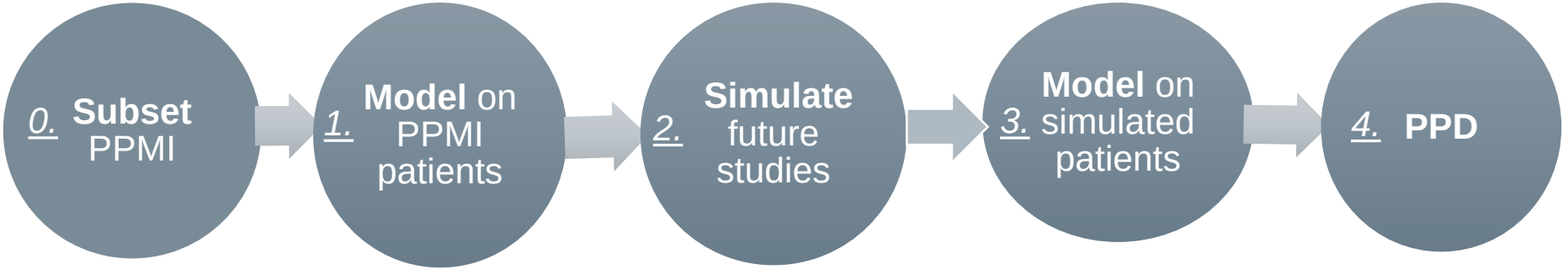
A Bayesian Disease progression model of Parkinson Disease combining RWD and natural history data to evaluate a new treatment

Pissoort Antoine | Maud Hennion | Bruno Boulanger (Pharmalex)

Anne Bousseau | Caroline Denot (Brainever)

22 May 2019

Summary of the Methodology



- Available database
- Select relevant **historical data**

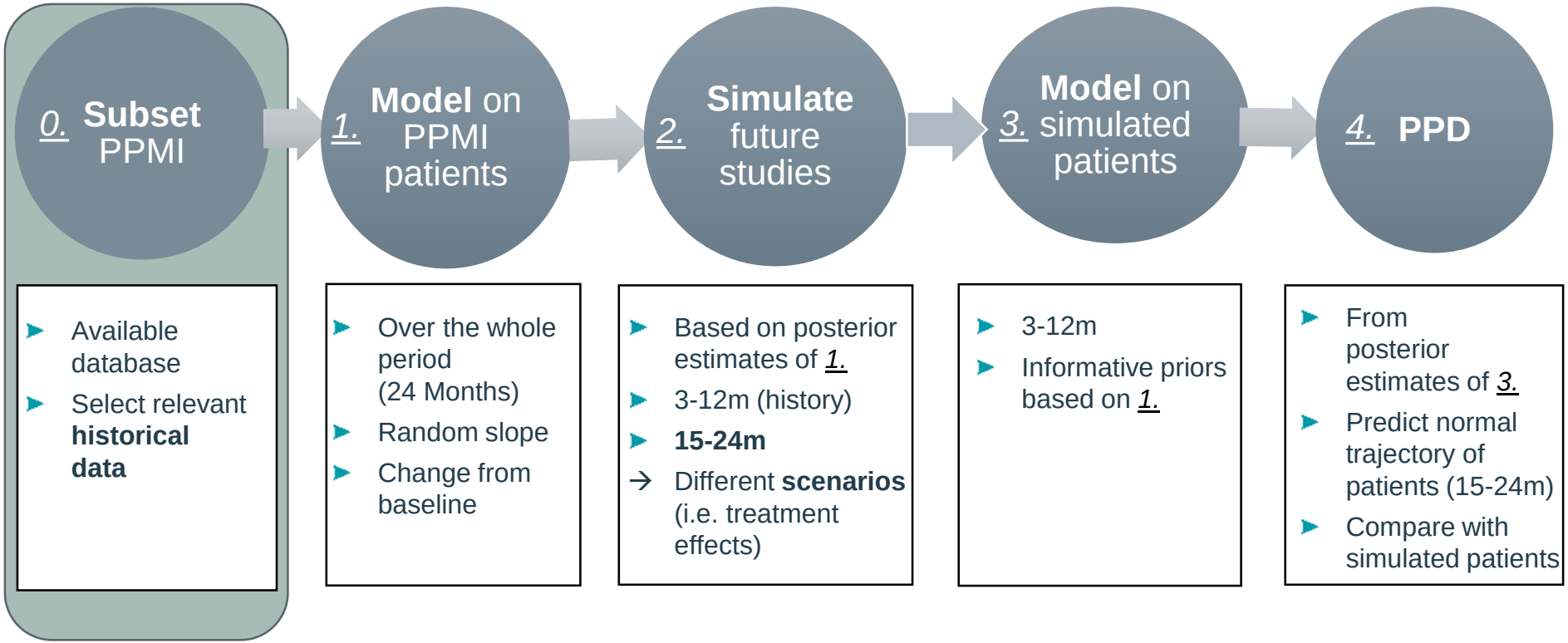
- Over the whole period (24 Months)
- Random slope
- Change from baseline

- Based on posterior estimates of *1.*
- 3-12m (history)
- **15-24m**
- → Different **scenarios** (i.e. treatment effects)

- 3-12m
- Informative priors based on *1.*

- From posterior estimates of *3.*
- Predict normal trajectory of patients (15-24m)
- Compare with simulated patients

Summary of the Methodology



Parkinson's Progression Markers Initiative (PPMI)

- The **Parkinson's Progression Markers Initiative** (PPMI) is an observational clinical study whose purpose is to identify clinical, imaging and biological markers of PD progression for use in clinical trials of disease-modifying therapies.

- Among parameters tracked to define PD progression, focus on the MDS-**UPDRS**m score.
- The endpoint of interest is the **change from baseline** (cfbl).

- 1870 patients are enrolled in the PPMI study from about 35 centers.
- Study period is 13 years

➔ As, the PPMI dataset gives a good representation of the **normal progression** of the disease (no treatment), it will be used to simulate virtual patients of a future study, define informative priors, evaluate operating characteristics of a future study…

The historical Data: a subset of the PPMI dataset

- Based on the inclusion/exclusion criteria defined in the protocol, only a subset of the PPMI database is included for the future analysis.

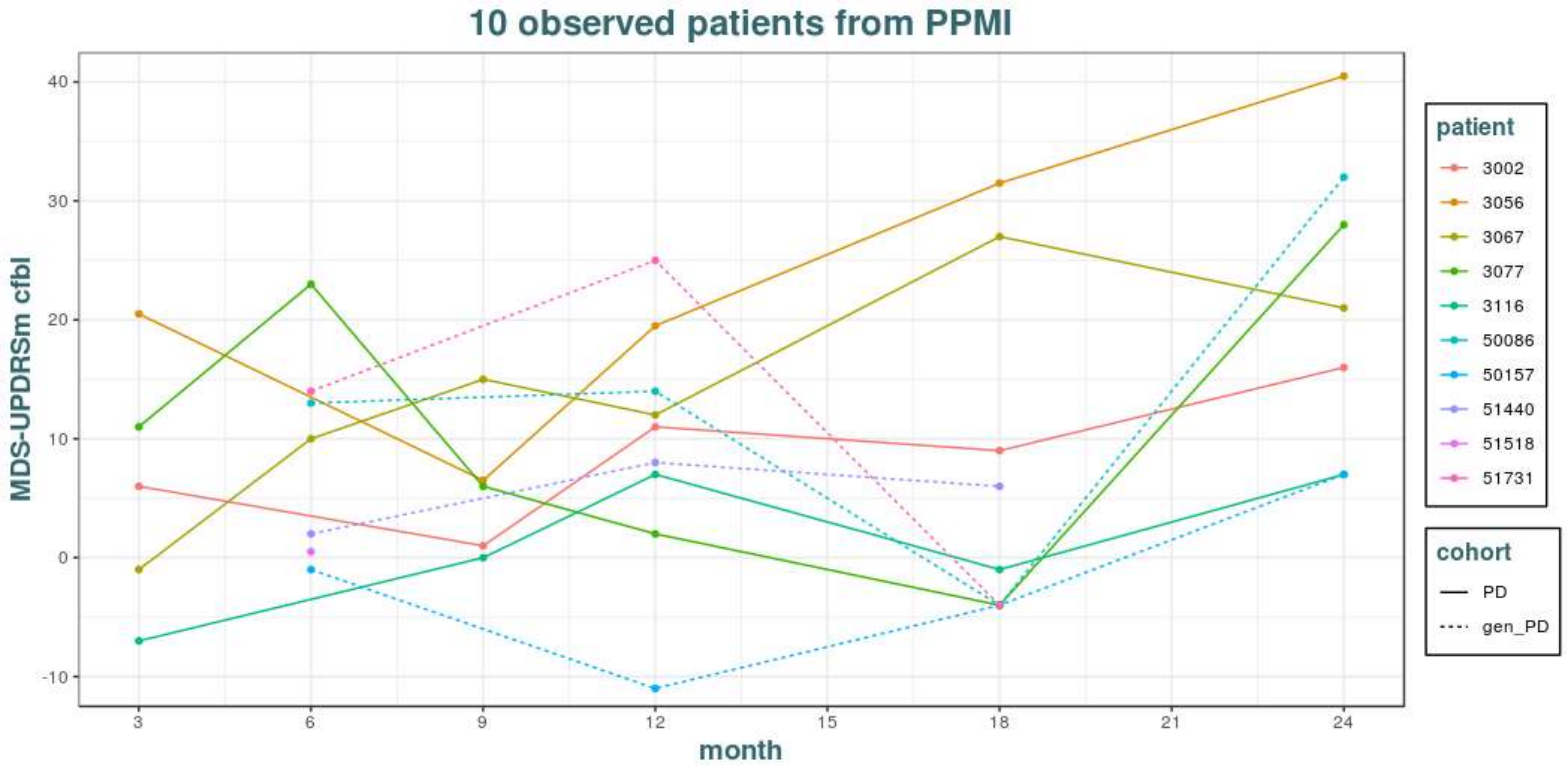
  → Inform the model only with relevant patients

