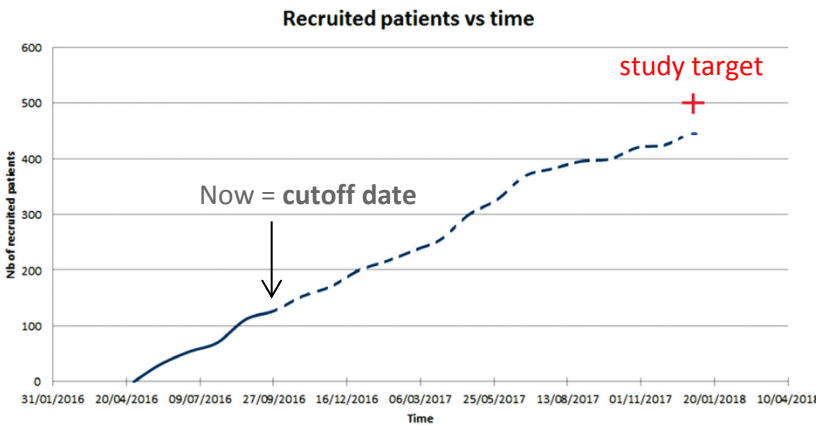
MAKING AN INFORMED DECISION ON PATIENT RECRUITMENT IN CLINICAL TRIALS USING MODELING AND SIMULATION

Anaïs Debard

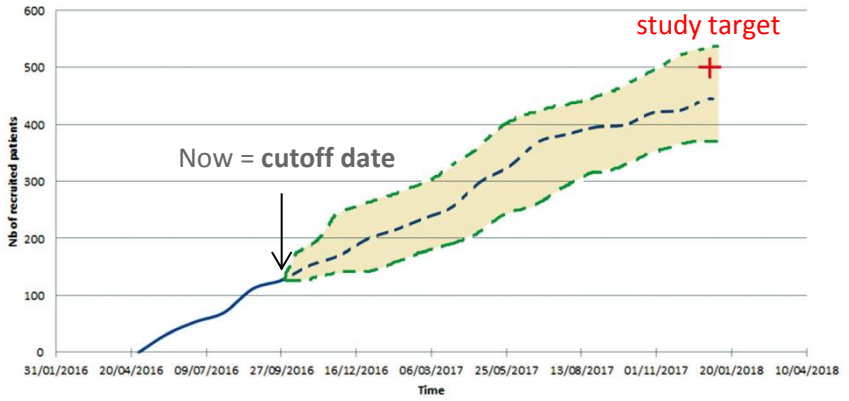
SERVIER

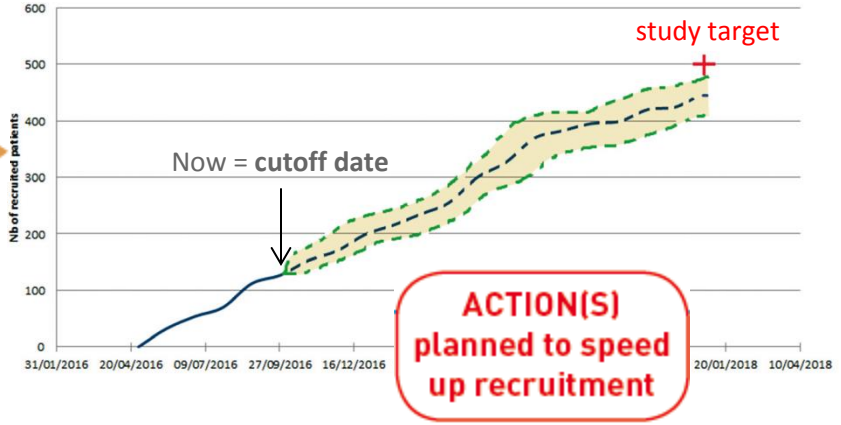
Goal

Current solution

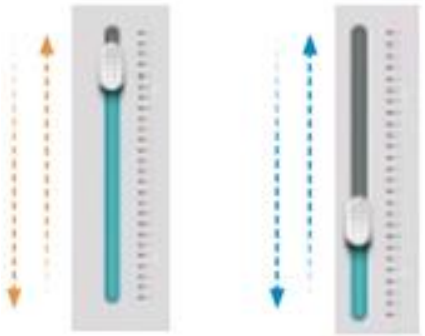


NEED A **CONFIDENCE INDEX** TO MAKE AN INFORMED DECISION





Goal



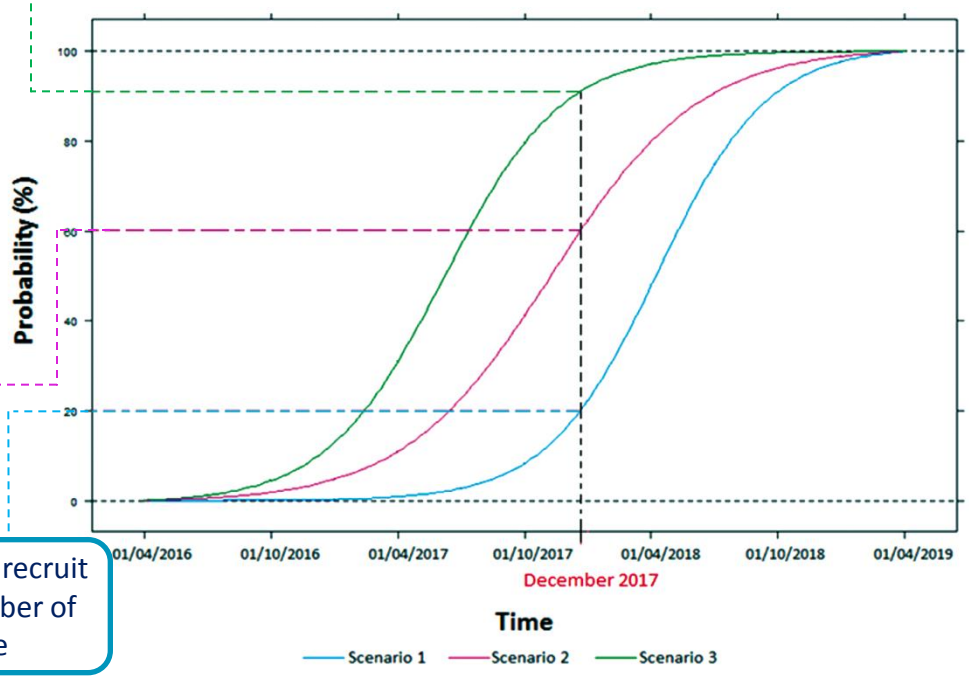
Inclusion criteria of the study protocol

Number of centres enrolled in the study

90% chance to recruit the target number of patients in time

60% chance to recruit the target number of patients in time

20% chance to recruit the target number of patients in time



Modelisation

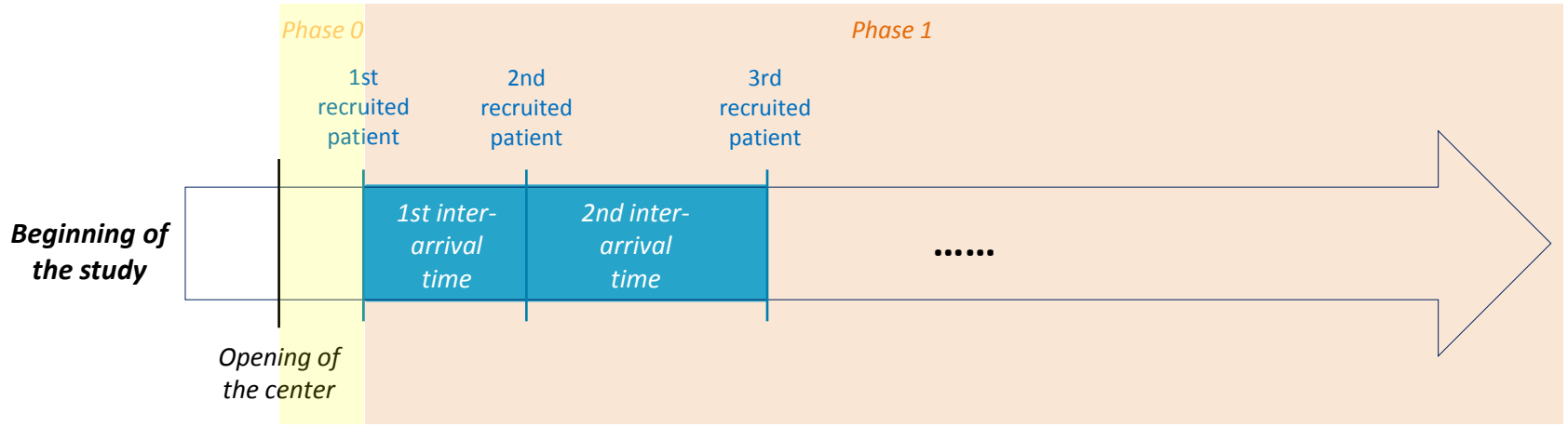
Output : ***TIME TO RECRUIT THE REMAINING NUMBER OF PATIENTS***

Variable to model:

INTER-ARRIVAL TIME t
(time between the recruitment of 2 patients)

