A Bayesian approach for event predictions in clinical trials with time-to-event outcomes

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Summary

1. Context
2. Algorithm
3. Modelisation
4. Case Study
5. Simulation Study

1 - Context

Context

In event driven trials, statistical analyses are planned at a pre specified number of events (X)

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Main objective: predict the date of the X^{th} event with an acceptable prediction interval

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3 identified methods:

- Emilia Bagiella and Daniel F Heitjan. Predicting analysis times in randomized clinical trials. *Statistics in medicine*, 20(14):2055-2063, 2001
- Gui-shuang Ying and Daniel F Heitjan. Weibull prediction of event times in clinical trials. *Pharmaceutical Statistics: The Journal of Applied Statistics in the Pharmaceutical Industry*, 7(2): 107-120, 2008
- Bayesian approach proposed by Servier

2 - Algorithm

Algorithm

Population at the cut-off

Patient waiting for recruitment

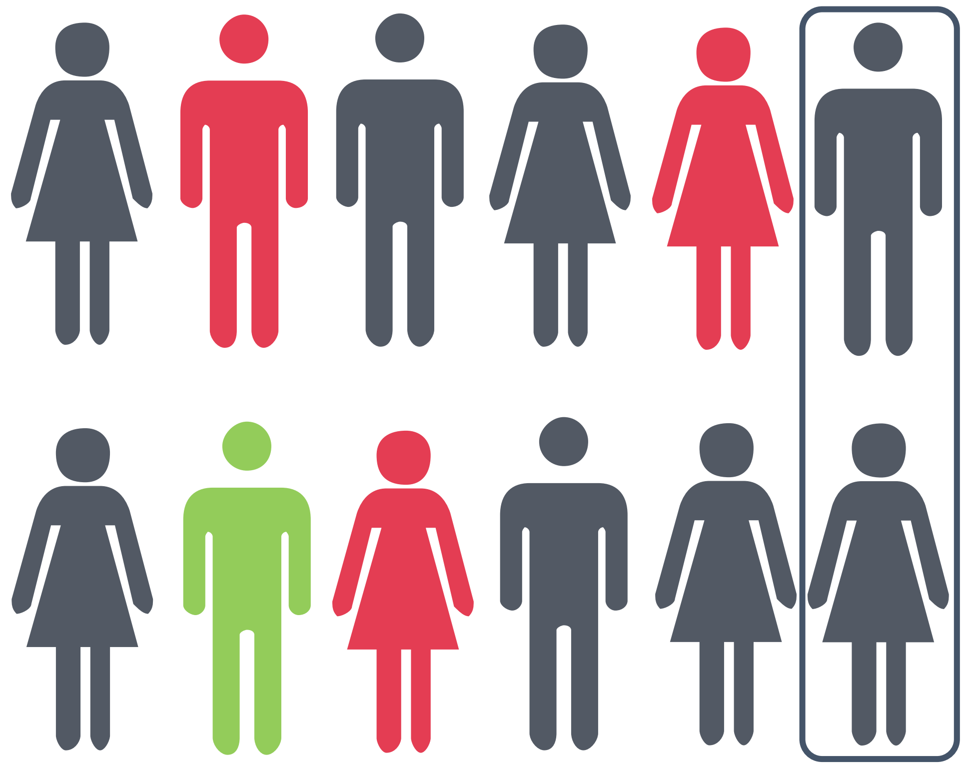
Patient still in follow-up

Patient who have experienced the event

Drop-out / Lost to follow-up patient

Algorithm

Population at the cut-off



Model 1:
Time-to-enrollment

Patient waiting for recruitment

Patient still in follow-up

Patient who have experienced the event

Drop-out / Lost to follow-up patient

Algorithm

Population at the cut-off

Model 1:
Time-to-enrollment

Model 2:
Time-to-event

Model 3:
Time-to-censorship

- Patient waiting for recruitment
- Patient still in follow-up
- Patient who have experienced the event
- Drop-out / Lost to follow-up patient

Algorithm

Population at the cut-off

Model 1:
Time-to-enrollment

Model 2:
Time-to-event

Model 3:
Time-to-censorship

X 1,000

- Patient waiting for recruitment
- Patient still in follow-up
- Patient who have experienced the event
- Drop-out / Lost to follow-up patient

3 - Modelisation

Modelisation

- MDL 1 — Time-to-enrollment
- MDL 2 — Time-to-event
- MDL 3 — Time-to-censorship

Modelisation

Time-to-enrollment

Time-to-enrollment $\sim HPP\left(\mu\right)$

Statistical model: $iat \,|\, \mu \sim Exp\left(\mu\right)$

Prior: $\mu \sim \Gamma\left(a_\mu, b_\mu\right)$

Posterior: $\mu \,|\, iat \sim \Gamma\left(N\left(t_c\right) + a_\mu, t_c + b_\mu\right)$

Notations:

iat: inter-arrival times = time elapsed between the recruitment of two consecutive patients

t_c: time of the cut-off (enrollment period observed)

$N\left(t_c\right)$: number of patients enrolled by the time of the cut-off

Modelisation

Time-to-event & Time-to-censorship

Method	Bagiella & Heitjan
Likelihood	$X_j \mid \lambda_j \sim Exp\left(\lambda_j\right)$
Prior distribution	$\lambda_j \sim \Gamma\left(A_j, B_j\right)$
Calculation of the posterior distribution	Analytical

Notations:

X_j: time-to-event (resp. time-to-censorship) in treatment arm j

Modelisation

Time-to-event & Time-to-censorship

Method	Bagiella & Heitjan	Ying & Heitjan
Likelihood	$X_j \mid \lambda_j \sim Exp\left(\lambda_j\right)$	$X_j \mid \rho_j, \lambda_j \sim Weibull\left(\rho_j, \lambda_j\right)$
Prior distribution	$\lambda_j \sim \Gamma\left(A_j, B_j\right)$	$\begin{cases} \rho_j \sim \Gamma\left(a_{\rho_j}, b_{\rho_j}\right) \\ \lambda_j \sim \Gamma\left(a_{\lambda_j}, b_{\lambda_j}\right) \end{cases}$
Calculation of the posterior distribution	Analytical	MCMC