- For example, based on
  - Category: Parkinson disease cohort, genetic cohort, …
  - Enrollment Age
  - Disease Duration
  - …

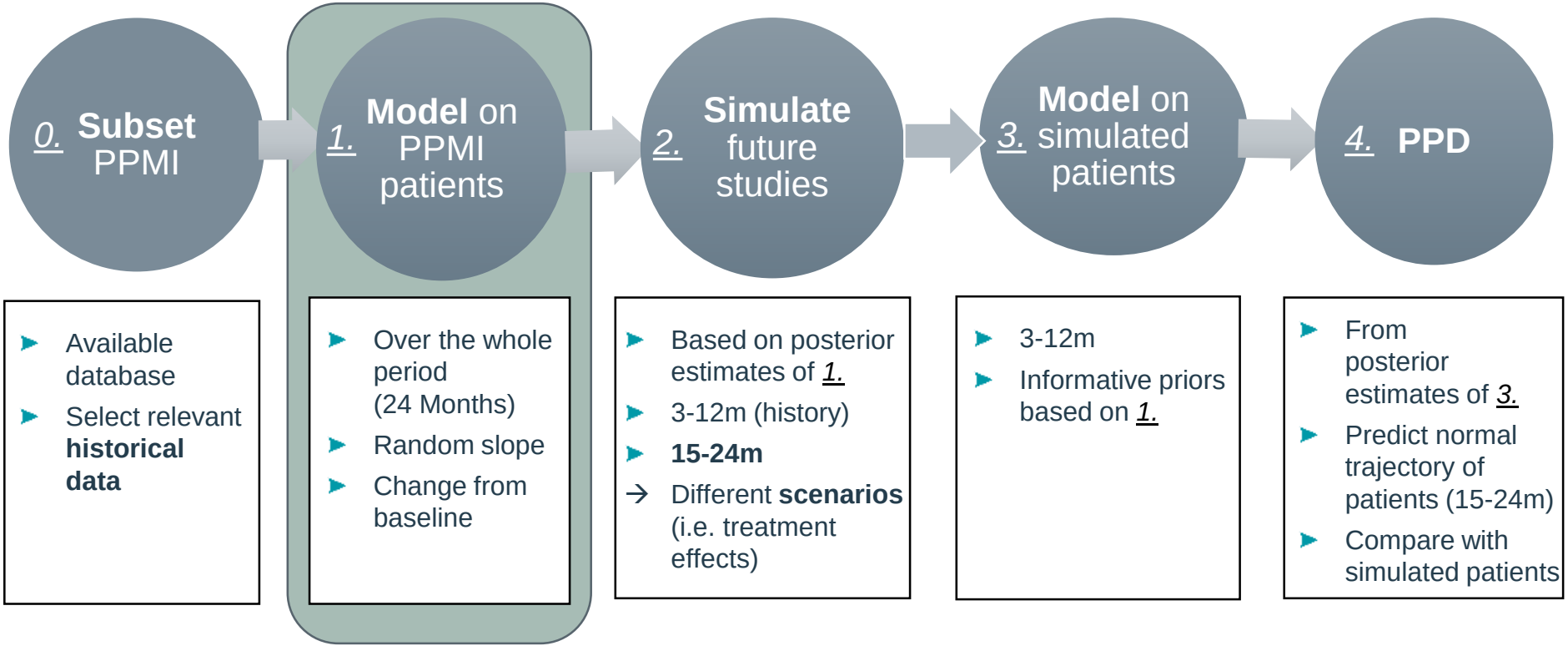
  → N = 163 patients are selected in this study

- These patients should be the most similar to those expected in the future application.

Example of patients selected in the database



Summary of the Methodology



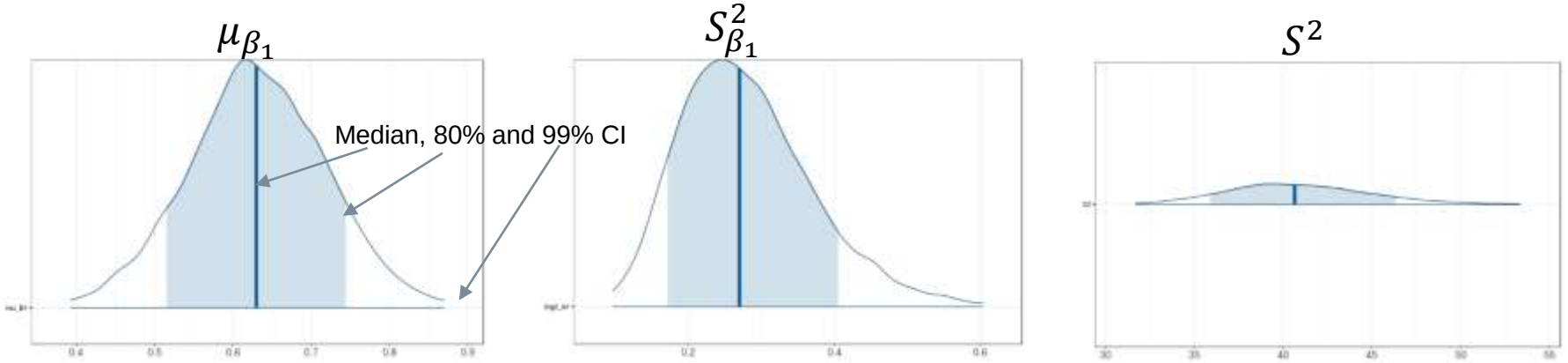
1. Model over 24 months

- Fit a **random slope model** on the selected subset of PPMI :

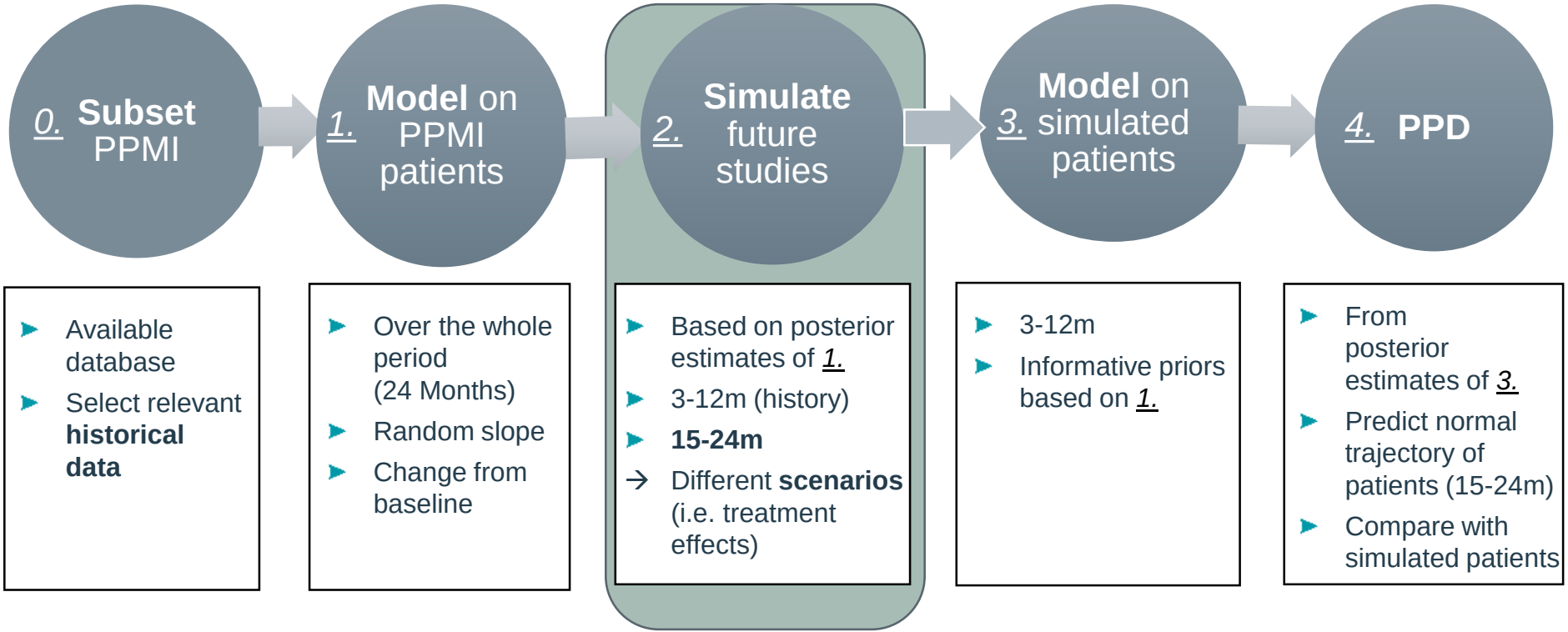
$$Y = \beta_1 \cdot t + \epsilon, \qquad \beta_1 \sim N(\mu_{\beta_1}, S^2_{\beta_1}), \qquad \epsilon \sim N(0, S^2),$$

where Y is the **MDS-UPDRSm change from baseline (cfbl)** and $t = \{3, 6, \ldots, 24\}$ is the month.