$\Rightarrow$ **WEIBULL DISTRIBUTION**

Modelisation



Phase 0 : 1st patient recruitment time

$$t \sim Weibull(\alpha_0, \sigma_0)$$

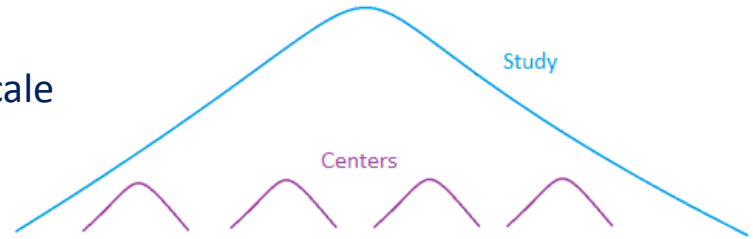
Shape Scale

Phase 1 : Inter-arrival times of following patients

$$t \sim Weibull(\alpha_1, \sigma_1)$$

Shape Scale

Hierarchical model



Modelisation

At the cutoff date, we still have to recruit **a total of n patients**

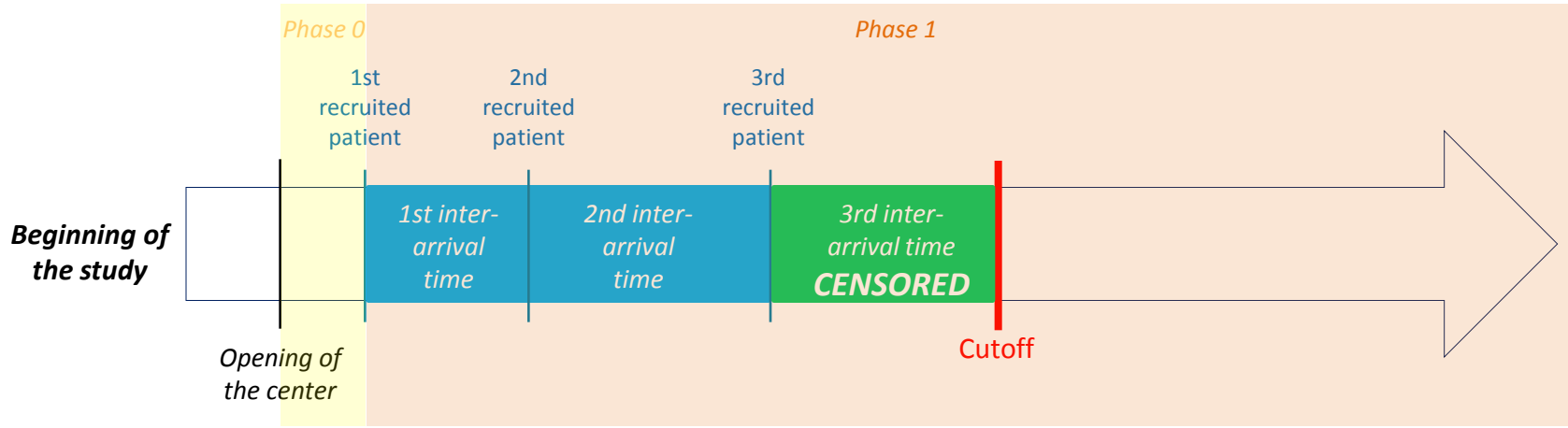
Predictions by centers of **n** inter-arrival times

$\Rightarrow$ 3 specific cases

- Center which has already recruited at least 1 patient
- Center already opened but which has not yet recruited
- Center not yet opened

Predictions – Center which has already recruited at least 1 patient

Predictions of **n** inter-arrival times



Predictions – Center which has already recruited at least 1 patient

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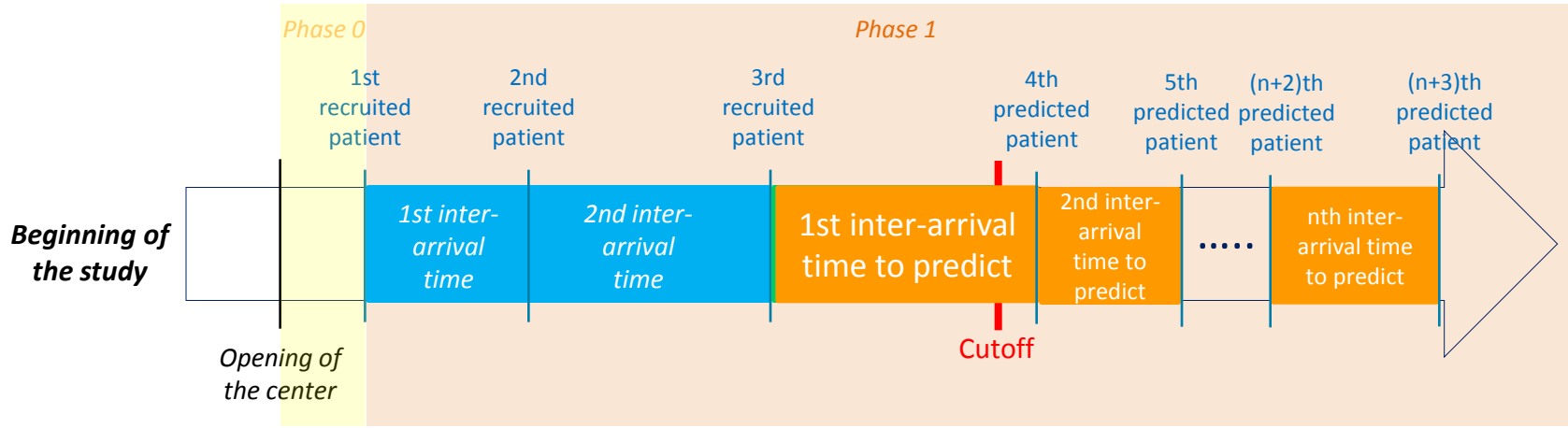
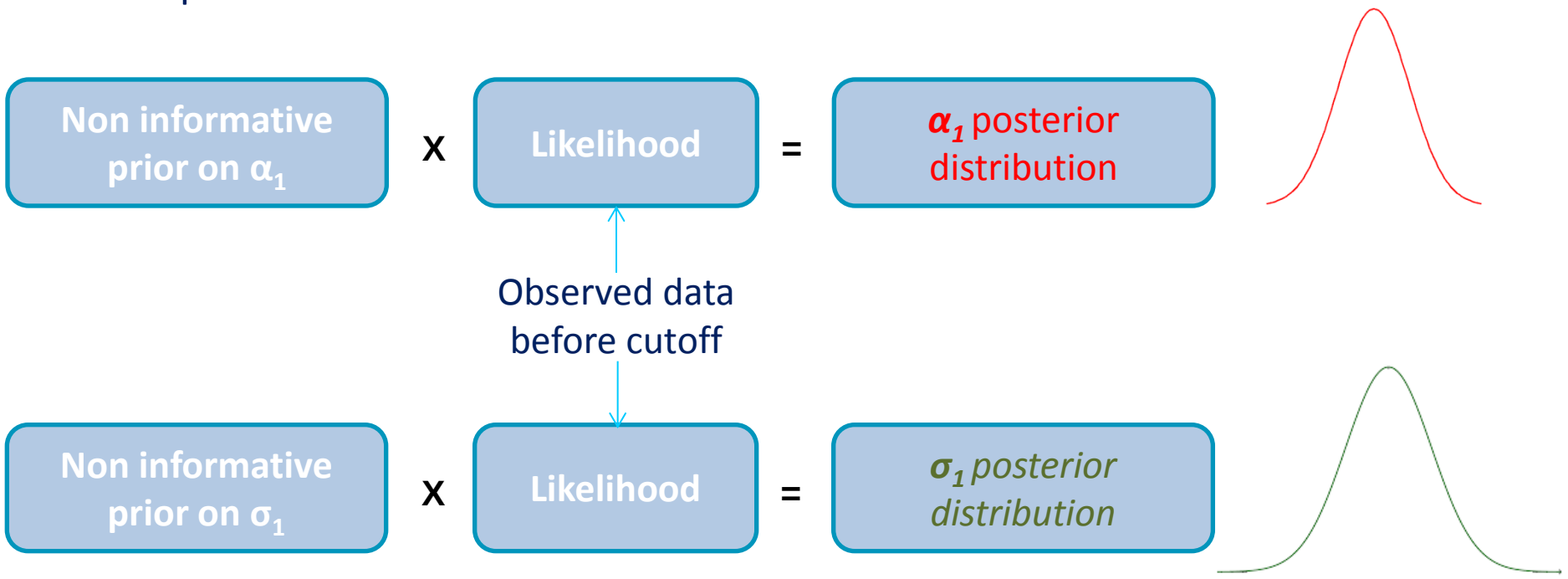