Notations:

X_j: time-to-event (resp. time-to-censorship) in treatment arm j

Modelisation

Time-to-event & Time-to-censorship

Method	Bagiella & Heitjan	Ying & Heitjan	Servier
Likelihood	$X_j \mid \lambda_j \sim Exp\left(\lambda_j\right)$	$X_j \mid \rho_j, \lambda_j \sim Weibull\left(\rho_j, \lambda_j\right)$	$X \mid \rho, \lambda \sim Weibull\left(\rho, \lambda\right)$
Prior distribution	$\lambda_j \sim \Gamma\left(A_j, B_j\right)$	$\begin{cases} \rho_j \sim \Gamma\left(a_{\rho_j}, b_{\rho_j}\right) \\ \lambda_j \sim \Gamma\left(a_{\lambda_j}, b_{\lambda_j}\right) \end{cases}$	$\begin{cases} \rho \sim \Gamma\left(a_\rho, b_\rho\right) \\ \lambda_0 \sim \Gamma\left(a_\lambda, b_\lambda\right) \end{cases}$ $\lambda = \lambda_0 e^{\sum \beta_i X_i}$
Calculation of the posterior distribution	Analytical	MCMC	MCMC

Notations:

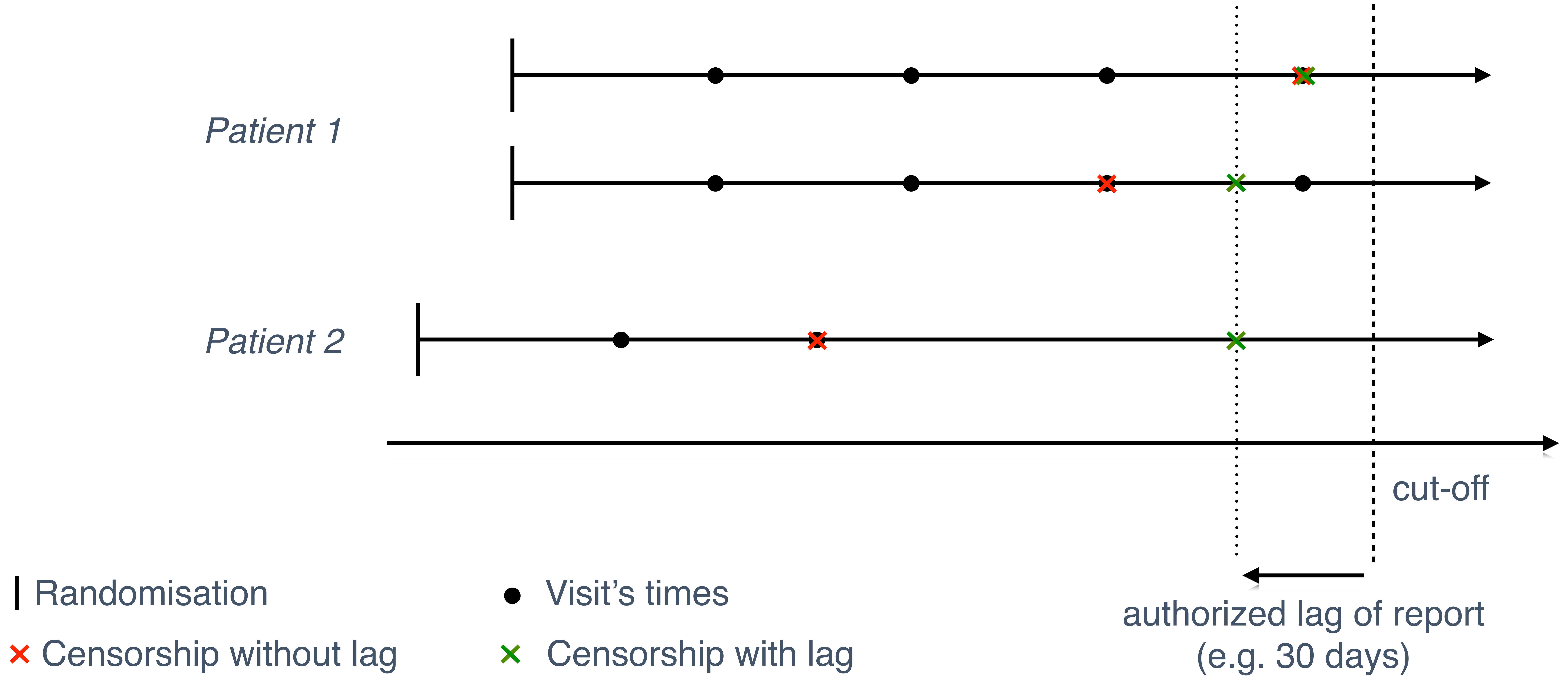
X_j: time-to-event (resp. time-to-censorship) in treatment arm j

X_i: i^{th} covariate

β_i: parameter associated to the i^{th} covariate

Modelisation

Lag



Lag: authorized time for the investigator to report the information in the database