- Gibbs sampling (PROC MCMC) to estimate the parameters
- 3 parameters (μ_{β_1} , $S^2_{\beta_1}, S^2$) → posterior chains:



Summary of the Methodology



2. Simulate Future Studies Based on the Fitted Model

- Based on parameter posterior chains, simulate **12 patients** from **100 studies:**

9 Treated : $Y = s_1 \cdot t - I_{t>12} \cdot \beta \cdot (1 - \exp[-r \cdot (t - 12)])$

3 Placebo: $Y = (s_1 + I_{t>12} \cdot \gamma) \cdot t - I_{t>12} \cdot \beta \cdot (1 - \exp[-r \cdot (t - 12)])$

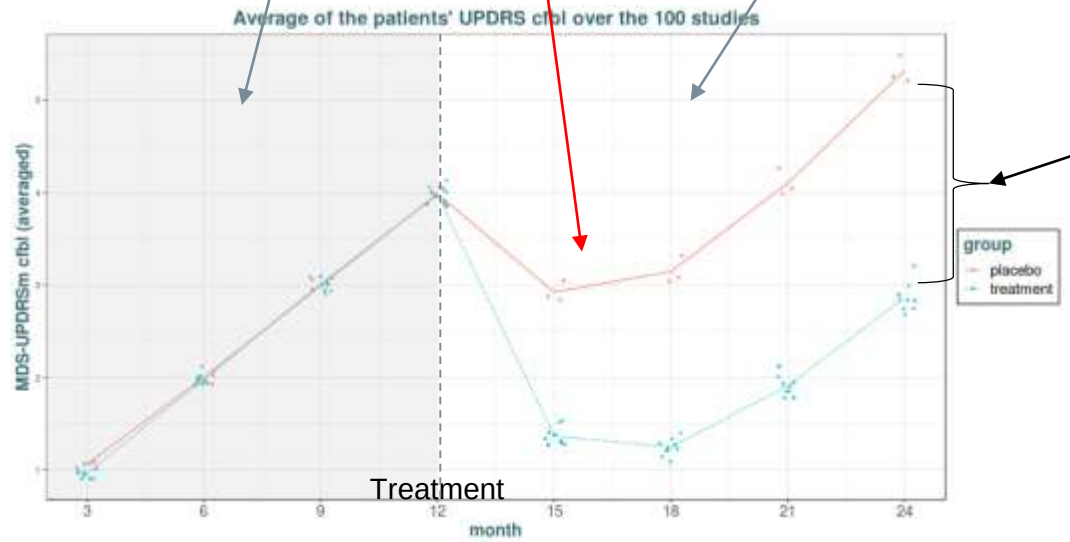
- Time period (t) of 3 to 24 months:
  - 3-12 months → Normal evolution of the disease (~ PPMI)
  - 15-24 months → Introduce treatment and placebo effects

Study 1:	9+3 patients
Study 2:	9+3 patients
⋮	⋮
Study 100:	9+3 patients

- Note: Different scenarios should be compared
  - Sensitivity analysis

2. Simulate 12 new patients (100 studies)

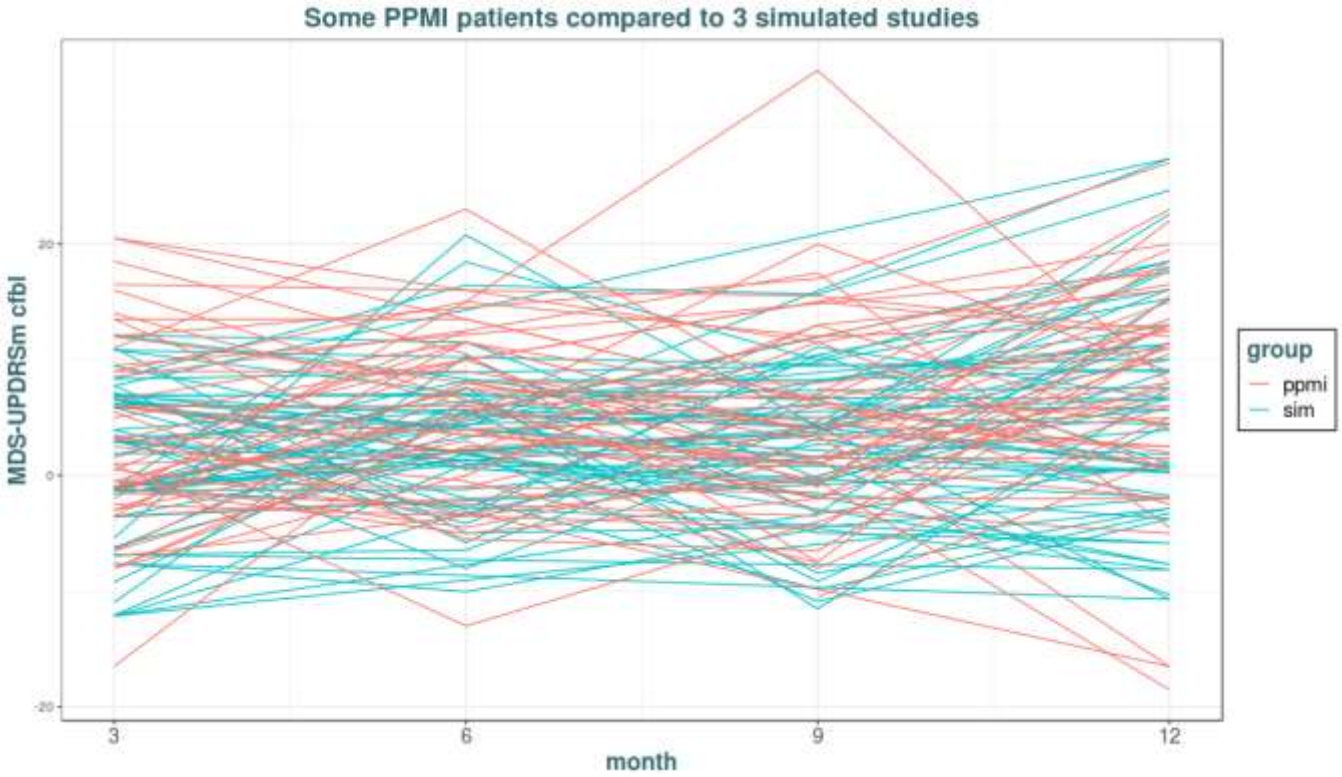
$$Y = s_1 \cdot t + I_{t>12} \cdot \gamma \cdot t \; - \; I_{t>12} \cdot \beta \cdot (1 - \exp[-r \cdot (t - 12)])$$



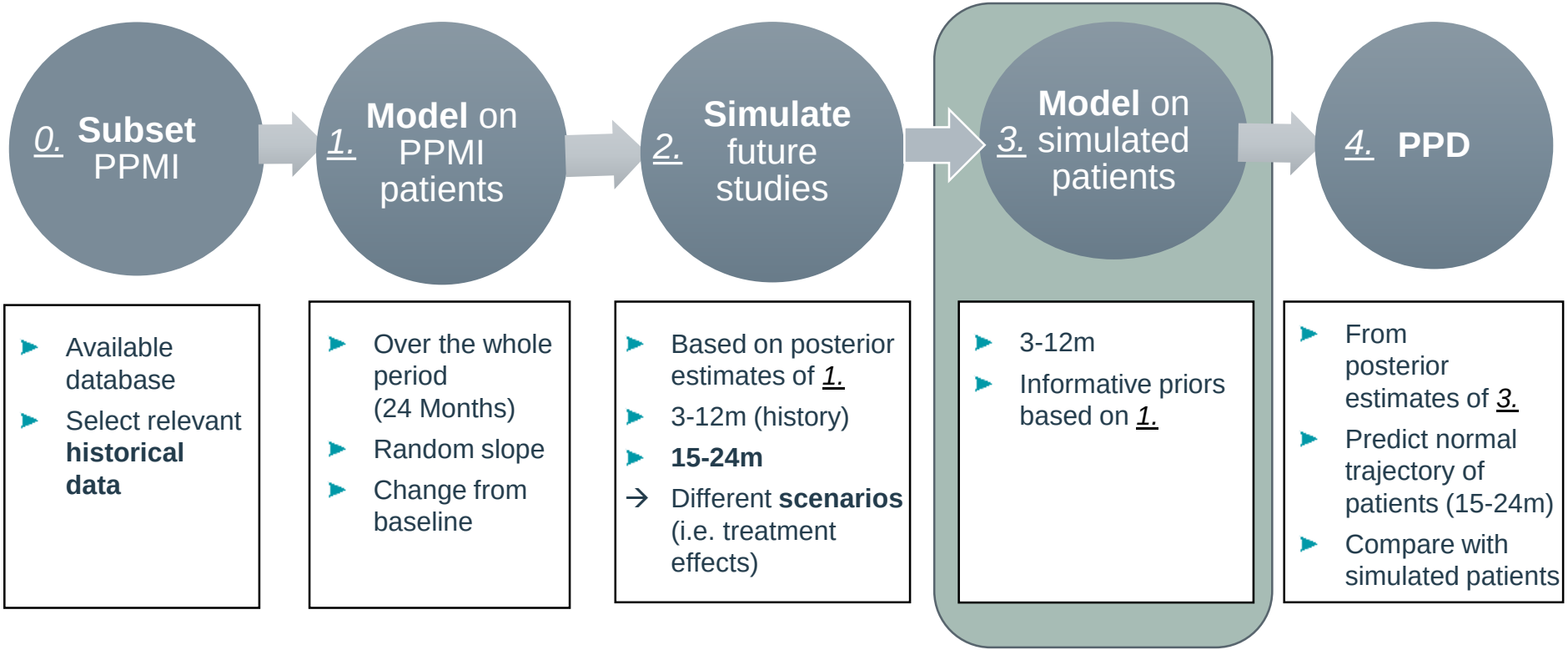
- Fix the parameters:
  - $s_1 = 0.331$ → Slope before treatment
    Value given by the model on PPMI data
  - $\gamma = 0.1$ → Difference placebo to treatment
  - $\beta = 5.2$ ≈ growth range
  - $r = 0.4$ ≈ growth rate