Predictions – Center which has already recruited at least 1 patient

Predict n inter-arrival times of <u>phase 1</u>

$$t \sim Weibull(\alpha_1, \sigma_1)$$

- Obtain posterior distributions



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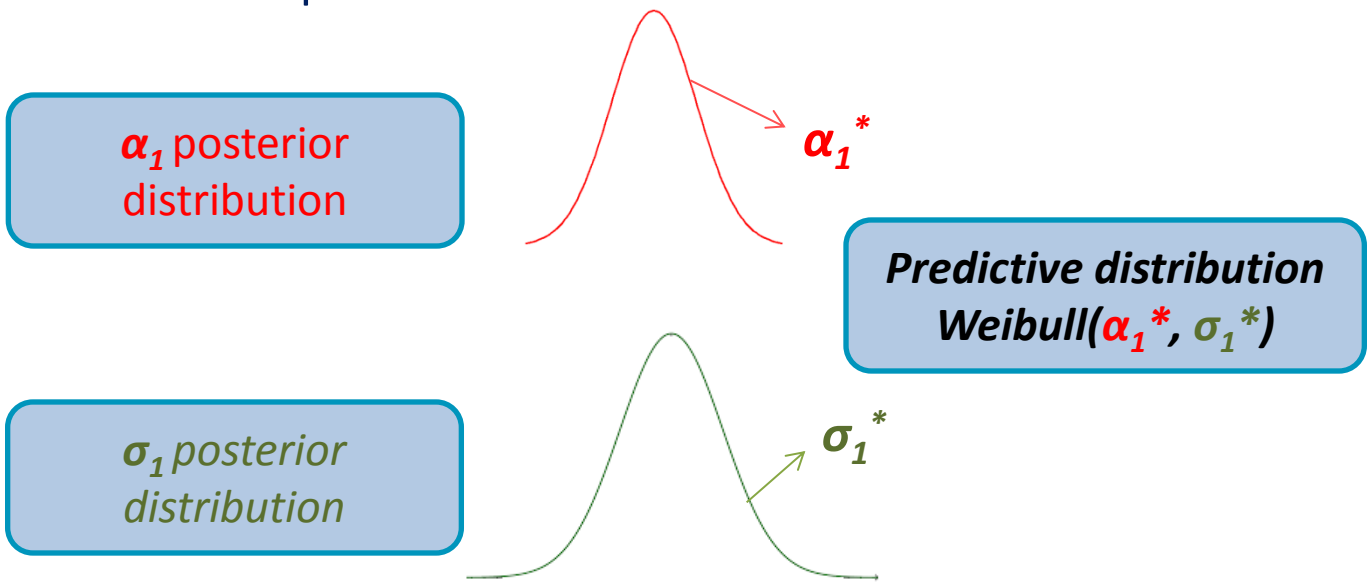

Predictions – Center which has already recruited at least 1 patient

Predict n inter-arrival times of <u>phase 1</u>

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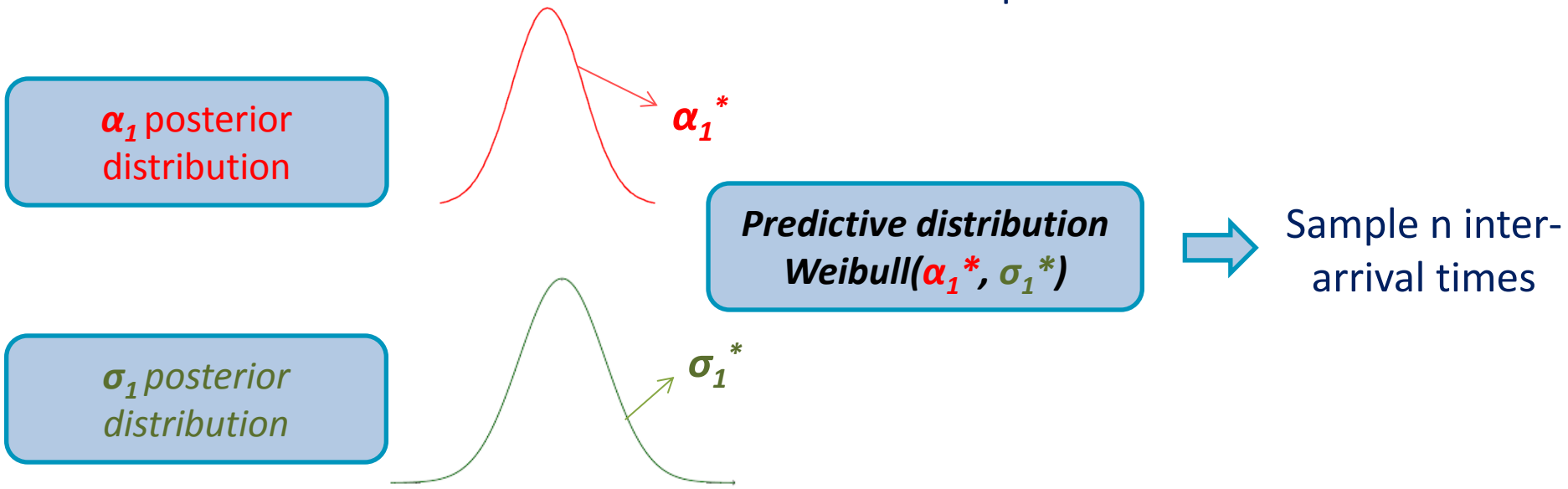
- Predict the n inter arrival times in the center in question



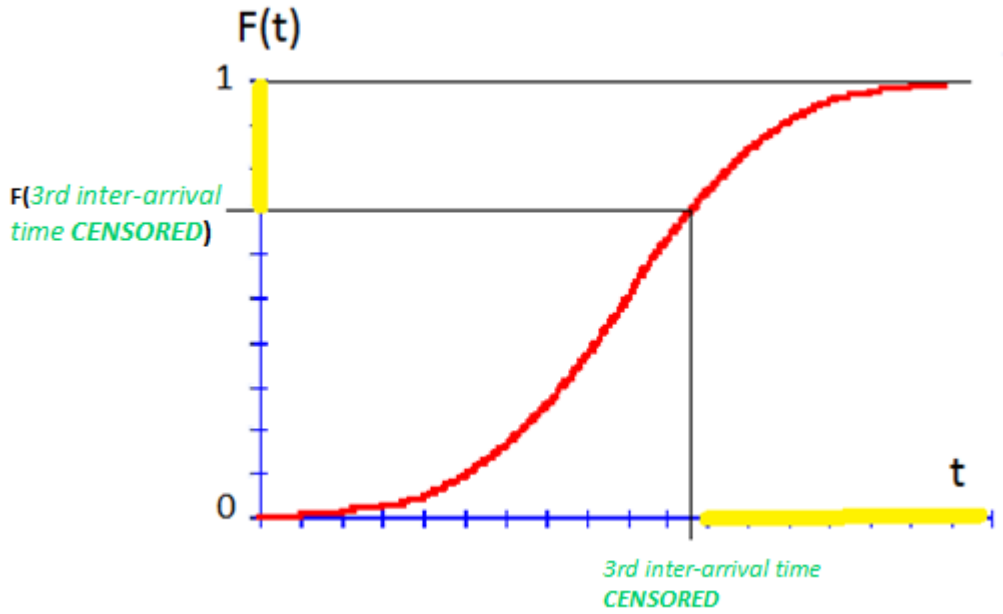
Predictions – Center which has already recruited at least 1 patient

Predict n inter-arrival times of <u>phase 1</u>

$$t \sim Weibull(\alpha_1, \sigma_1)$$

/!\ *<u>Constraint</u> :* ***1st inter-arrival time to predict*** > *3rd inter-arrival time* ***CENSORED***

⇒ Inverse probability method



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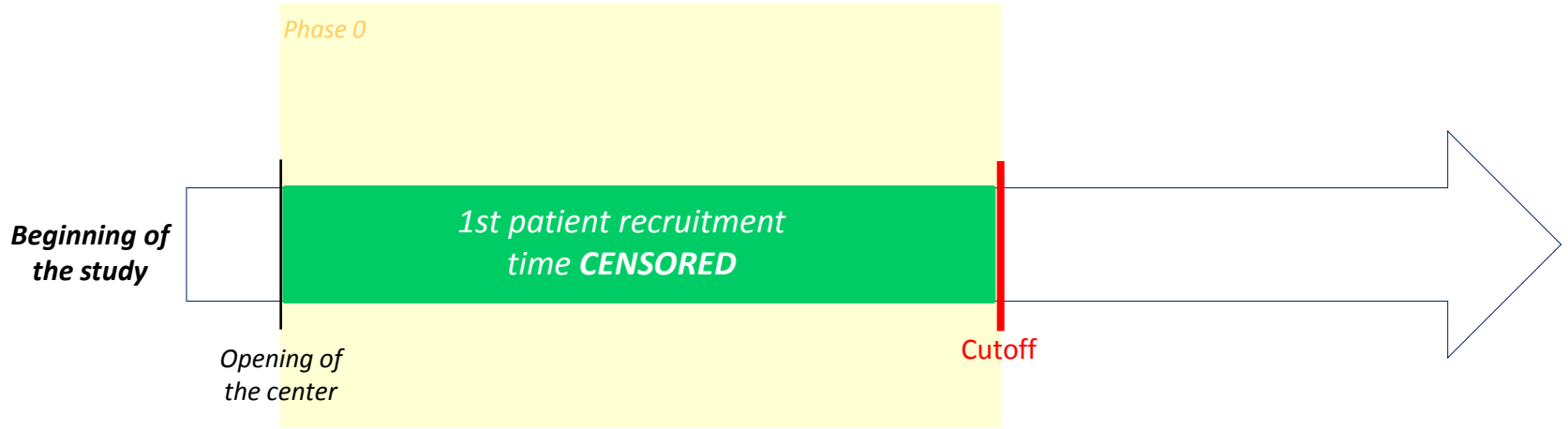