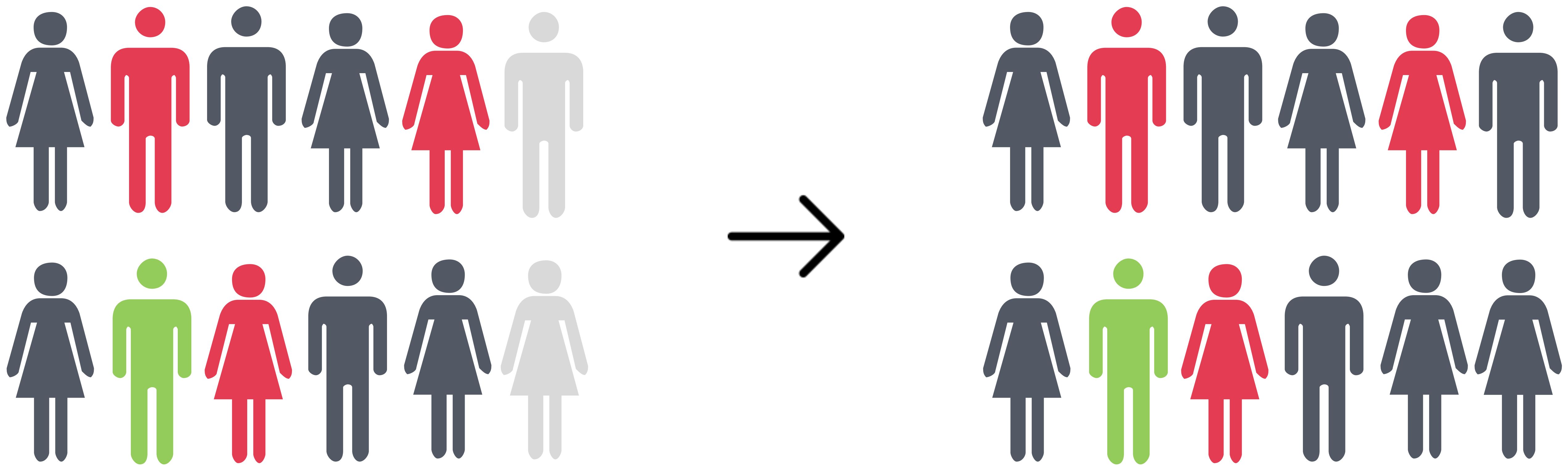
Methods’ comparison

Source	Distribution	Treatment	Lag	Covariates	Implementation
Bagiella & Heitjan	Exponential	✗			Analytical
Ying & Heitjan	Weibull	✗			MCMC[1]
Servier	Weibull		✗	✗	MCMC[1]

[1] Two implementation approaches (*Sampling Importance Resampling* and *Hamiltonian Monte Carlo*) have presented similar results (all other things being equal) on a set of simulated datasets.

Prediction

Enrollment



- Sample μ^p in parameter posterior distribution
- Generate inter arrival times to derive randomisation date for the patients to be recruited

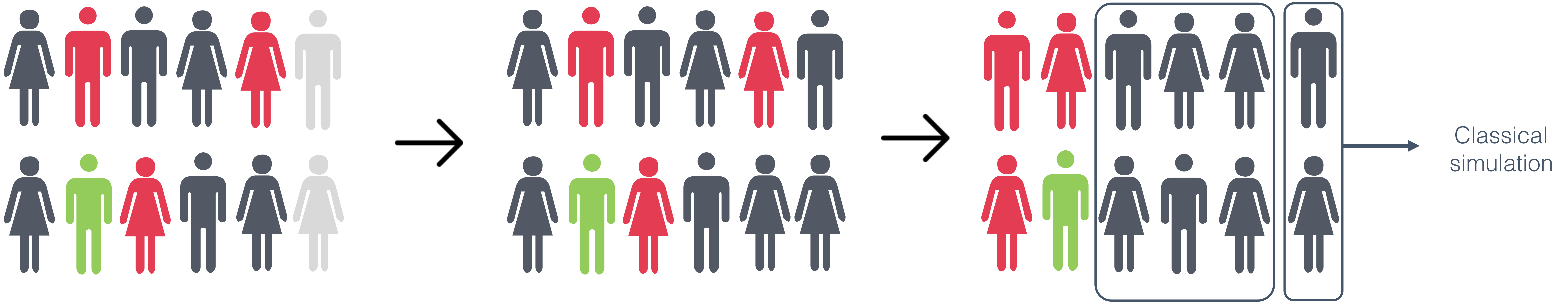
Prediction

Time-to-event & Time-to-censorship

Method	Sample	Predictive
Bagiella & Heitjan	λ_j^p	$X_j \sim Exp\left(\lambda_j^p\right)$
Ying & Heitjan	ρ_j^p, λ_j^p	$X_j \sim Weibull\left(\rho_j^p, \lambda_j^p\right)$
Servier	$\rho^p, \lambda_0^p, \beta_i^p$	$X \sim Weibull\left(\rho^p, \lambda_0^p e^{\Sigma \beta_i^p X_i}\right)$