- Open question: What placebo effect ?
- Need to consider several scenarios

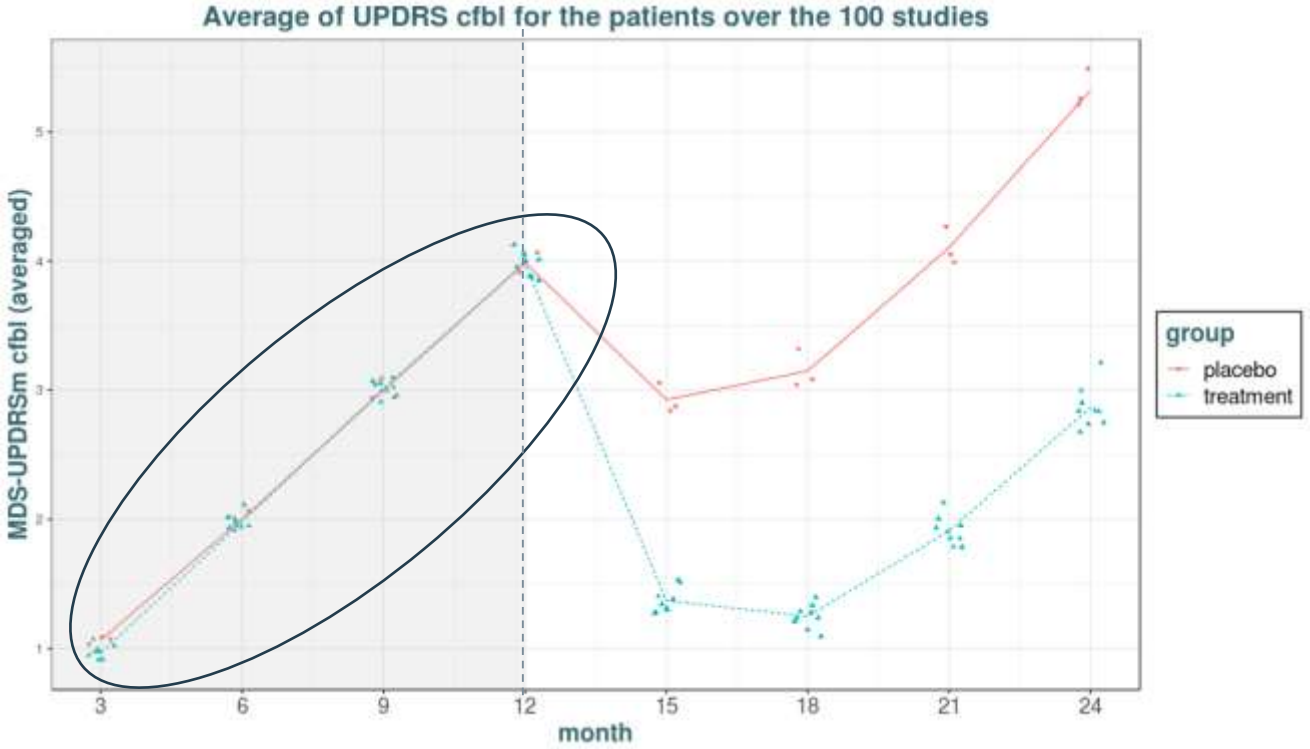
Check the simulations on 3-12 months



Summary of the Methodology



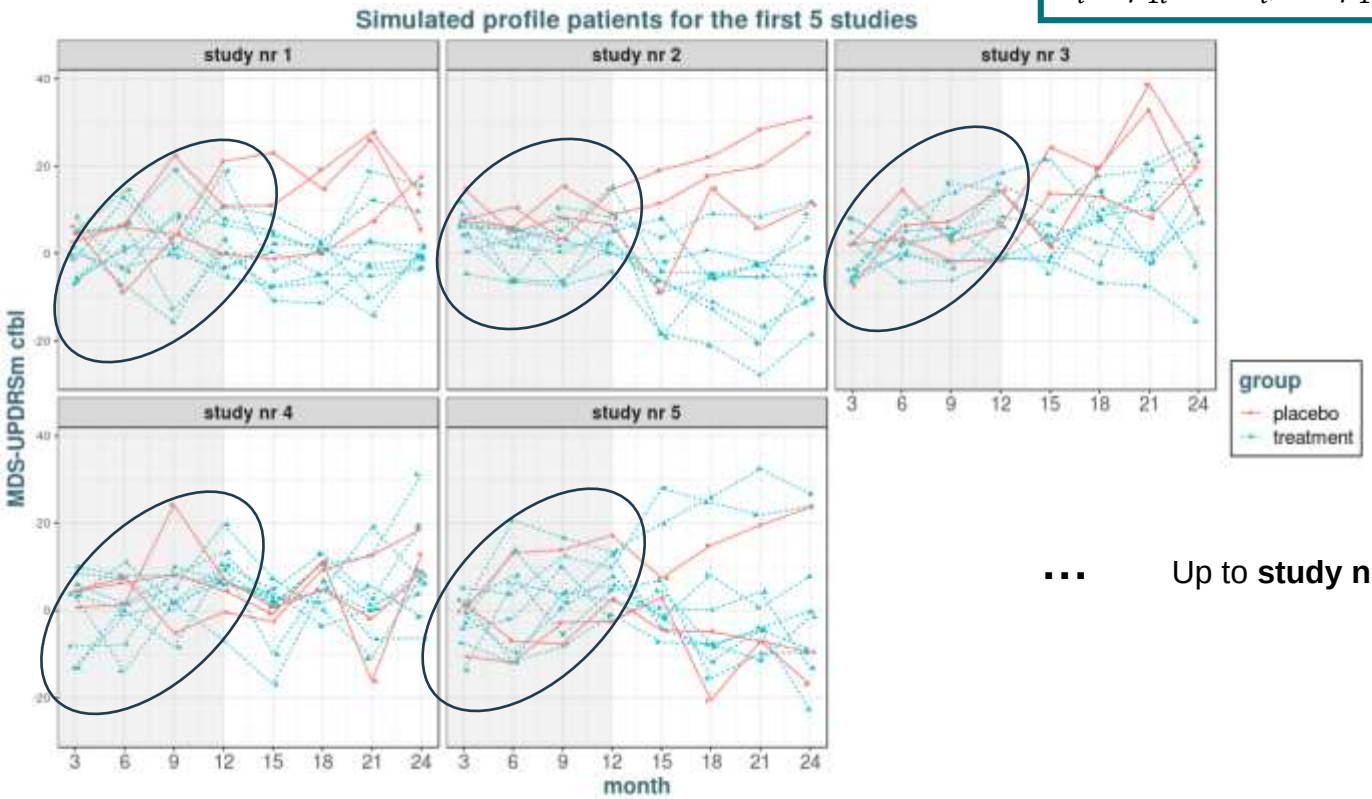
Model only the first part of the simulated data



Model only the first part of the simulated data: by study

$$Y_i = \beta_{1i} \cdot t + \epsilon_i, \qquad \beta_{1i} \sim N\left(\mu_{\beta_{1i}}, S^2_{\beta_{1i}}\right), \quad \epsilon_i \sim N\left(0, S_i^2\right)$$

Study $i = 1, 2, \ldots, 100$



… Up to **study nr 100**

Informative priors : Method of Moments

$$Y = \beta_1 \cdot t + \epsilon, \qquad \beta_1 \sim N(\mu_{\beta_1}, S^2_{\beta_1}), \qquad \epsilon \sim N(0, S^2),$$

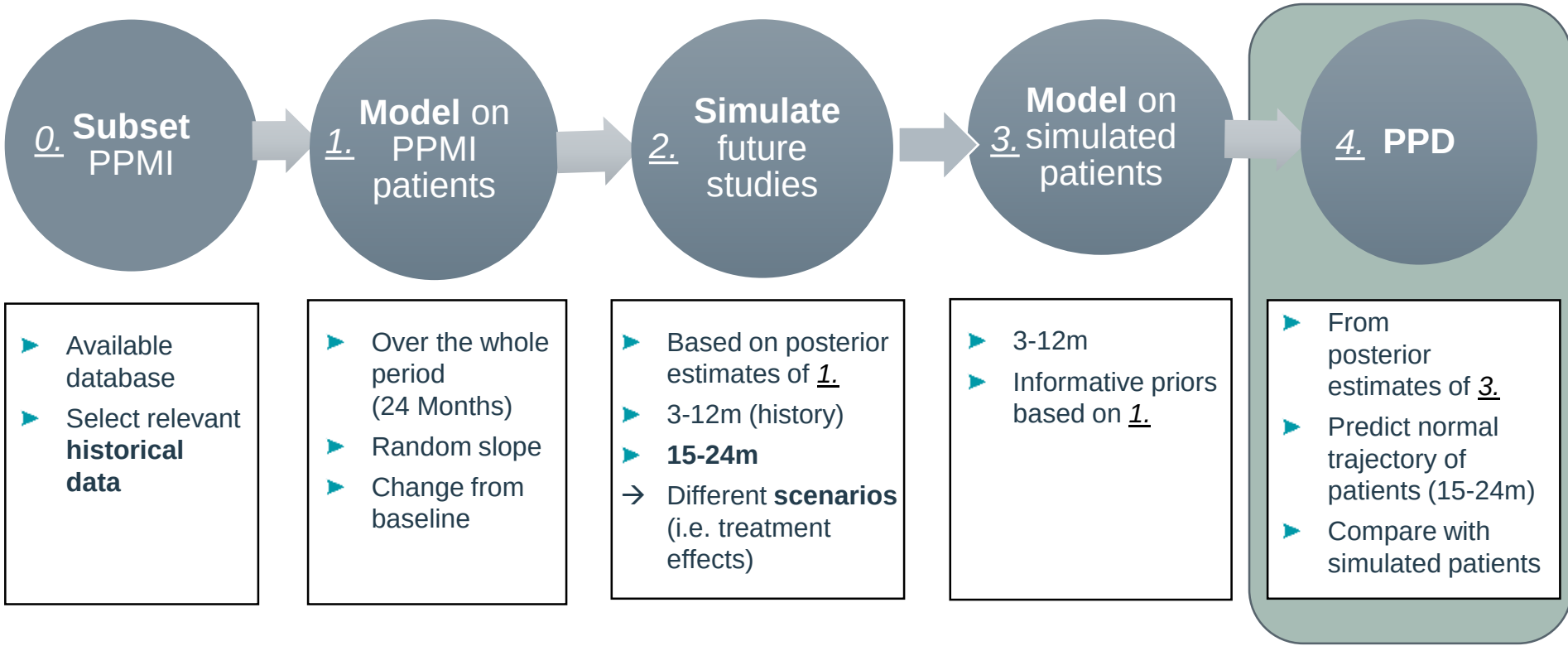
- Fit a new model (also random slope) on the simulated patients over the first 12 months
  → Use the PPMI data model's posterior chains to inform this new model

