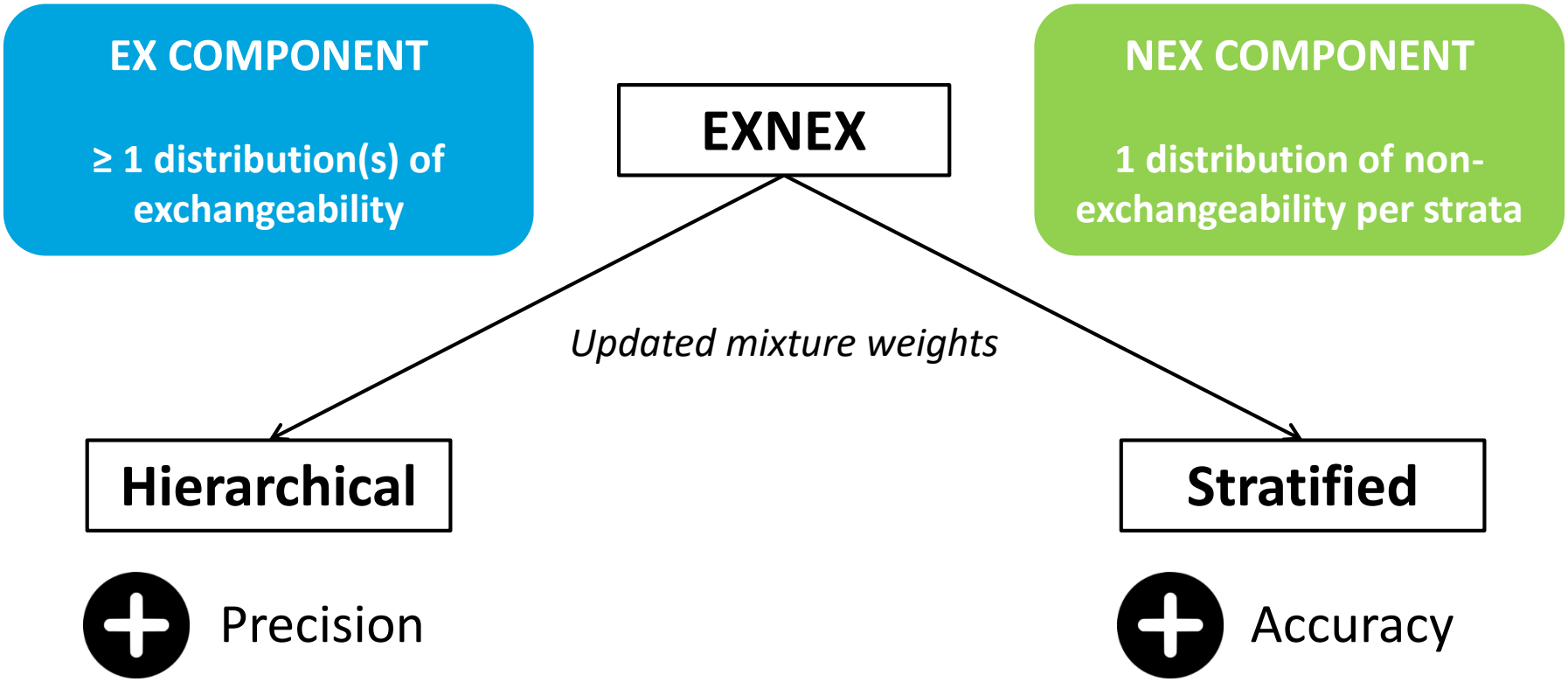
Heterogeneous situation

True response rate	65%	35%	40%	30%

Posterior distributions				
Strata	**1**	**2**	**3**	**4**
EX component				
$\hat{m}^1$	logit(0.24)			
$\hat{w}_j^1$	0.22	0.26	0.26	0.25
$\hat{m}^2$	logit(0.38)			
$\hat{w}_j^2$	0.31	0.34	0.35	0.33
NEX component				
$\hat{m}_j$	logit(0.39)	logit(0.25)	logit(0.26)	logit(0.23)
$\hat{w}_j^3$	0.47	0.40	0.38	0.42

Priors:
$\hat{m}^1$ = logit(0.1)
$\hat{m}^2$ = logit(0.3)
$\hat{m}_j$ = logit(0.2)
$\hat{w}_j$ = (0.25, 0.25, 0.50)

Summary


EX COMPONENT
≥ 1 distribution(s) of exchangeability
EXNEX
NEX COMPONENT
1 distribution of non-exchangeability per strata
Updated mixture weights
Hierarchical
Precision
Stratified
Accuracy

Simulations

- **42** scenarii
- **2 000** simulated clinical trials for each scenario
- **2, 3, 4 or 6** subgroups
- Several **degrees of heterogeneity** inter-strata
- **3 metrics**: probability of success, bias and MSE