Prediction

Time-to-event & Time-to-censorship



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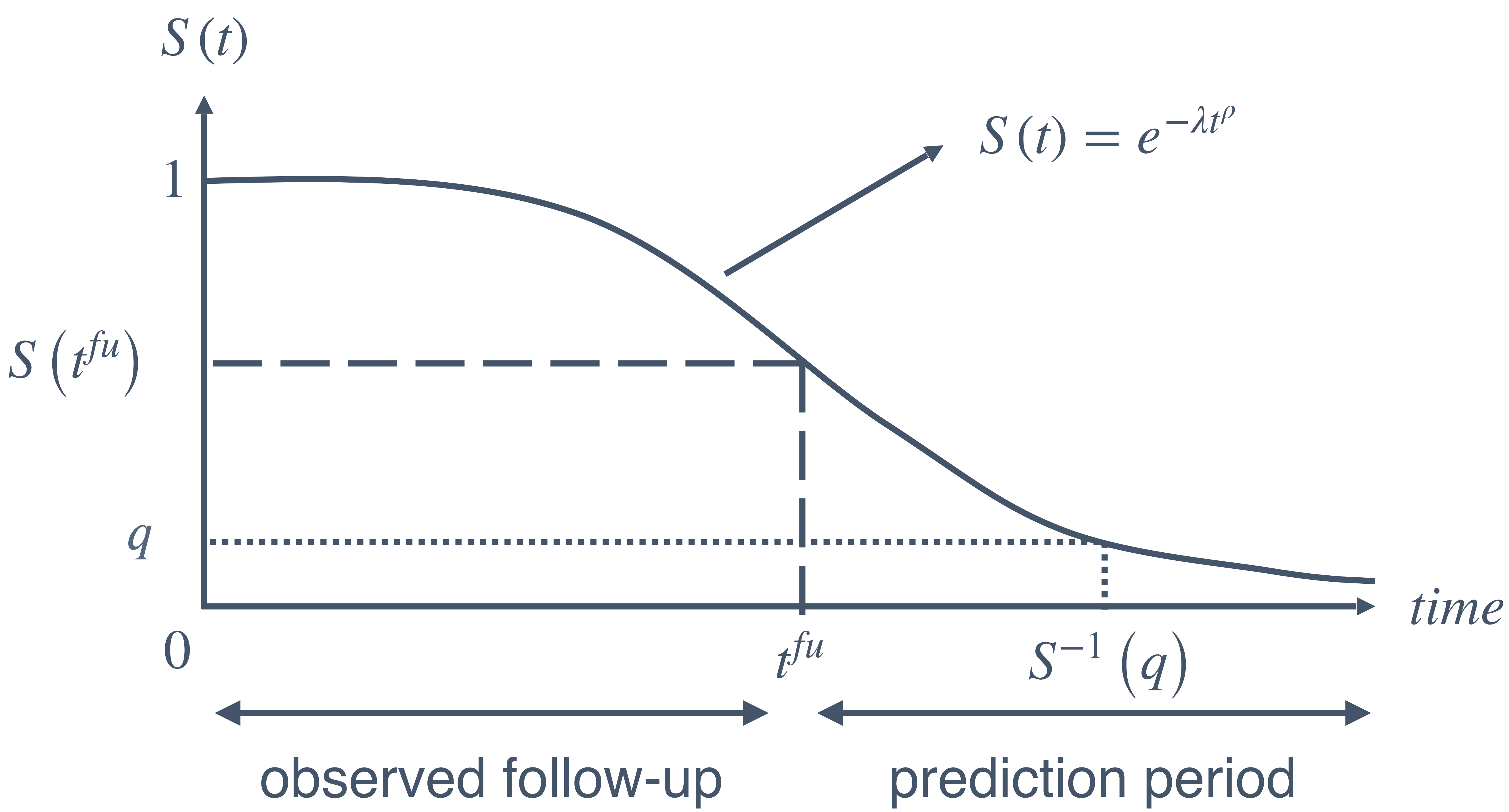
Prediction

Inverse Transform Sampling



- Sample $q \sim U\left[0, S\left(t^{fu}\right)\right]$
- Calculates $S^{-1}\left(q\right) > t^{fu}$

4 - Case Study

Case Study

Phase II

Phase II in oncology

Recruitment: 153 patients (FVFP: 29/04/2016 – 12 months enrollment)

Target: 100 events (completion target event : 15/01/2018)

Primary outcome: Progression Free Survival

Design hypotheses: $median_{ctrl} = 9.1$ months, $HR = 0.77$

Drop-out rate: 1 % per year

Case Study

Phase II

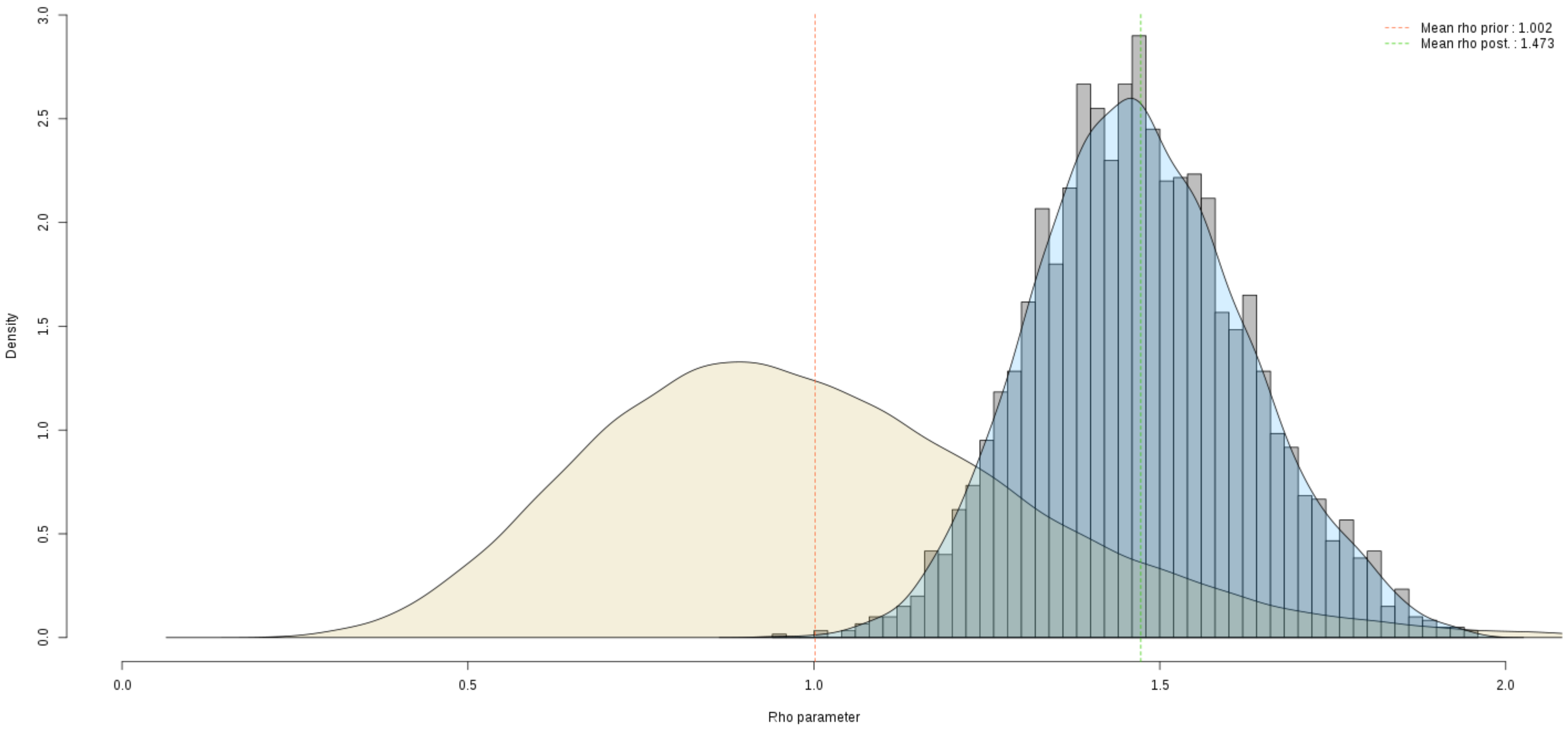
Design hypothesis: exponential distribution supposed for events so $h(t) = \lambda \rho t^{\rho-1} = \lambda$