- $If\ X \sim Inverse\ Gamma(\alpha, \beta)$,
  - $E(X) = \frac{\beta}{\alpha - 1}, \qquad V(X) = \frac{\beta^2}{(\alpha-1)^2 \cdot (\alpha-2)}$
- Estimate $E(x)$ with $\hat{\mu}$ and V(X) with $\hat{\sigma}^2$ of the corresponding chain of the PPMI data model.
- Solve the system of 2 equations and find the α and β to use in the prior.
  - $\hat{\alpha} = \frac{\hat{\mu}^2}{\hat{\sigma}^2} + 2$
  - $\hat{\beta} = \hat{\mu} \cdot (\frac{\hat{\mu}^2}{\hat{\sigma}^2} + 1)$

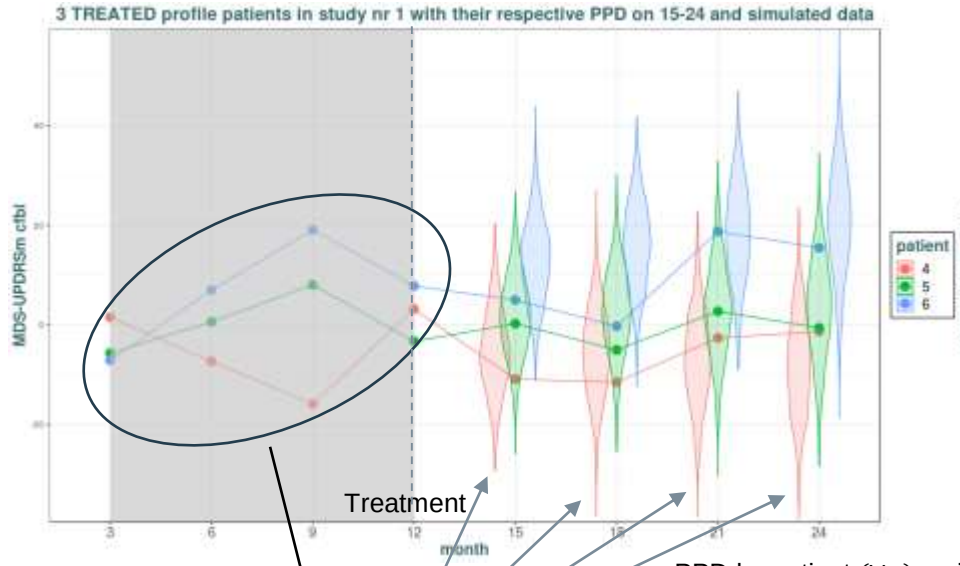
→ To use in the *IG* prior of $\boldsymbol{S^2}$ and $\boldsymbol{S^2_{\beta_1}}$

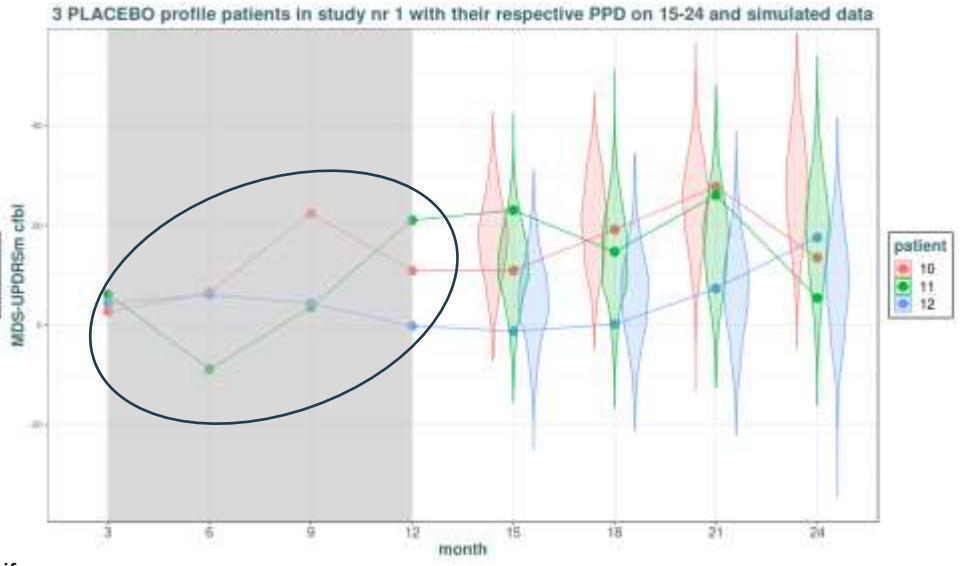
- For $\boldsymbol{\mu_{\beta_1}}$, simply take the empirical mean and sd of μ_{β_1} of the 1st model in the normal prior.

Summary of the Methodology



Illustrate with 3 patients in one study: Treated vs Placebo





Treatment

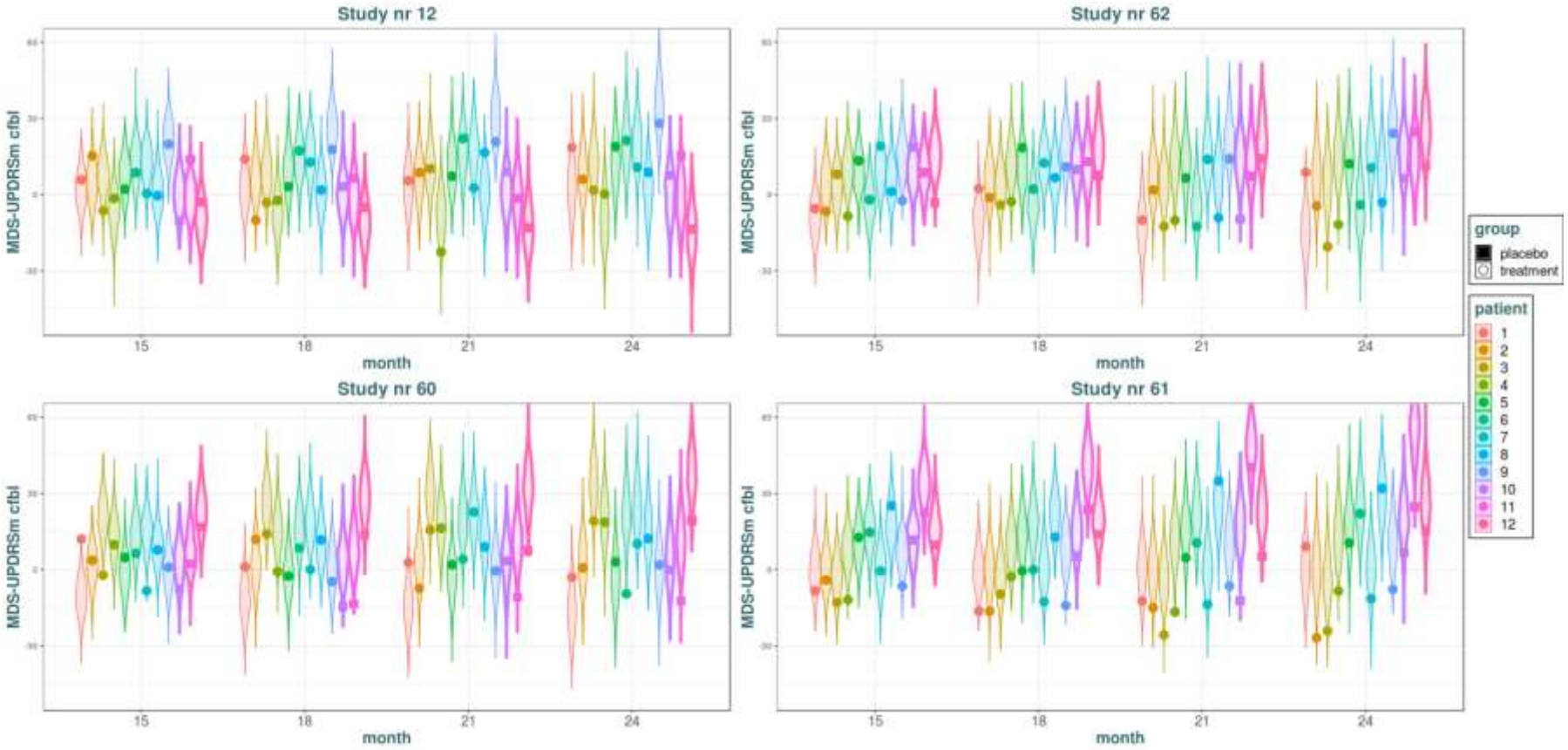
Normal evolution of the disease

- PPD <u>by patient</u> ($\forall\ t$) as if disease evolves normally
- Compare to simulations (with treatment): the dots