Predictions – Center already opened but which has not yet recruited

Predictions of **n** inter-arrival times

Predictions – Center already opened but which has not yet recruited

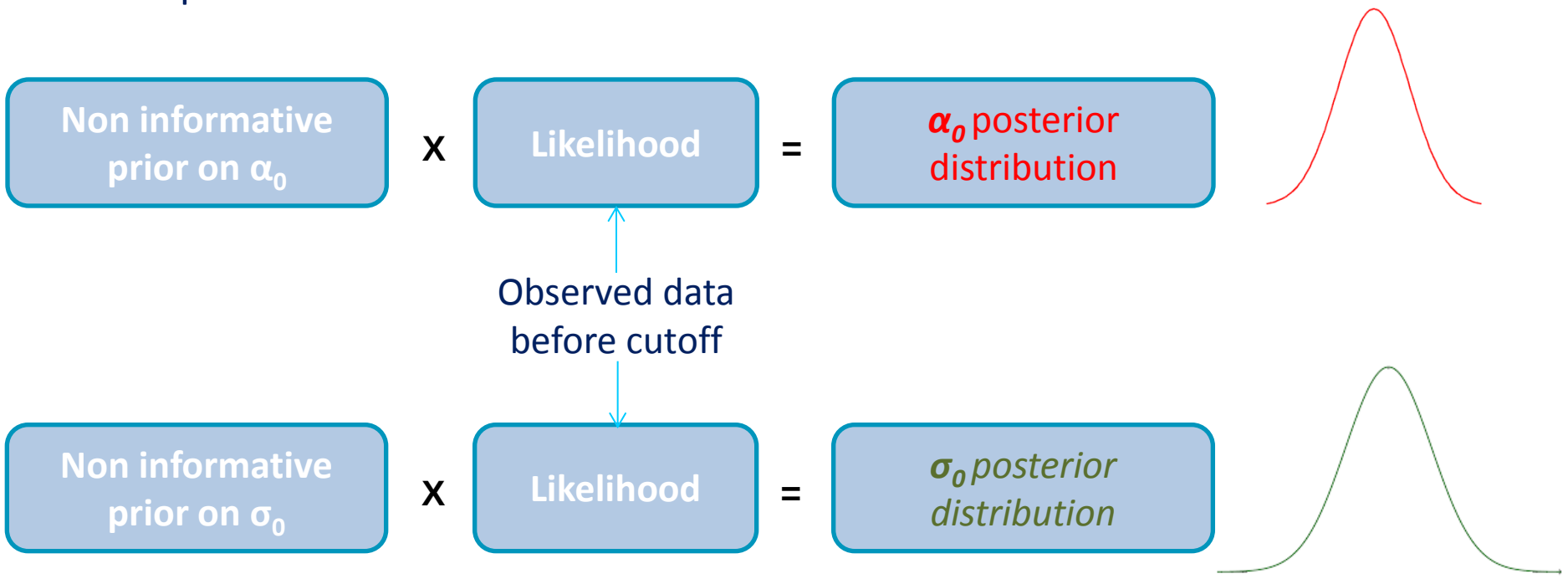
Predictions of **n** inter-arrival times

Predictions – Center already opened but which has not yet recruited

Predict 1st patient recruitment time - phase 0

$$t \sim Weibull(\alpha_0, \sigma_0)$$

- Obtain posterior distributions



Predictions – Center already opened but which has not yet recruited

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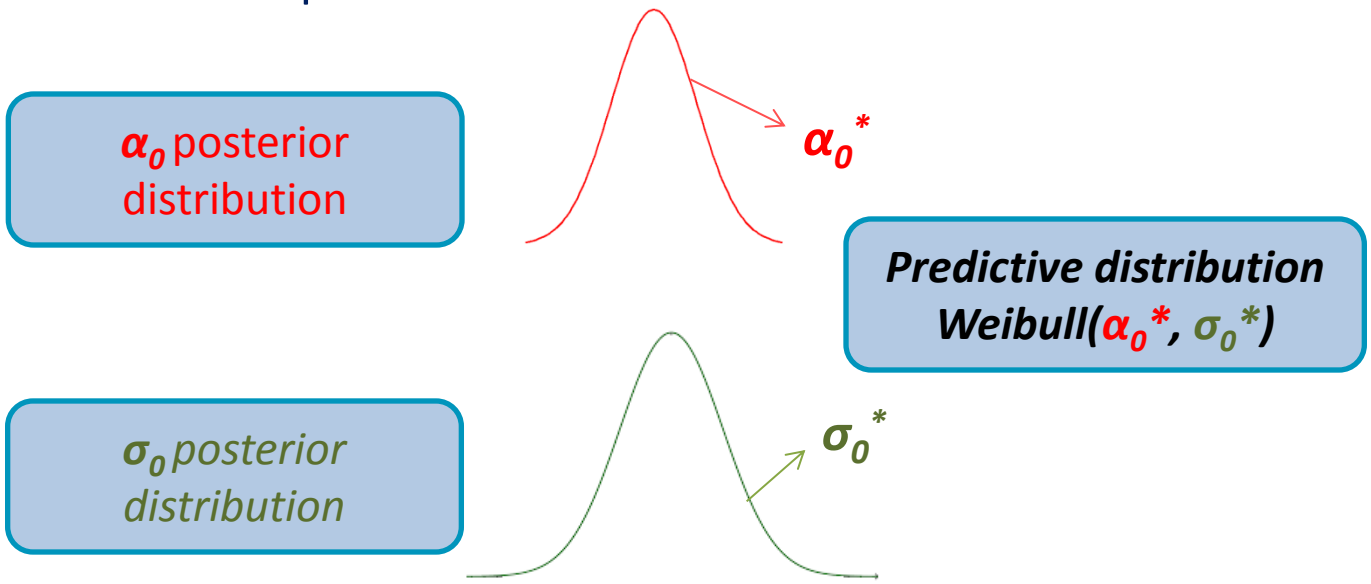
- Obtain predictive distribution



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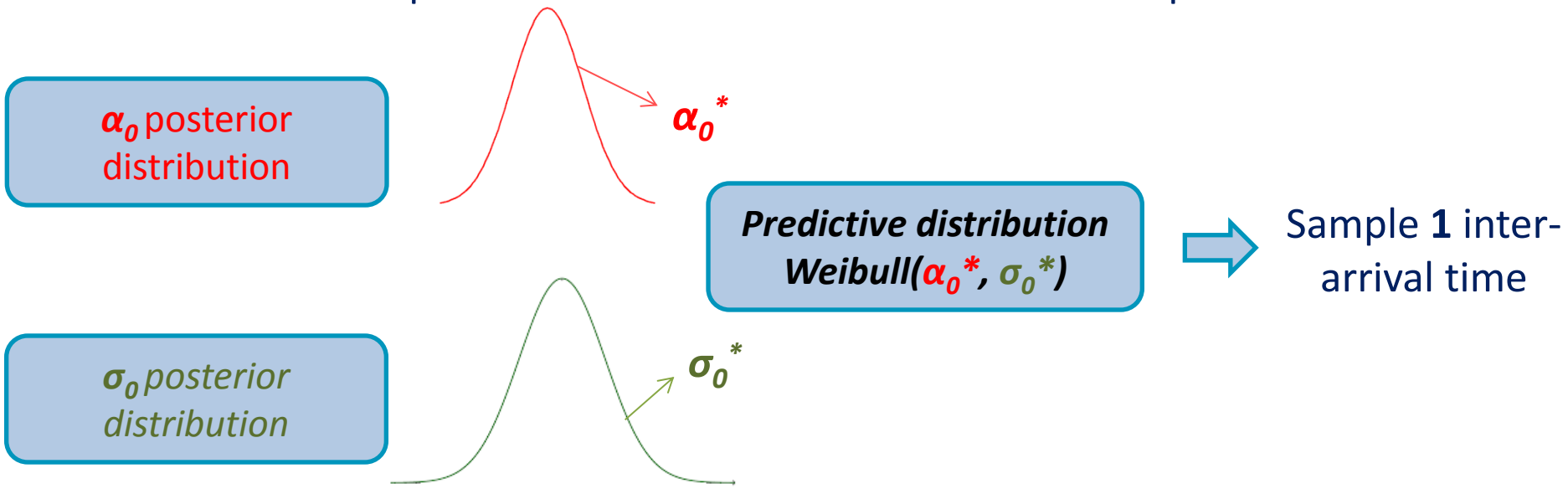