Proposition: $\rho \sim \Gamma(1,1)$ $\quad \mathbb{E}(\rho) = 1$ $\quad \mathbb{V}(\rho) = 1$

Gamma distribution
(scale notation)

$$f(x) = \frac{x^{\alpha-1}}{\beta^{\alpha}\Gamma(\alpha)} e^{-\frac{x}{\beta}}$$

$\mathbb{E}(X) = \alpha\beta$ et $\mathbb{V}(X) = \alpha\beta^2$



Case Study

Phase II

Hypothesis: $\lambda \sim \Gamma(C, D)$ represents the speed of events' occurence

$$median = \left(\frac{log\,(2)}{\lambda}\right)^{\frac{1}{\rho}} = \frac{log\,(2)}{\lambda} \quad \Rightarrow \quad \mathbb{E}\,(\lambda) = CD = \frac{log\,(2)}{median}$$

$$\rho = 1$$

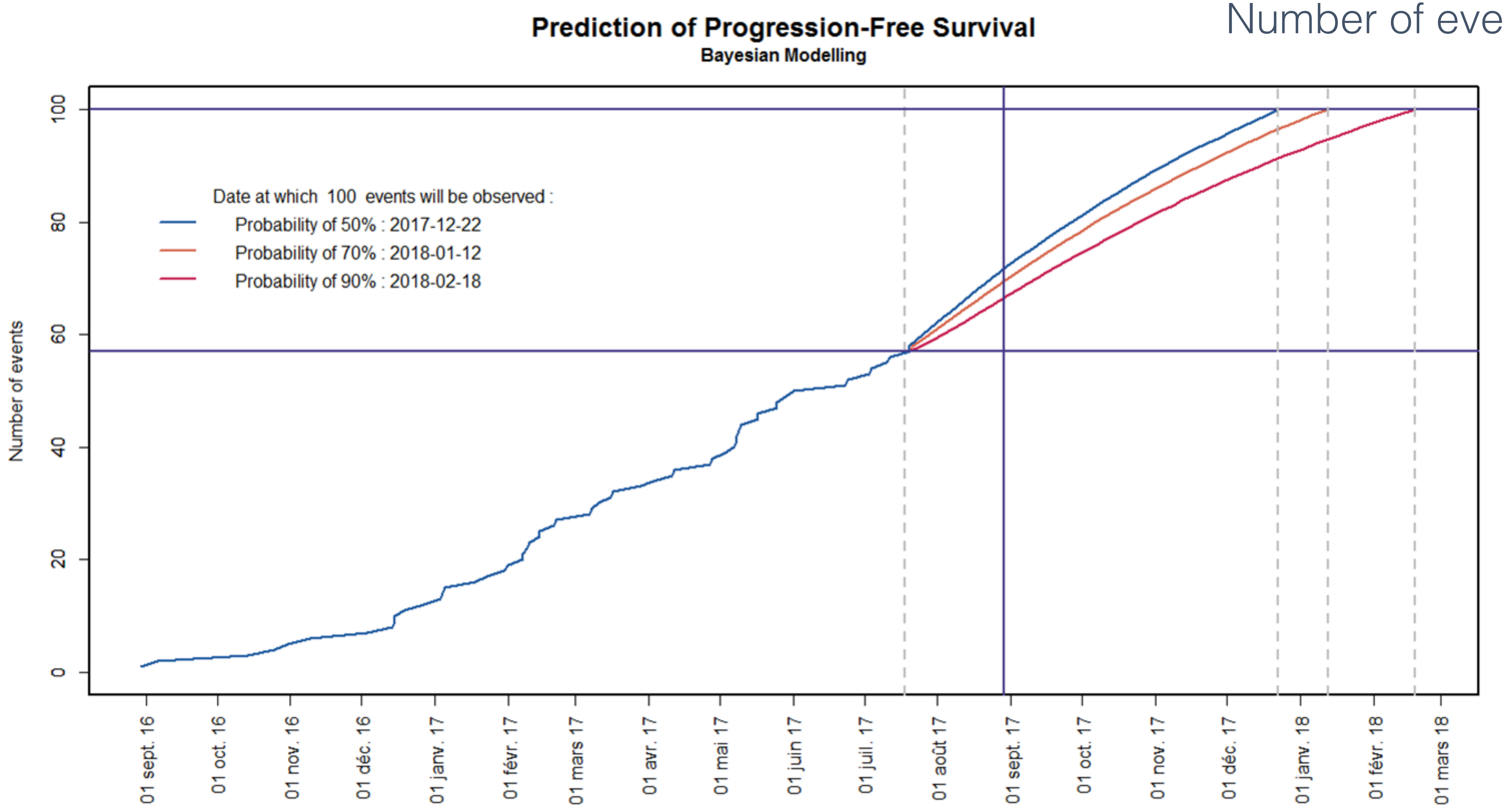
$$\lambda \sim \Gamma\left(1, \frac{log\,(2)}{median}\right) \qquad \mathbb{E}\,(\lambda) = \frac{log\,(2)}{median} \qquad \mathbb{V}(\lambda) = \left(\frac{log\,(2)}{median}\right)^2$$