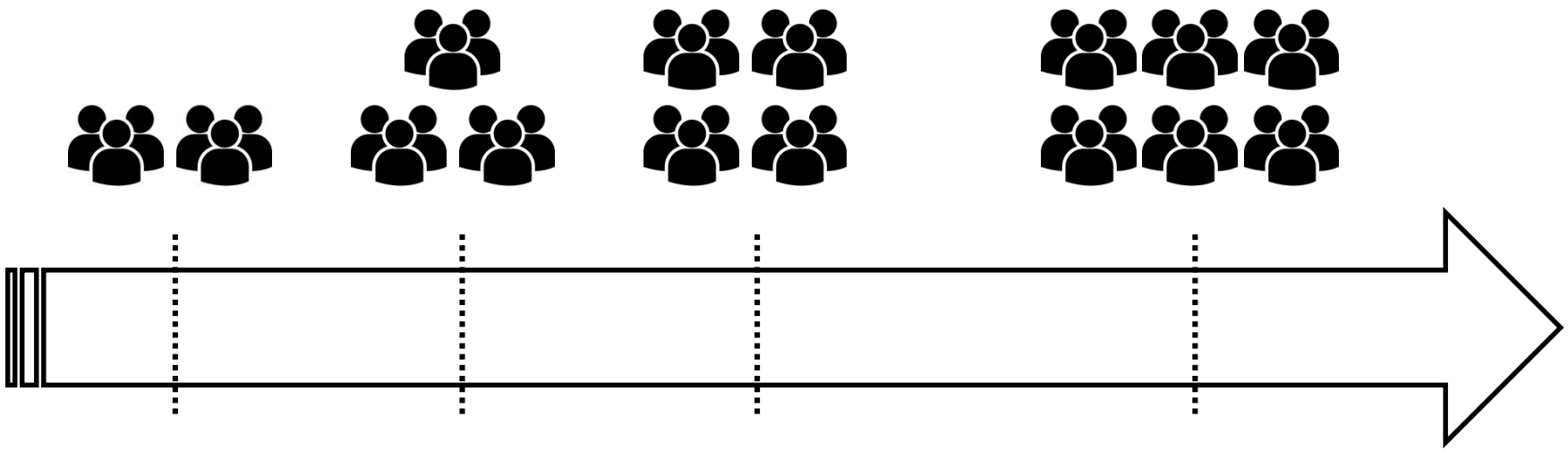
Visualization

Results

REALITY

Homogeneous situation	Unknown situation	Heterogeneous situation
⇩	⇩	⇩
Hierarchical	EXNEX	Stratified EXNEX