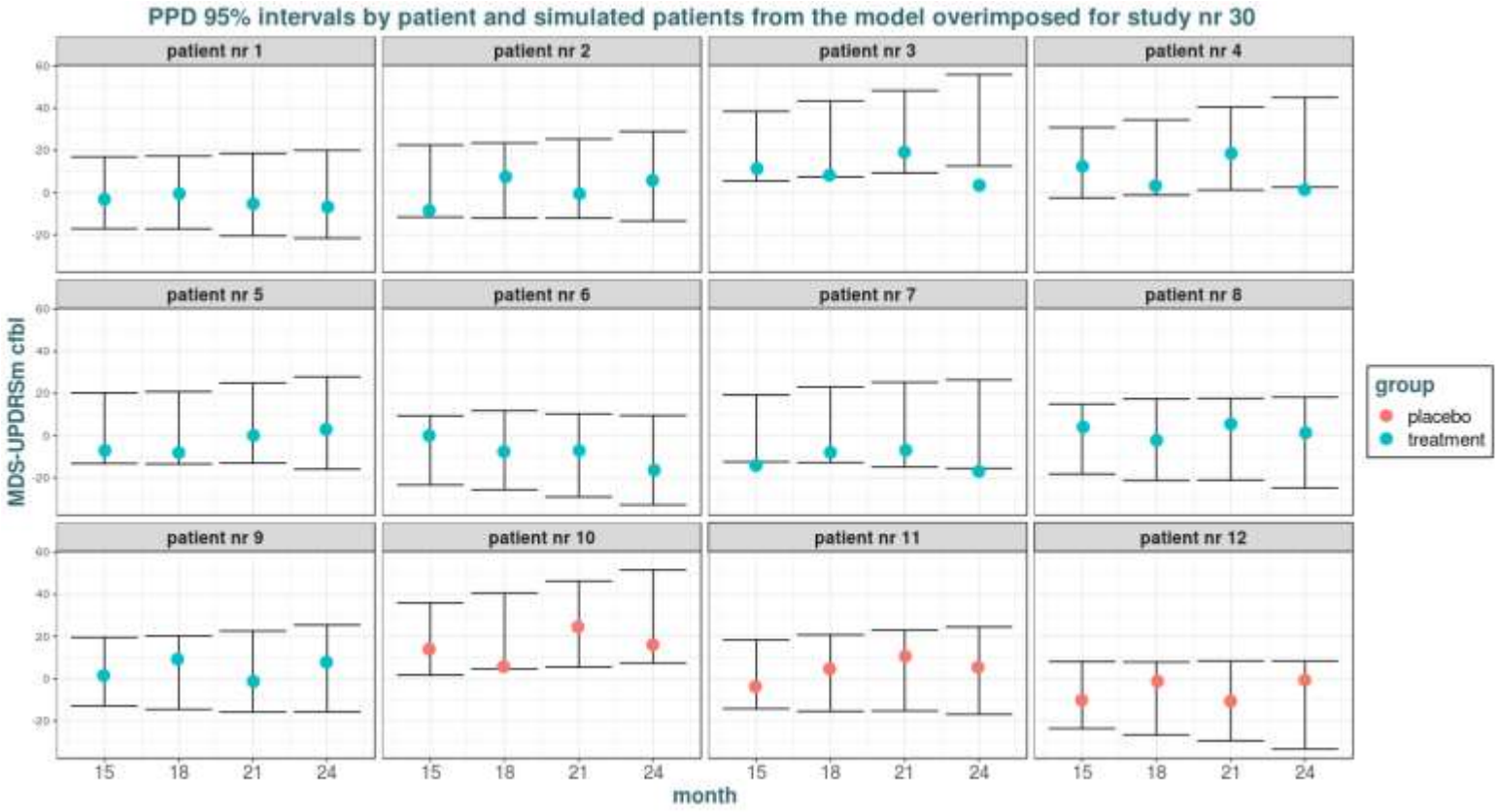
$$Y = \beta_1 \cdot t + \epsilon,\quad \beta_1 \sim N\left(\mu_{\beta_1}, S^2_{\beta_1}\right), \epsilon \sim N(0, S^2)$$