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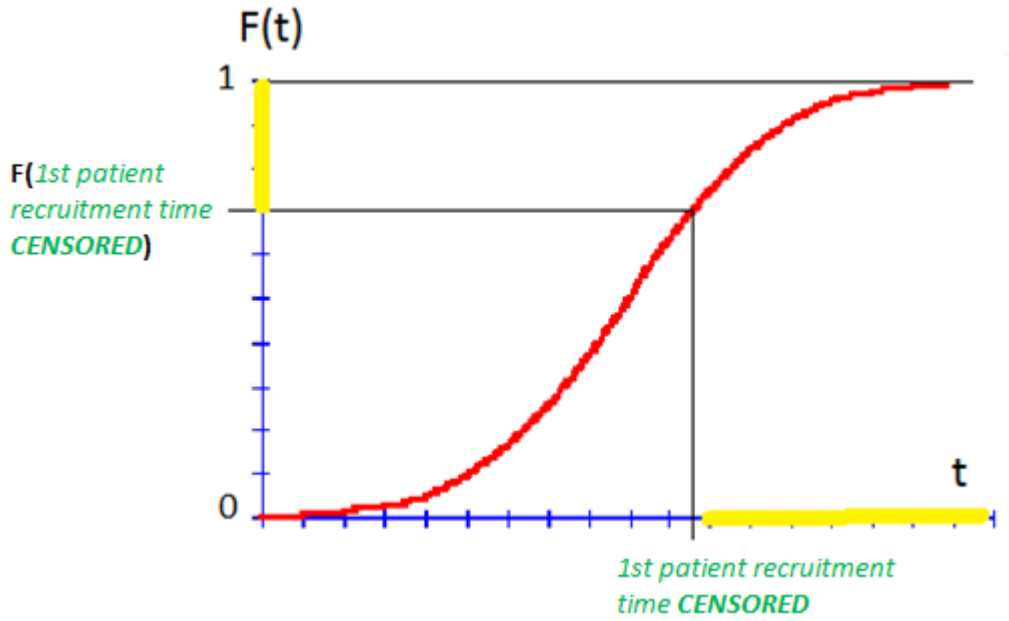
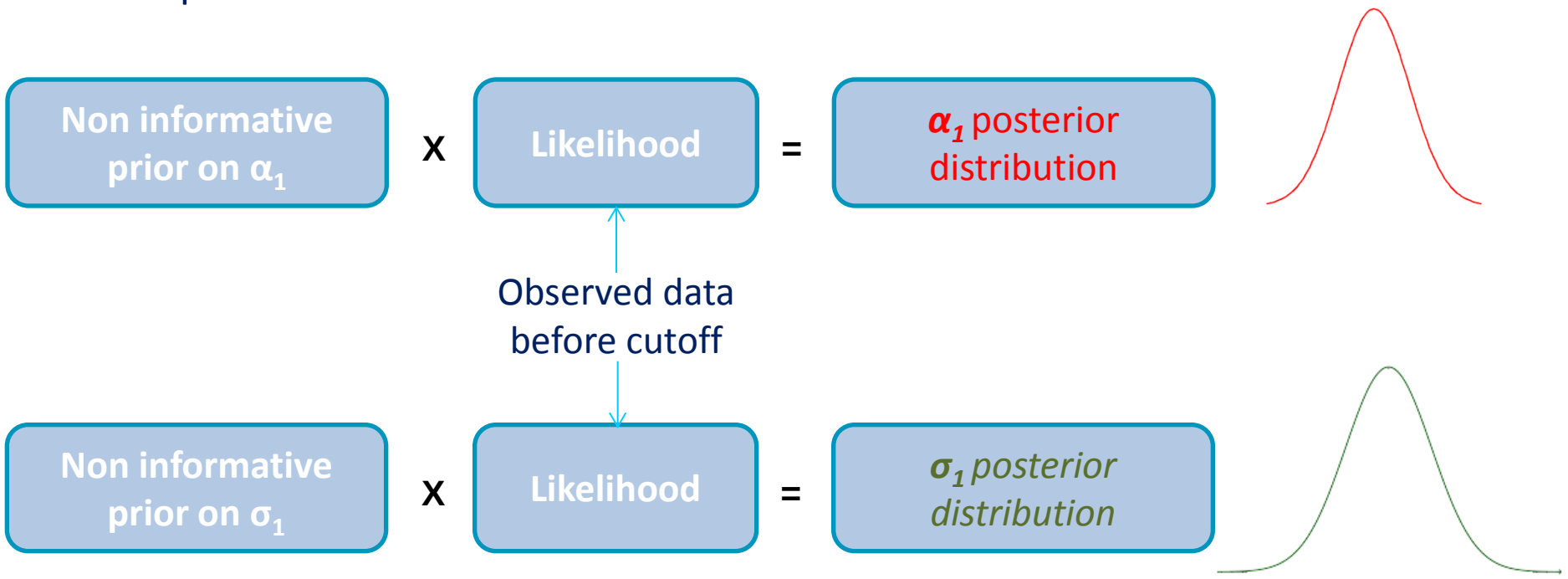


Predictions – Center already opened but which has not yet recruited

Predict n-1 inter-arrival times of <u>phase 1</u>

$$t \sim Weibull(\alpha_1, \sigma_1)$$

- Obtain posterior distributions



Predictions – Center already opened but which has not yet recruited

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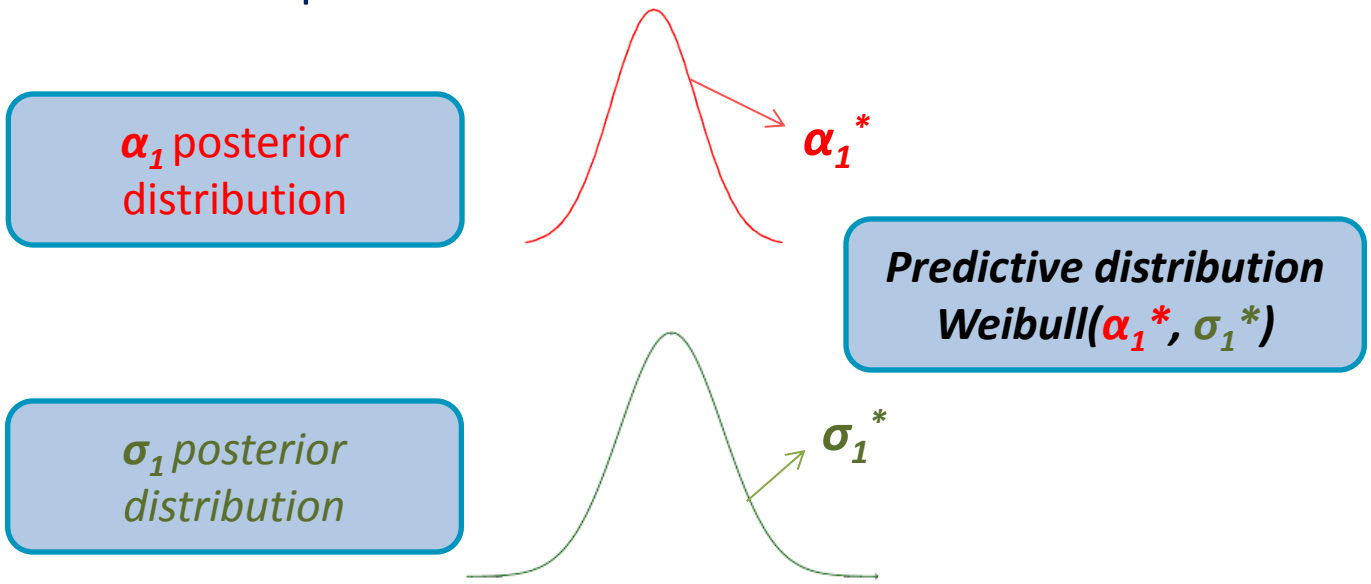

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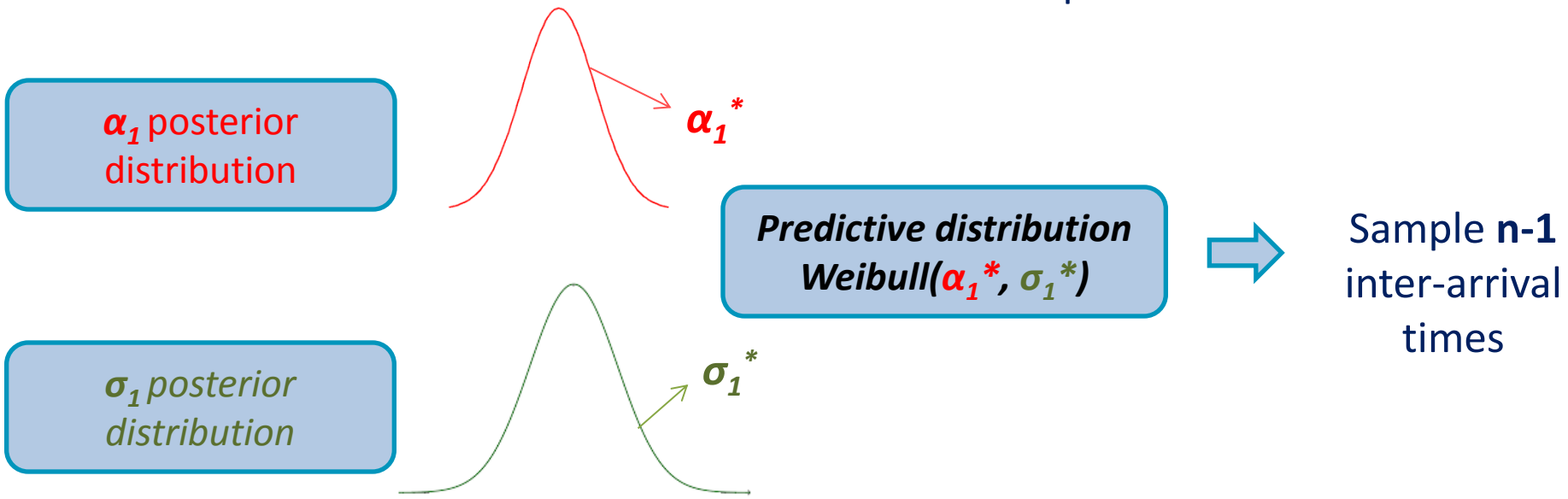
- Predict the n-1 inter-arrival times in the center in question