Results



Stratified

EXNEX **EXNEX**

Take-home messages

BAYESIAN **MIXTURE** MODEL

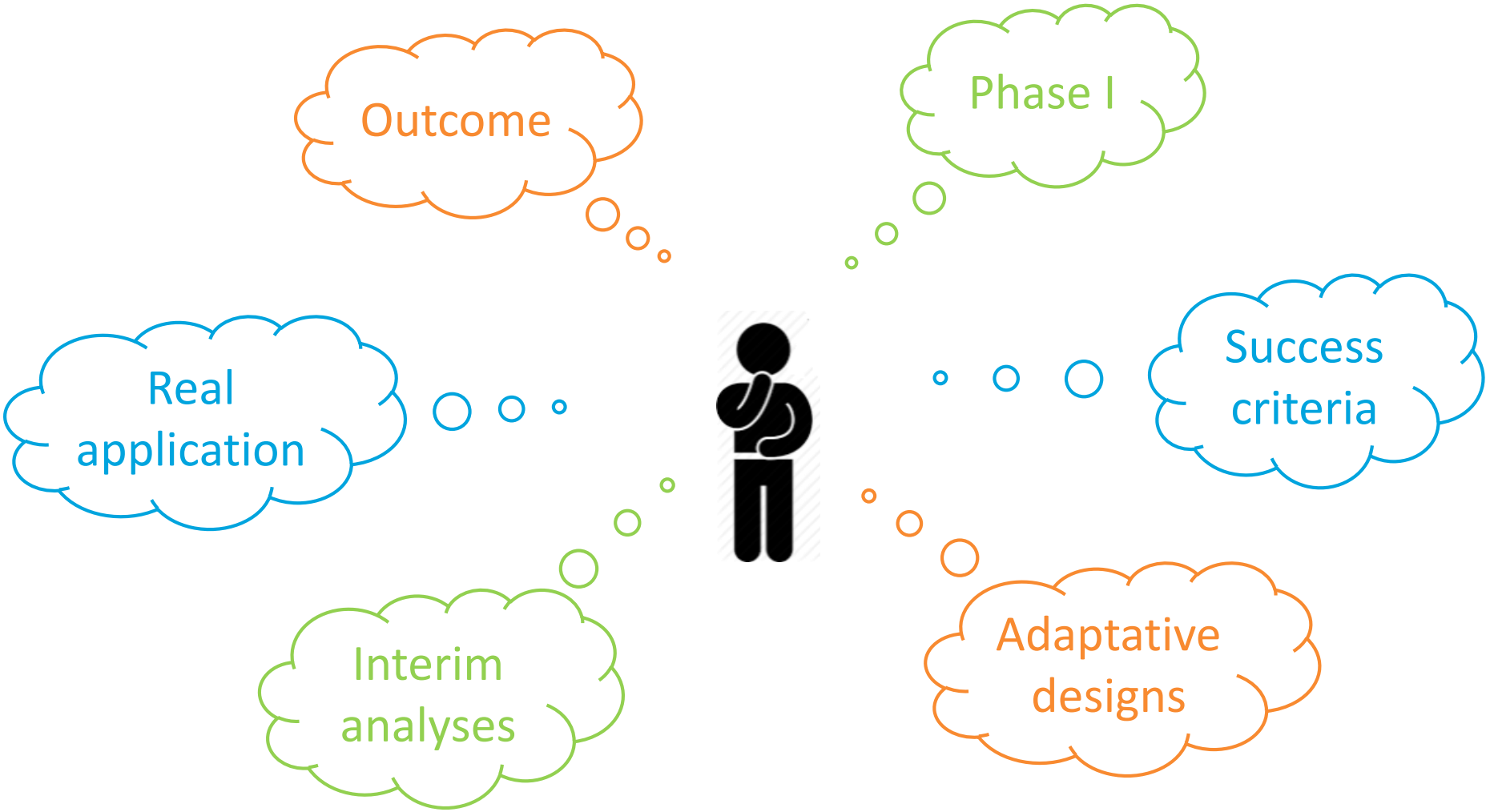
GOOD **COMPROMISE**

CHALLENGING **PRIOR SPECIFICATIONS**

PLUS-VALUE WITH ≥ 3 **SUBGROUPS**

EXCHANGEABILITY ASSUMPTION

Discussion


Outcome
Phase I
Real application
Success criteria
Interim analyses
Adaptative designs

Thank you for your attention!

Any questions?

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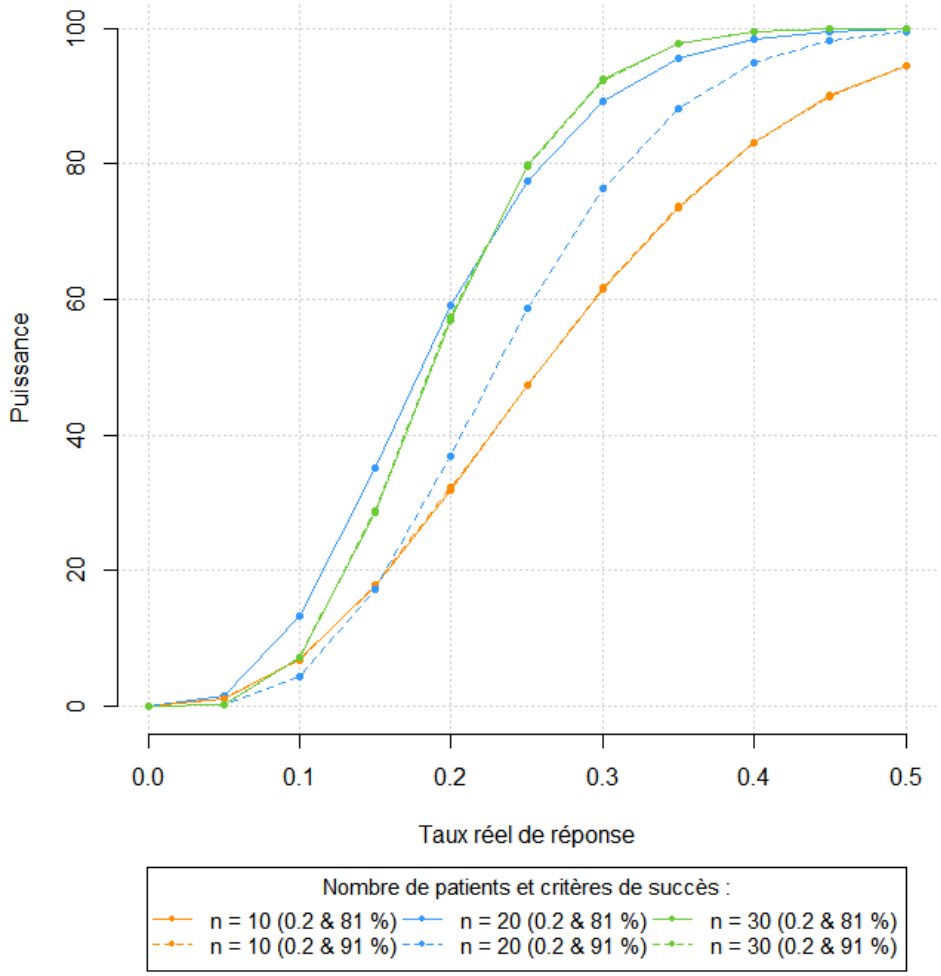
Back-up