Same for placebo

Compare simulated patients with their PPD: illustration with some studies

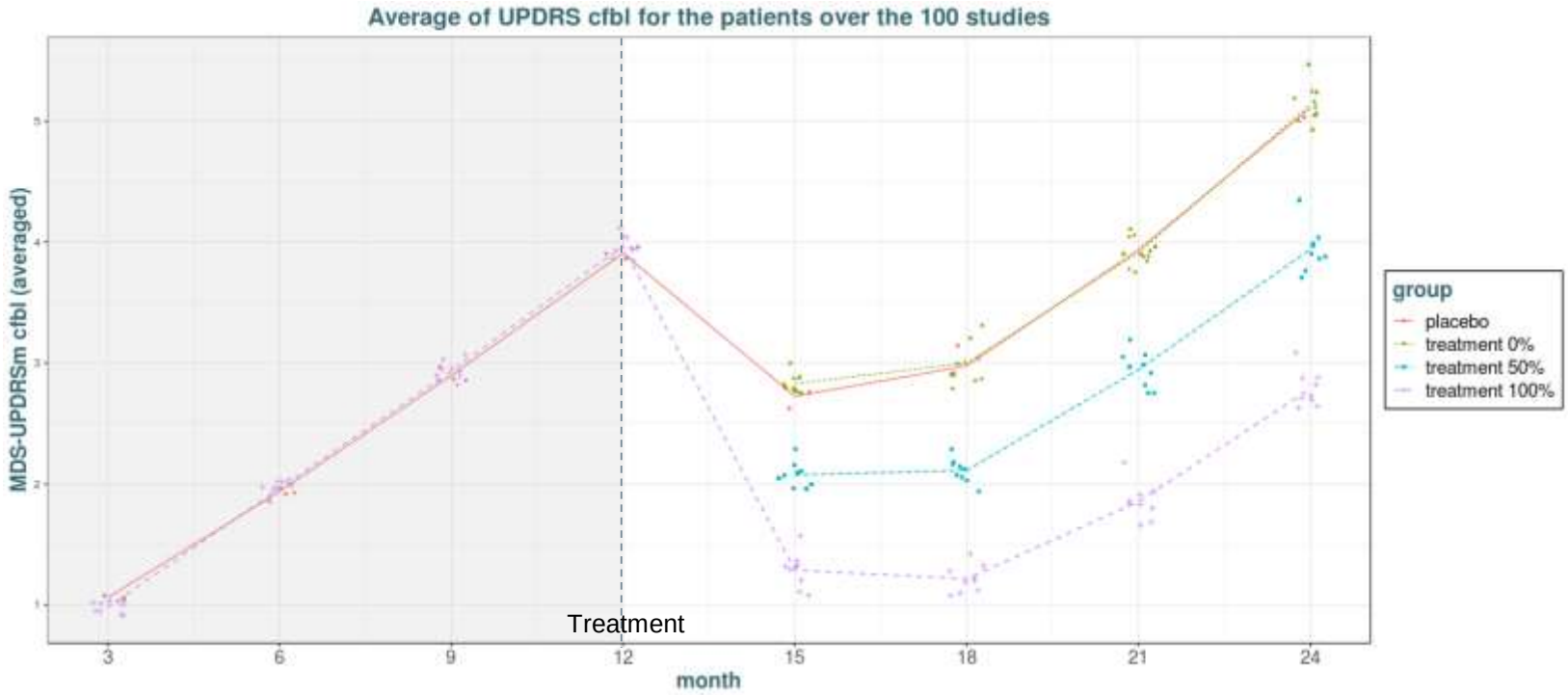


Other illustrations: predictive intervals

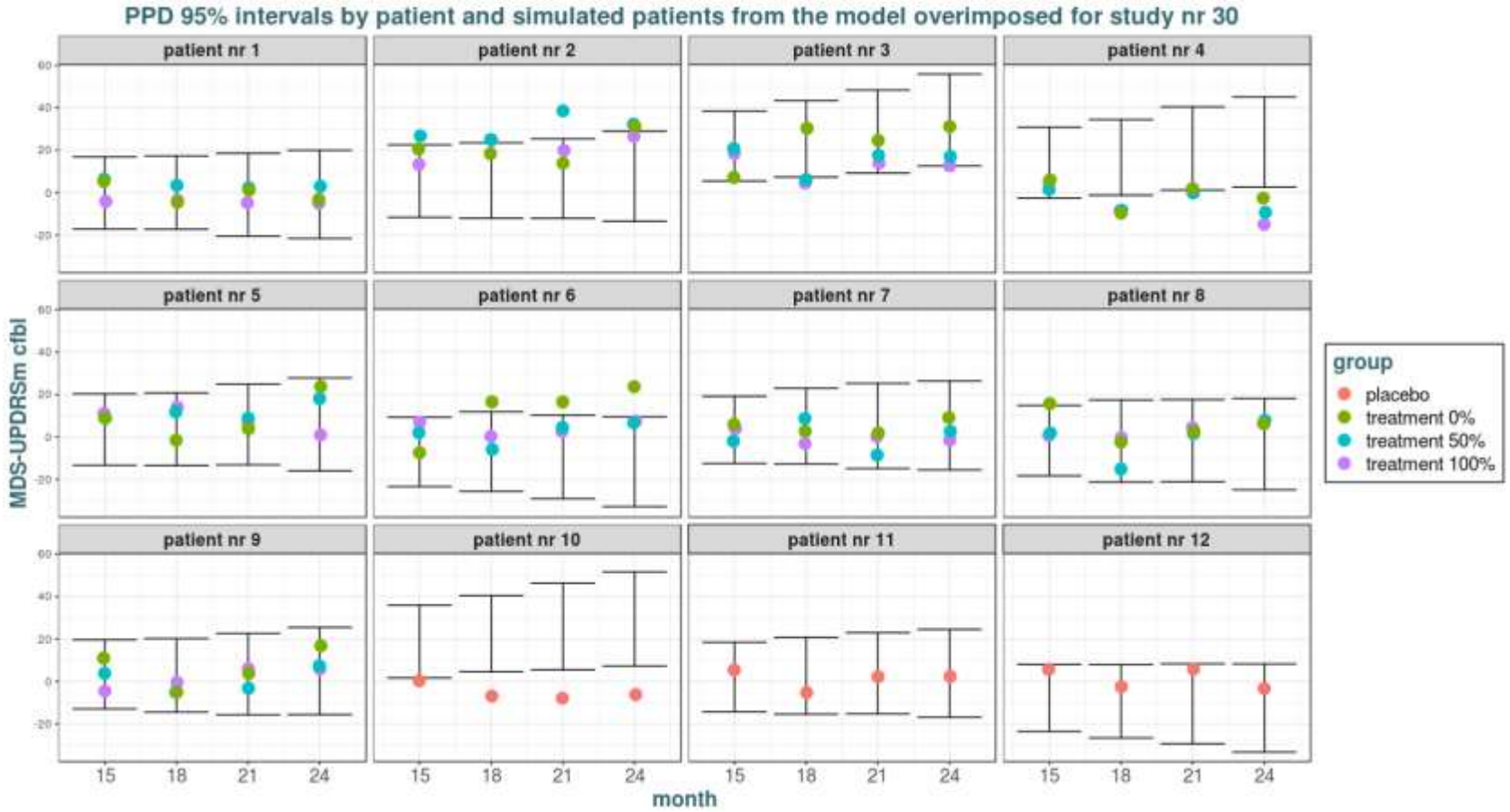


Results

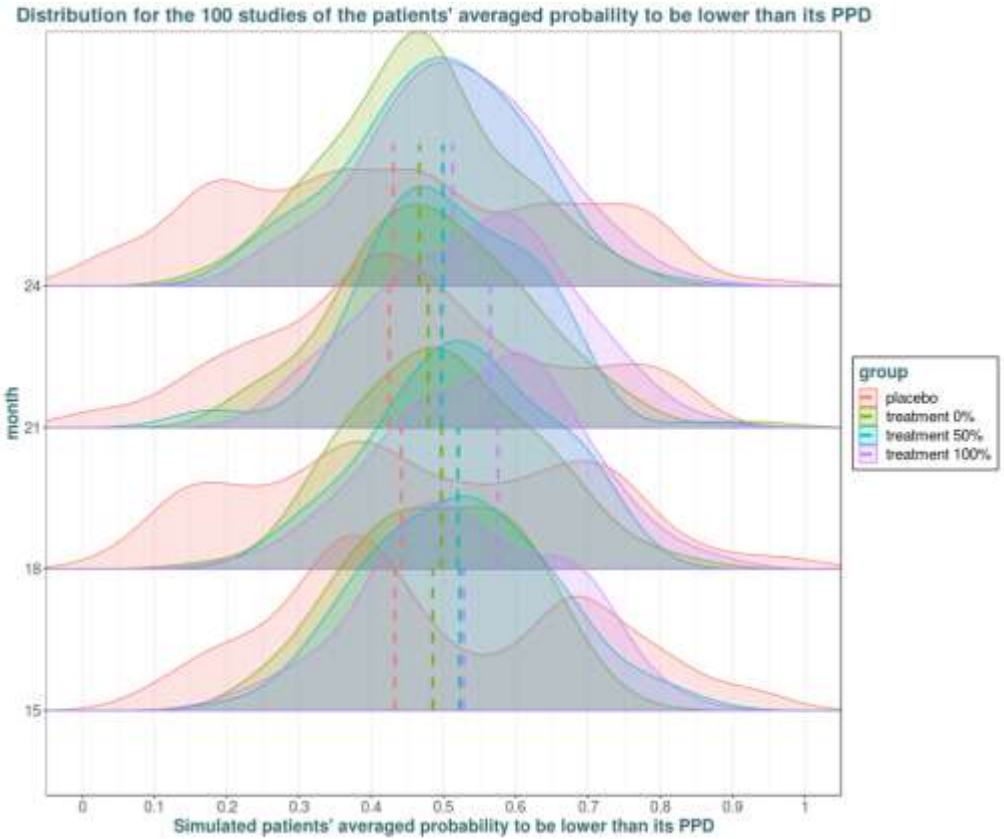
The different scenarios to show treatment effect



- **Power**: treatment 100% and placebo “significantly” different
- Controlling **type 1 error**: treatment 0% and placebo should be similar

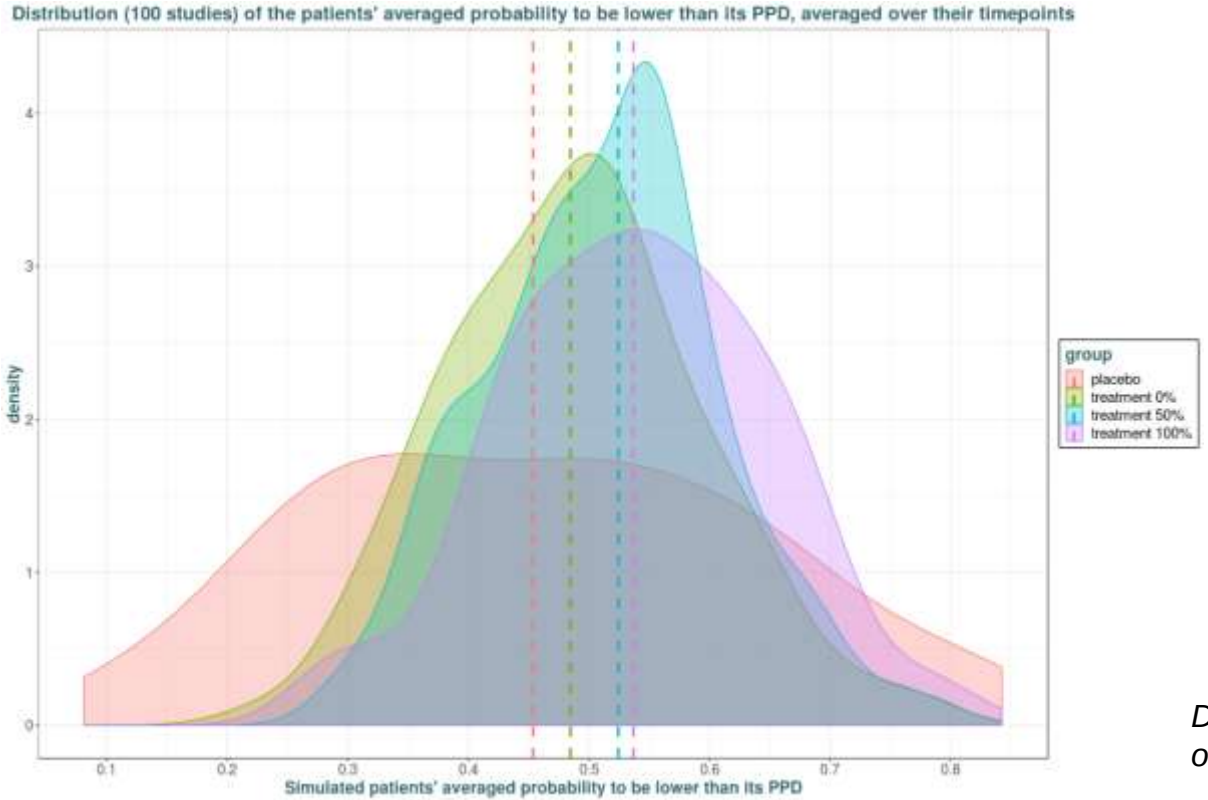

PPD 95% intervals by patient and simulated patients from the model overimposed for study nr 30
patient nr 1
patient nr 2
patient nr 3
patient nr 4
patient nr 5
patient nr 6
patient nr 7
patient nr 8
patient nr 9
patient nr 10
patient nr 11
patient nr 12
MDS-UPDRSm cfbl
month
group
placebo
treatment 0%
treatment 50%
treatment 100%