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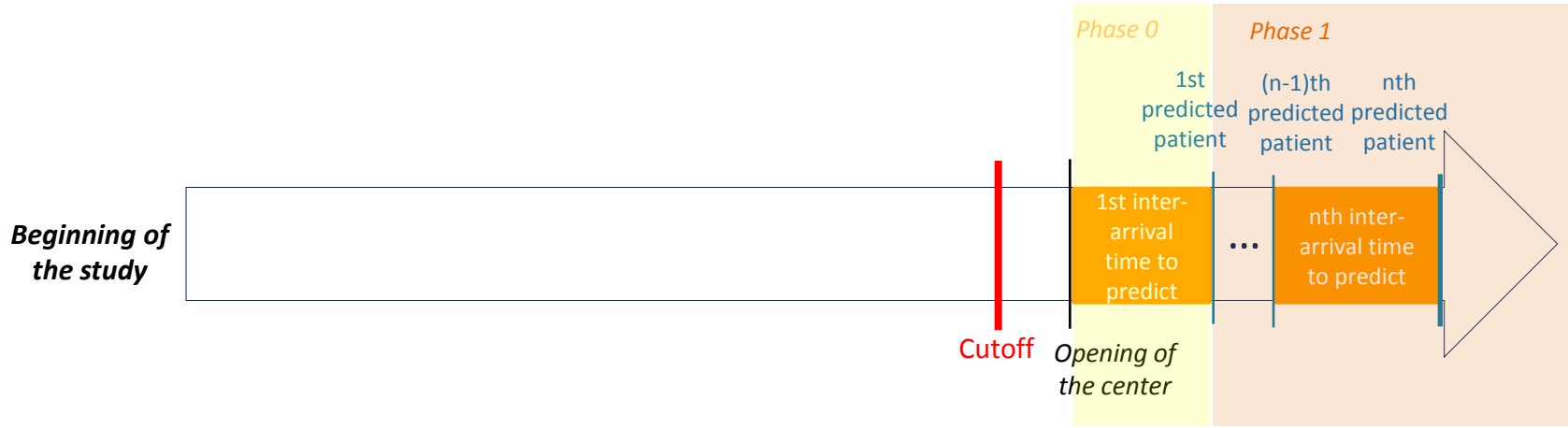
Predictions of **n** inter-arrival times



The same as Center already opened but which has not yet recruited

without constraint on the 1st patient recruitment time

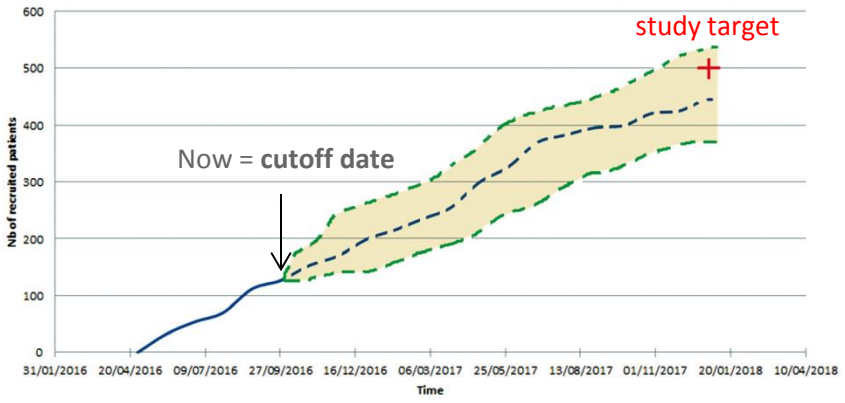
Predictions

- **Do this for all planned centers according its type**
- **Convert predicted inter-arrival times in dates**
- **Sort all the dates of pooled centers**
- **Obtain the predicted time to recruit the n remaining patients**

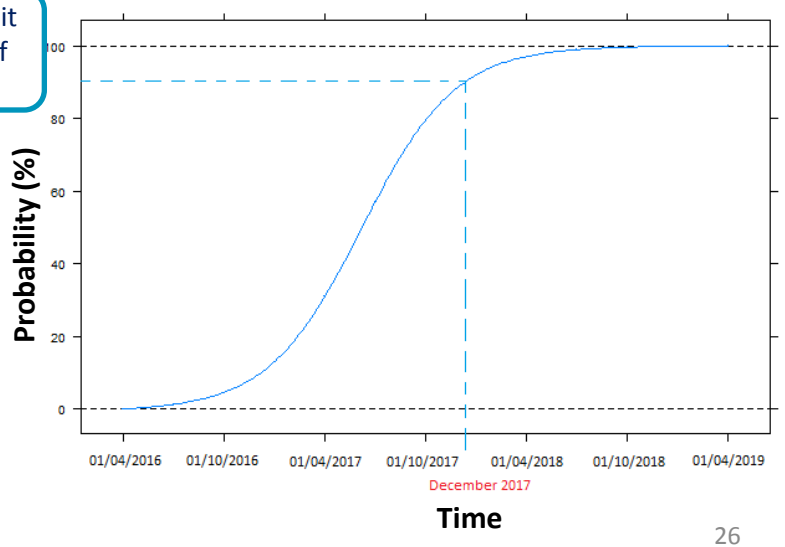
->This is the first simulation

-> do this 1000 times

by drawing other α_0^*, σ_0^*, α_1^* *and* σ_1^* *from posterior distributions*



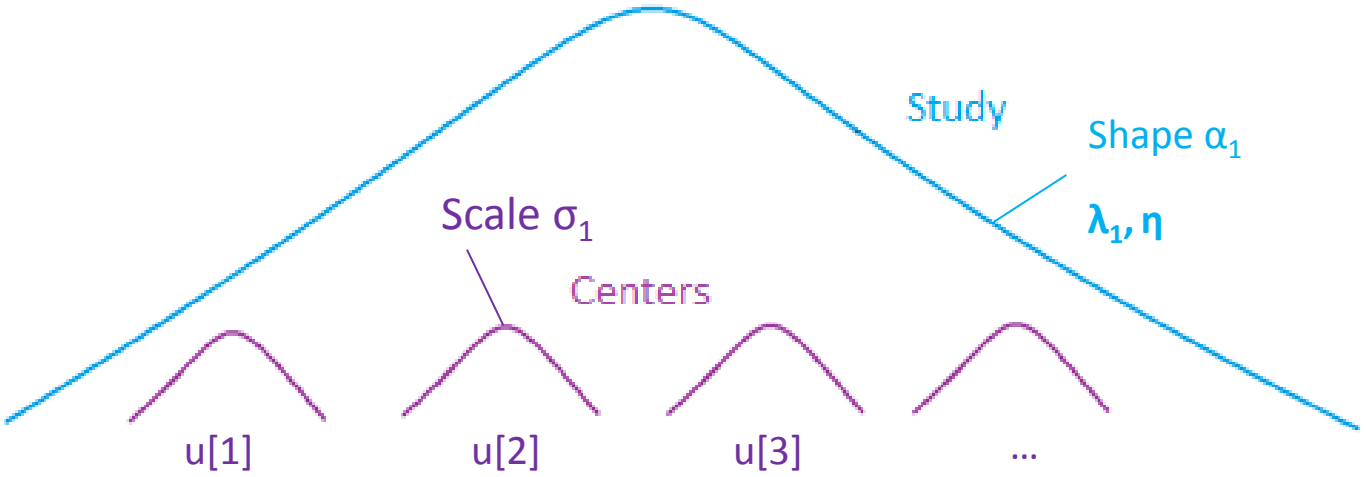
90% chance to recruit the target number of patients in time



Predictions – Some focus

Center which has already recruited at least 1 patient

Phase 1 : $t \sim Weibull(\alpha_1, \sigma_1)$



$$\sigma_1 = \lambda^{1/\alpha 1}$$

where $\lambda = \lambda_1 \times u[center] \times \exp(\eta)$

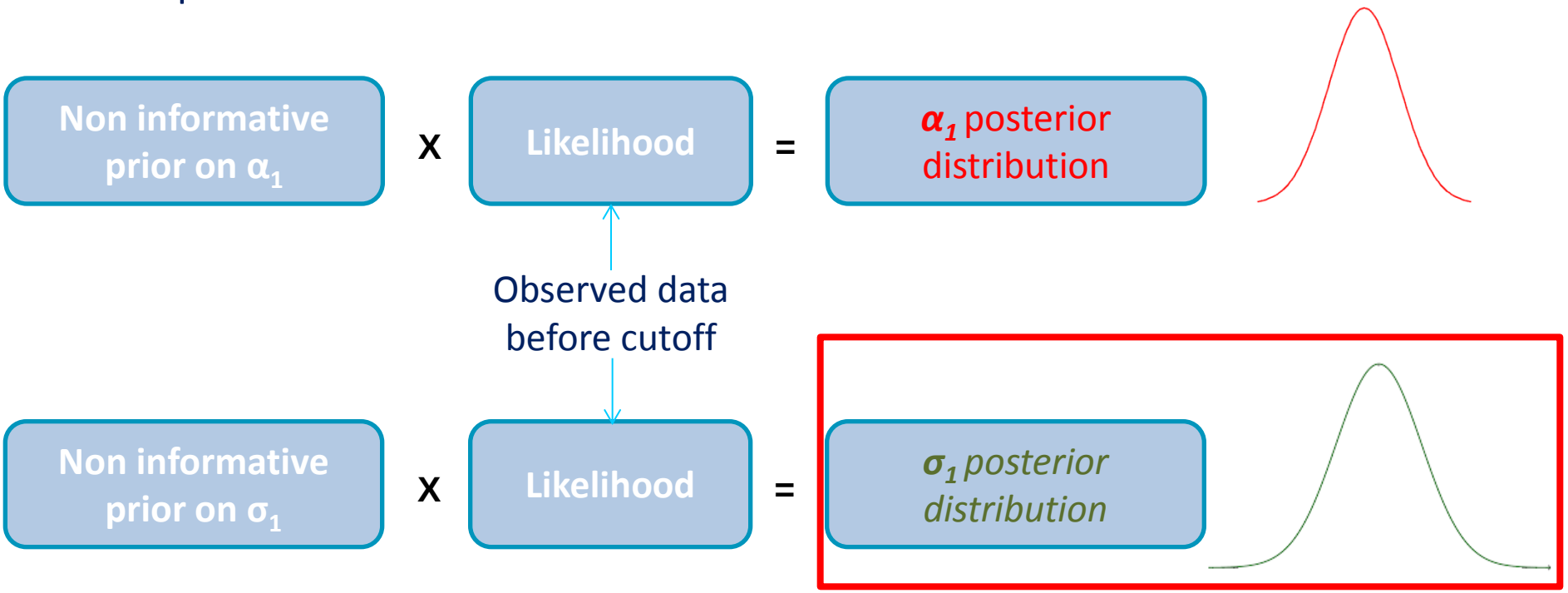
- λ_1: Study recruitment rate parameter
- $u[center]$: Center corrective recruitment rate parameter
- η: Covariate