- **Probability of success in stratified model (logit(0.2)):**



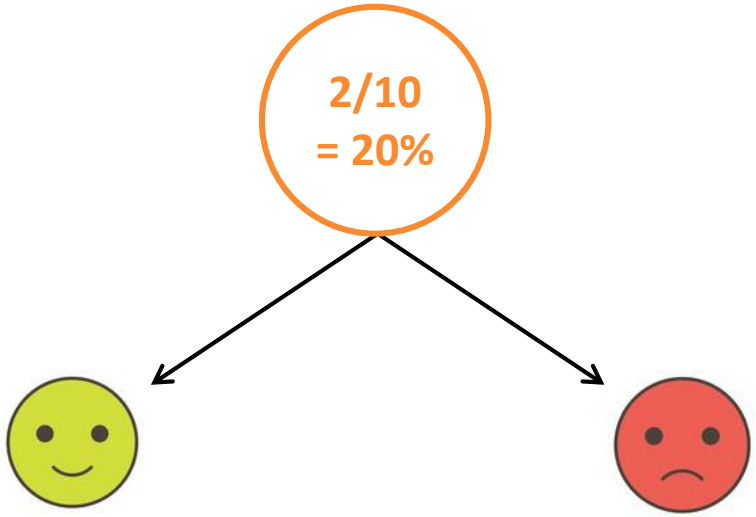
Back-up

- **Success criteria for each strata:**

$$\hat{\pi} \geq 20\% \ \& \ P(\pi > 10\%) \geq 80\% \ or \ 90\%$$

⇩

⚠ **Borderline cases** in **stratified** analyses



Back-up

- **Prior specifications:** weakly informative setting (1)

$$\theta_j = \log\left(\frac{\pi_j}{1-\pi_j}\right) \qquad \theta_j \sim N(m_j, v_j) \qquad \mu \sim N(m, v)$$

$$\tau \sim HN(1^2)$$

$$v_j = V(\theta_j) = \frac{1}{p} + \frac{1}{1-p}$$

One observation

$$v = \underbrace{V(\theta_j)}_{\text{Between variance}} - \underbrace{E(\tau^2)}_{\text{Within variance}} = V(\theta_j) + E(\tau)^2 - V(\tau)$$

Back-up

- **Prior specifications:** weakly informative setting (2)

$$\theta_j = \log\left(\frac{\pi_j}{1-\pi_j}\right) \qquad \theta_j \sim N(m_j, v_j) \qquad \mu \sim N(m, v)$$

$$\tau \sim HN(1^2)$$

$$v_j = V(\theta_j) = \frac{1}{0.2} + \frac{1}{1-0.2} = \mathbf{6.3}$$

One observation

$$v = V(\theta_j) - E(\tau^2) = V(\theta_j) + E(\tau)^2 - V(\tau)$$
$$= 6.3 + 0 - 1^2 = \mathbf{5.3}$$

Back-up

- **Gibbs sampling**

Iterative algorithm:

1. Initialization of the *p* parameters: $\theta^0 = \left(\theta_1^0, \dots, \theta_p^0\right)$
2. Updating (t^{th} iteration):

$$\theta_1^t = \pi_1\left(. \middle| \theta_2^{t-1}, \dots, \theta_p^{t-1}\right)$$
$$\theta_2^t = \pi_2\left(. \middle| \theta_1^t, \theta_3^{t-1}, \dots, \theta_p^{t-1}\right)$$
$$\vdots$$
$$\theta_p^t = \pi_p\left(. \middle| \theta_1^t, \dots, \theta_{p-1}^t\right)$$

Back-up

- **Case studies: homogeneous scenario**

True response rate	30%	35%	40%	30%

Posterior distributions (median)				
Strata	**1**	**2**	**3**	**4**
EX component				
$\hat{m}^1$	logit(0.28)			
$\hat{m}^2$	logit(0.32)			
NEX component				
$\hat{m}_j$	logit(0.26)	logit(0.29)	logit(0.31)	logit(0.25)

Back-up

- **Case studies: heterogeneous scenario**

True response rate	65%	35%	40%	30%

Posterior distributions (median)				
Strata	**1**	**2**	**3**	**4**
EX component				
$\hat{m}^1$	logit(0.33)			
$\hat{m}^2$	logit(0.39)			
NEX component				
$\hat{m}_j$	logit(0.56)	logit(0.30)	logit(0.32)	logit(0.25)