Probability of a simulated patient to be below its Predictive Distribution



Dashed vertical lines represent the medians over the studies for each timepoint

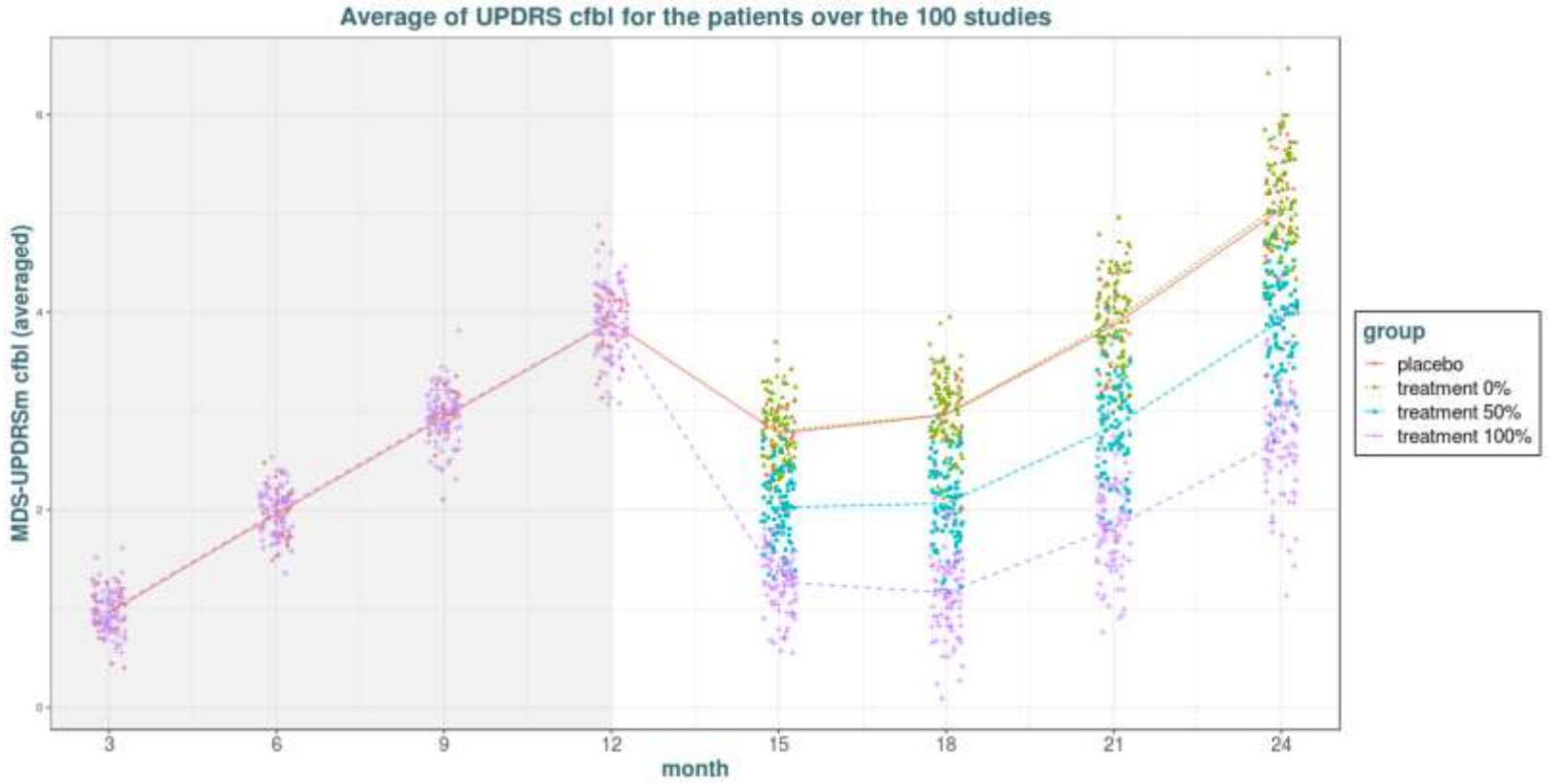
Probability of a simulated patient to be below its Predictive Distribution (2)



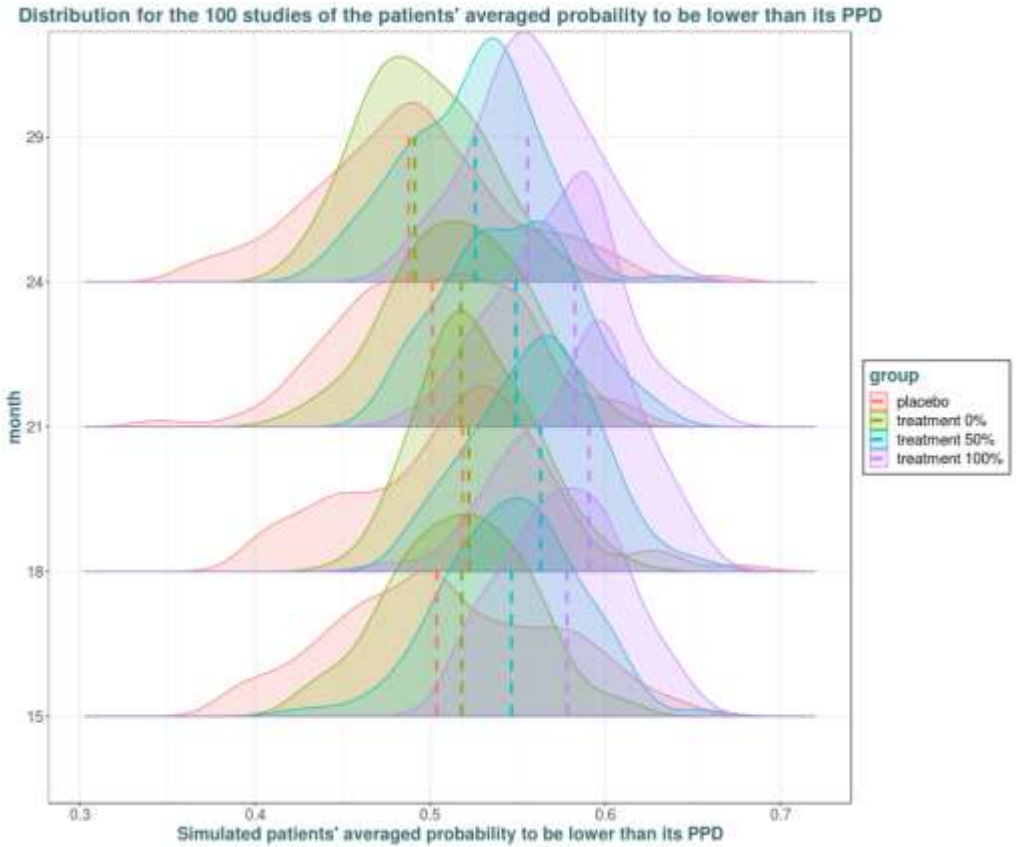
Dashed vertical lines represent the medians over the studies

Results with 90 + 30 patients

The different scenarios

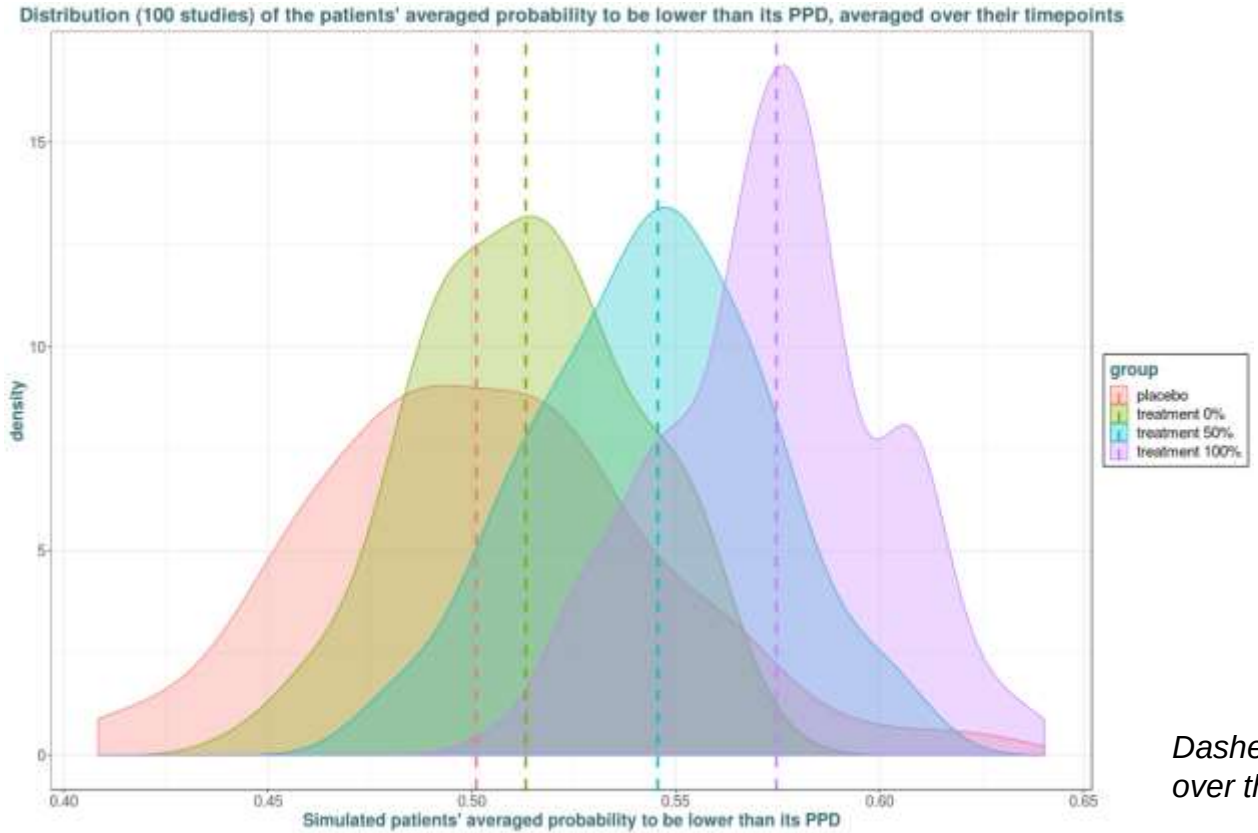


Probability of a simulated patient to be below its Predictive Distribution



Dashed vertical lines represent the medians over the studies for each timepoint

Probability of a simulated patient to be below its Predictive Distribution (2)



(Consider more than 100 studies to obtain smoother densities)

Dashed vertical lines represent the medians over the studies

Conclusion

- A complete framework is set up and can be used in similar applications
  - E.g. Charcot disease

- Bayesian analysis provides meaningful metrices to inform the scientist.

- The variability observed in such measurements (UPDRS) is very high.
- As a result, treatment effect is hard to discriminate from placebo effect.

- It is easier to discriminate between placebo and treated patients if the sample size increases.

Antoine Pissoort
Manager Statistics
+0479582291
Antoine.Pissoort@pharmalex.com
PharmaLex GmbH