Center which has already recruited at least 1 patient

Predict n inter-arrival times of phase 1

$$t \sim Weibull(\alpha_1, \sigma_1)$$

- Obtain posterior distributions

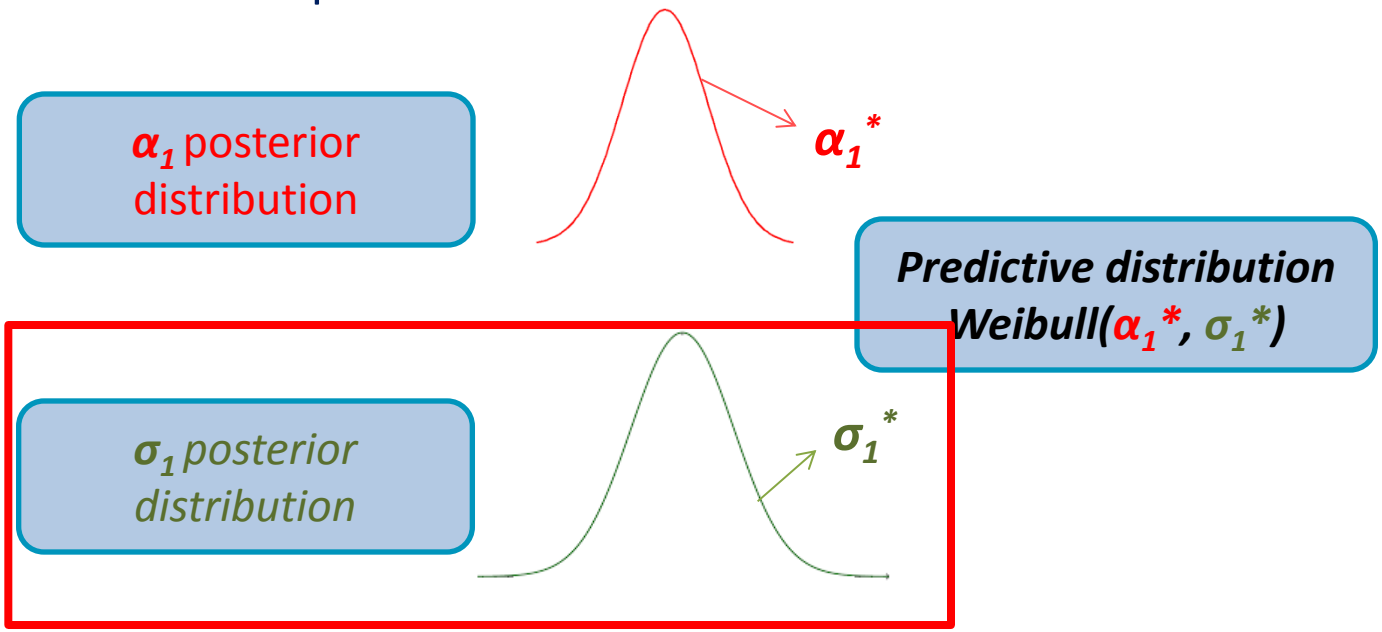


Center which has already recruited at least 1 patient

Predict n inter-arrival times of <u>phase 1</u>

$$t \sim Weibull(\alpha_1, \sigma_1)$$

- Obtain predictive distribution



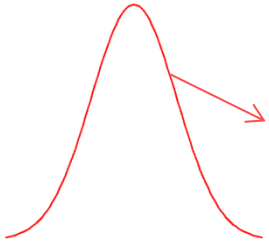
Center which has already recruited at least 1 patient

Predict n inter-arrival times of <u>phase 1</u>

$$t \sim Weibull(\alpha_1, \sigma_1)$$

- Obtain predictive distribution

α_1 posterior distribution



α_1^*

Predictive distribution Weibull(α_1^*, σ_1^*)

$$\sigma_1^* = \lambda^{*1/\alpha 1^*}$$

Center which has already recruited at least 1 patient

Predict n inter-arrival times of <u>phase 1</u>

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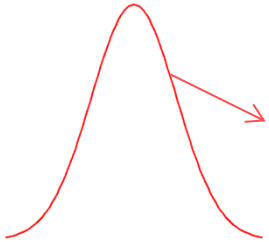

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Center which has already recruited at least 1 patient

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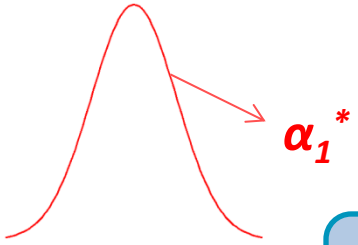


Predictive distribution Weibull(α_1^*, σ_1^*)

$$\sigma_1^* = \lambda^{*1/\alpha 1^*}$$

$$\lambda^* = \lambda_1^* \times u[center]^* \times \exp(\eta^*)$$

Center which has already recruited at least 1 patient

Predict n inter-arrival times of <u>phase 1</u>

$$t \sim Weibull(\alpha_1, \sigma_1)$$

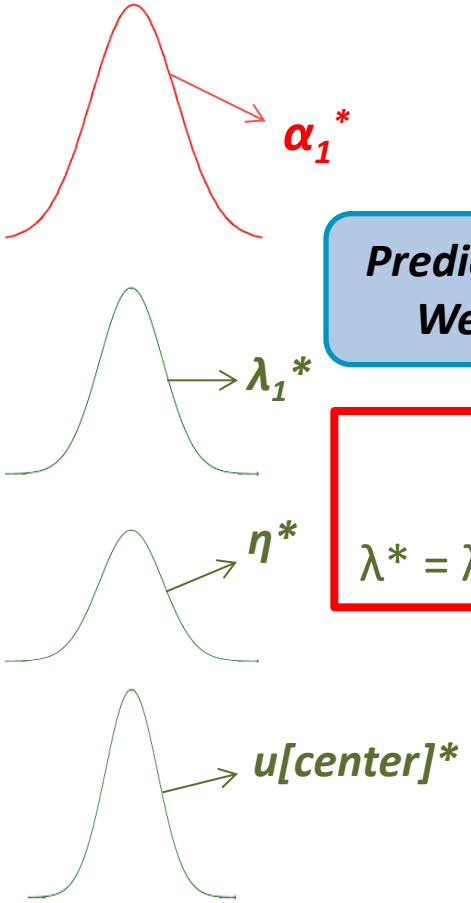
- Obtain predictive distribution

α_1 posterior distribution

λ_1 posterior distribution

η posterior distribution

u[center] posterior distribution



Predictive distribution Weibull(α_1^*, σ_1^*)

$$\sigma_1^* = \lambda^{*1/\alpha 1^*}$$

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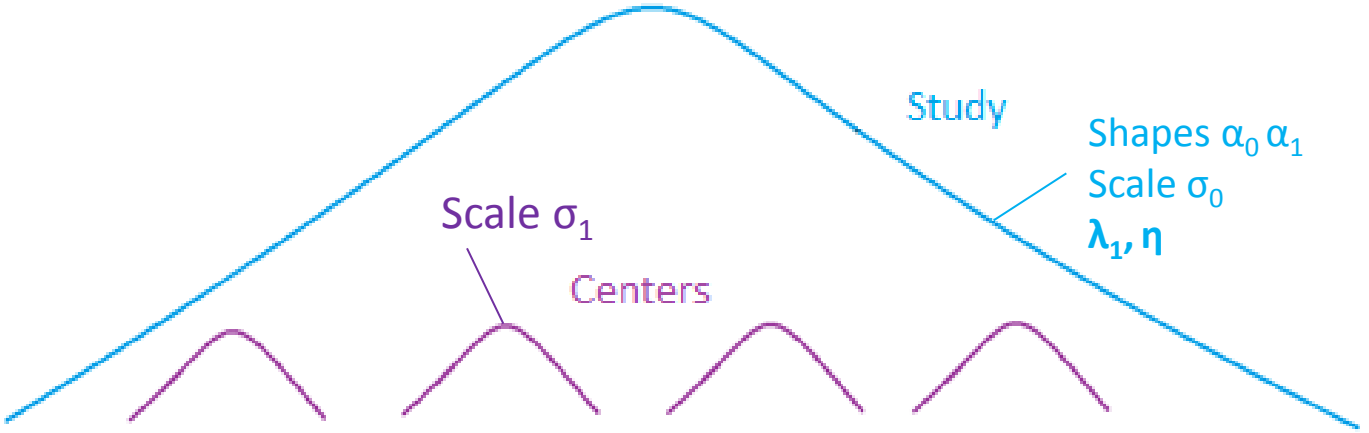
Sample n inter-arrival times