Case Study

Phase II

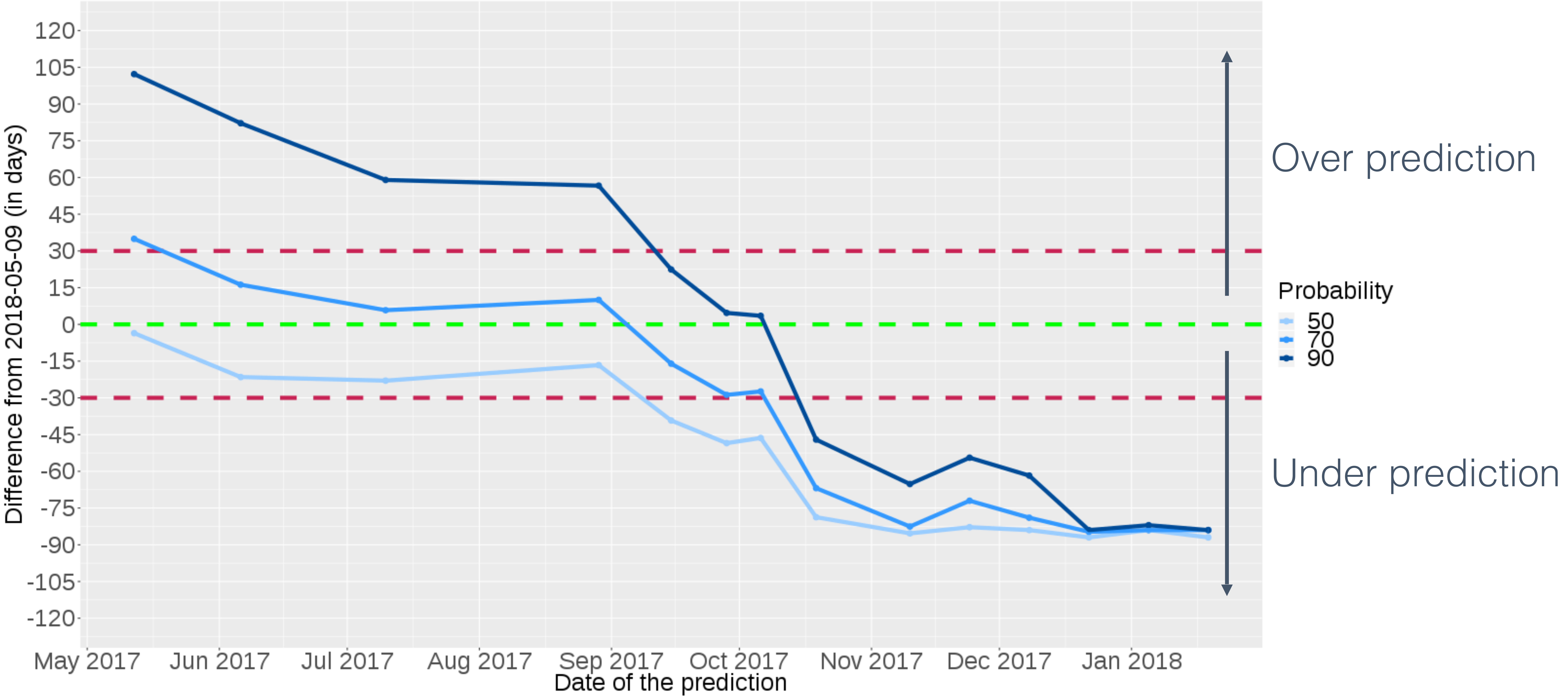
Cut-off: 29/08/2017

Number of events: 57



Case Study

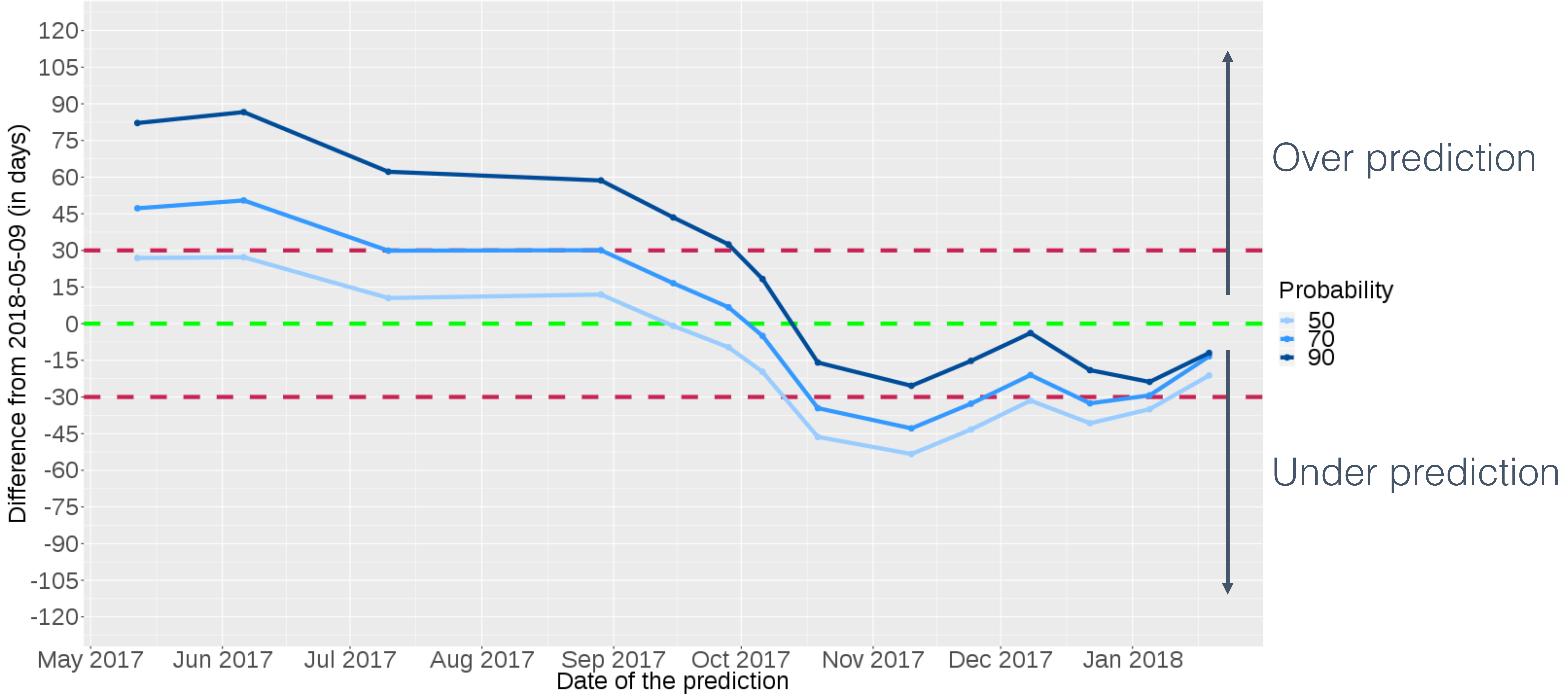
Phase II



Bagiella & Heitjan Approach

Case Study

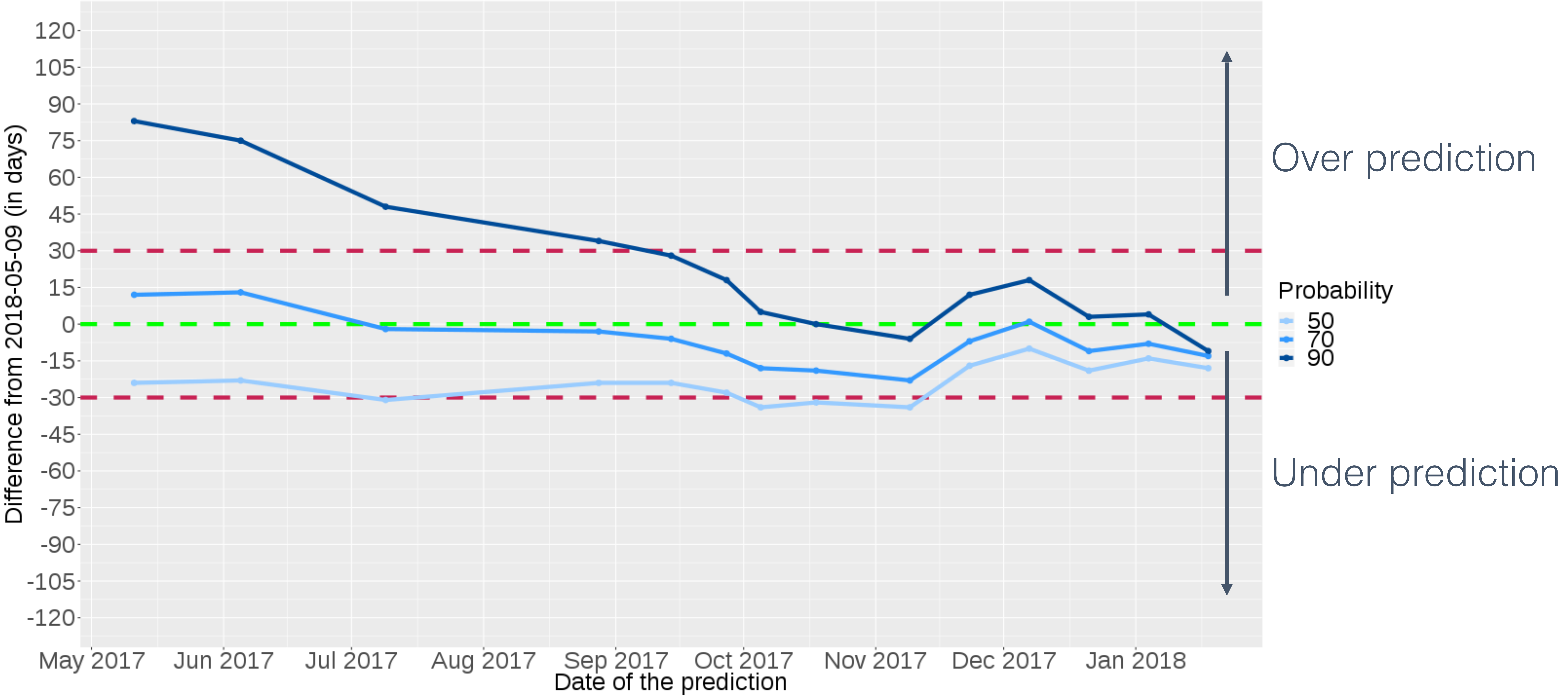
Phase II



Ying & Heitjan Approach

Case Study

Phase II



Servier Approach

5 - Simulation Study

Results & Comparison

Distribution: exponential / Weibull

Unblinded

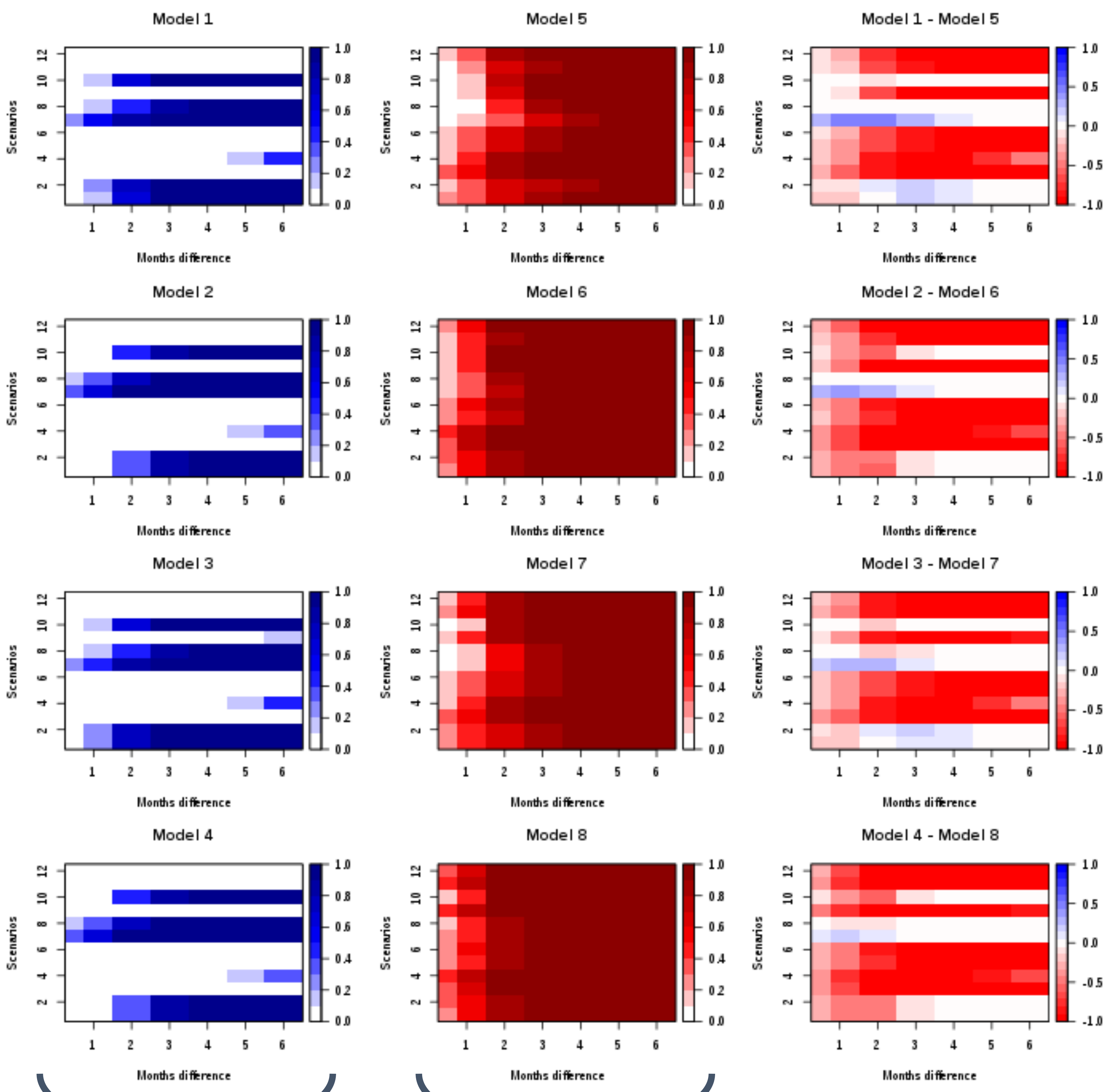
Lag

No Lag

Blinded

Lag

No Lag



Exponential

Weibull

- Cut-off: 75% of the time of the simulated study
- Probability threshold: 0.5

Results & Comparison

Unblinded / Blinded

No interest in separating data by treatment arm in 2 different models

More parameters to estimate in Weibull models → pooling treatment arms may improve the estimations