Phase 0 : $t \sim Weibull(\alpha_0, \sigma_0)$
Phase 1 : $t \sim Weibull(\alpha_1, \sigma_1)$



$$\sigma_1 = \lambda^{1/\alpha 1}$$

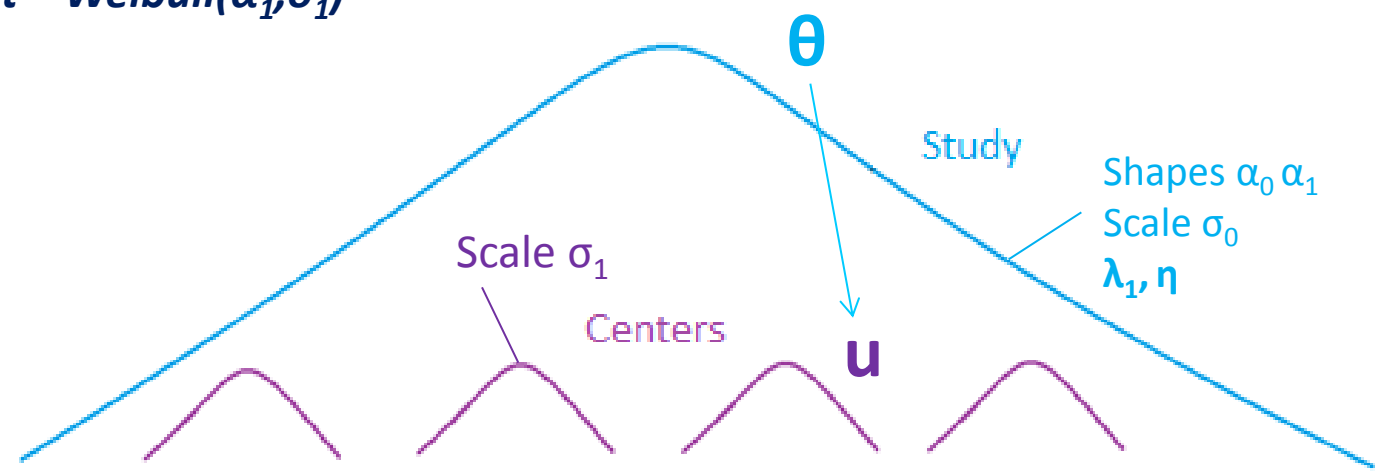
where $\lambda = \lambda_1 \times u[centre] \times \exp(\eta)$

Study recruitment rate parameter

Center corrective recruitment rate parameter

Covariate

Phase 0 : $t \sim Weibull(\alpha_0,\sigma_0)$
Phase 1 : $t \sim Weibull(\alpha_1,\sigma_1)$



$$\sigma_1 = \lambda^{1/\alpha 1}$$

where $\lambda = \lambda_1 \times \mathbf{u} \times \exp(\eta)$

$\mathbf{u} \sim \Gamma(1/\theta, 1/\theta)$

Study recruitment rate parameter

Center corrective recruitment rate parameter

Covariate

Predict n-1 inter-arrival times of phase 1

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α_1 posterior distribution

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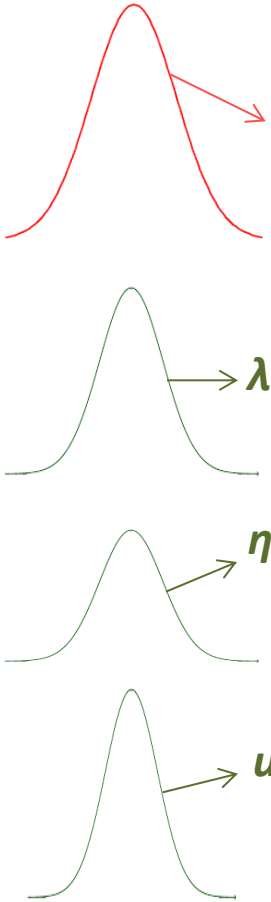

Predictive distribution
Weibull(α_1^*, σ_1^*)

$$\sigma_1^* = \lambda^{*1/\alpha 1^*}$$

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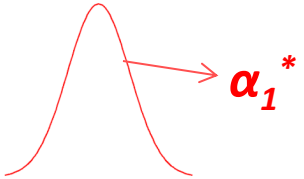
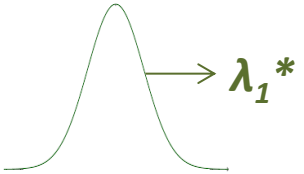
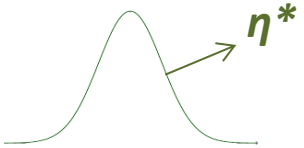
α_1 posterior distribution



λ_1 posterior distribution



η posterior distribution

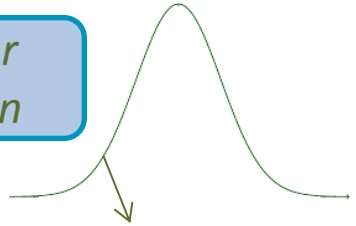


Predictive distribution Weibull(α_1^*, σ_1^*)

$$\sigma_1^* = \lambda^{*1/\alpha 1^*}$$

$$\lambda^* = \lambda_1^* \times u^* \times \exp(\eta^*)$$

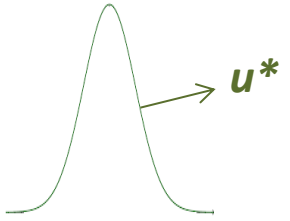
Non informative prior on θ **x** Likelihood **=** ϑ posterior distribution



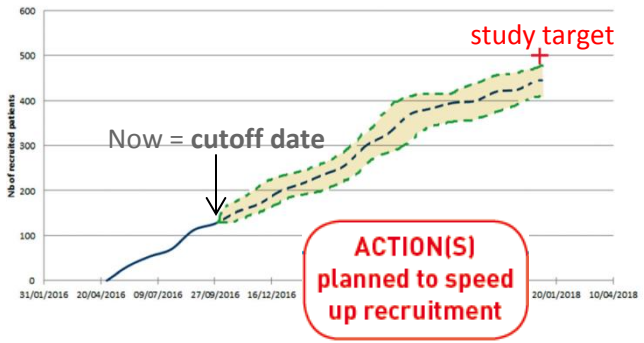
HYPERPRIOR

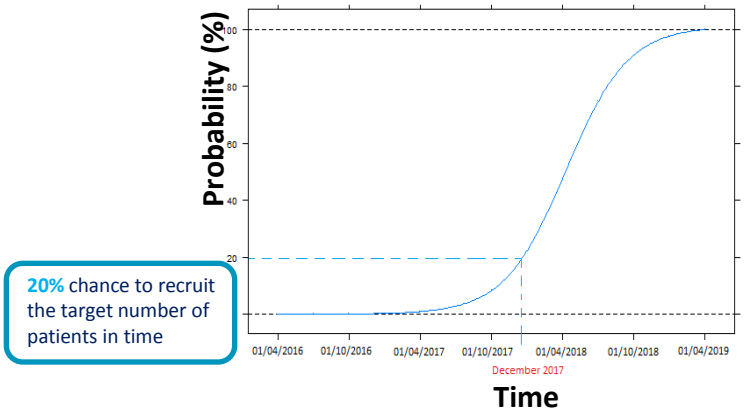
$\Gamma(1/\vartheta^*, 1/\vartheta^*)$

u predictive distribution



Simulations scenarios





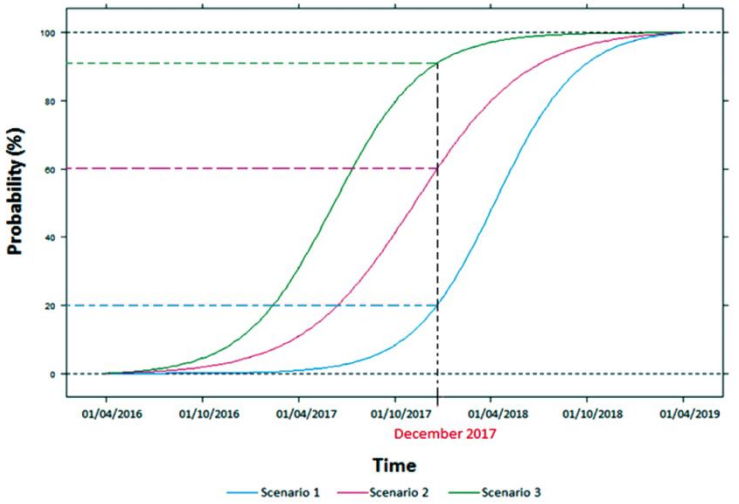
⇒ *Add some centers*

Simulate different scenarios by using the method described for Center not yet opened for different numbers of new centers

⇒ *And/or relax an inclusion criterion*

Translation in term of inter-arrival time and so of revaluation to apply to the scale of Weibull distribution

⇒ *And compare the different scenarios to choose the best*



Upcoming

- Model optimisation
- Test on an actual study
- Limits of the model
- Informative priors

THANK
YOU