Results & Comparison

Lag

With or without lag, good predictions with Weibull models

	Early predictions (cut-off 50%)	Mid-predictions (cut-off 75%)	Late predictions (cut-off 90%)
Exponential models	mixed	no difference	no difference
Weibull models	more precise without lag	mixed	no difference

Counter intuitive results: more investigations are needed

6 - Conclusion

Conclusion

Recommendations

Weibull

Best results when there are enough events in database

Blinded

Pooling data increases the number of events in the model

Lag?

Important on case studies but inefficient in simulations

Thanks for your attention

Weibull distribution

Density: $f(t) = \lambda \rho t^{\rho-1} e^{-\lambda t^{\rho}} = h(t) S(t)$

Survival: $S(t) = e^{-\lambda t^{\rho}} = 1 - F(t)$

Hazard rate: $h(t) = \lambda \rho t^{\rho-1}$

Median: $median = \left(\frac{log(2)}{\lambda} \right)^{\frac{1}{\rho}}$

Simulation Study

Scenarios

Distribution	Phase	Treatment effect
Exponential	Phase II	HR = 0.75
Exponential	Phase II	HR = 0.9
Exponential	Phase III PFS	HR = 0.65
Exponential	Phase III PFS	HR = 0.9
Exponential	Phase III OS	HR = 0.65
Exponential	Phase III OS	HR = 0.9
Weibull	Phase II	HR = 0.75
Weibull	Phase II	HR = 0.9
Weibull	Phase III PFS	HR = 0.65
Weibull	Phase III PFS	HR = 0.9
Weibull	Phase III OS	HR = 0.65
Weibull	Phase III OS	HR = 0.9

Phase II:

- 200 patients
- 12 months accrual
- 150 events targeted

Phase III:

- 1,000 patients
- 24 months accrual
- 600 events targeted

Simulation Study

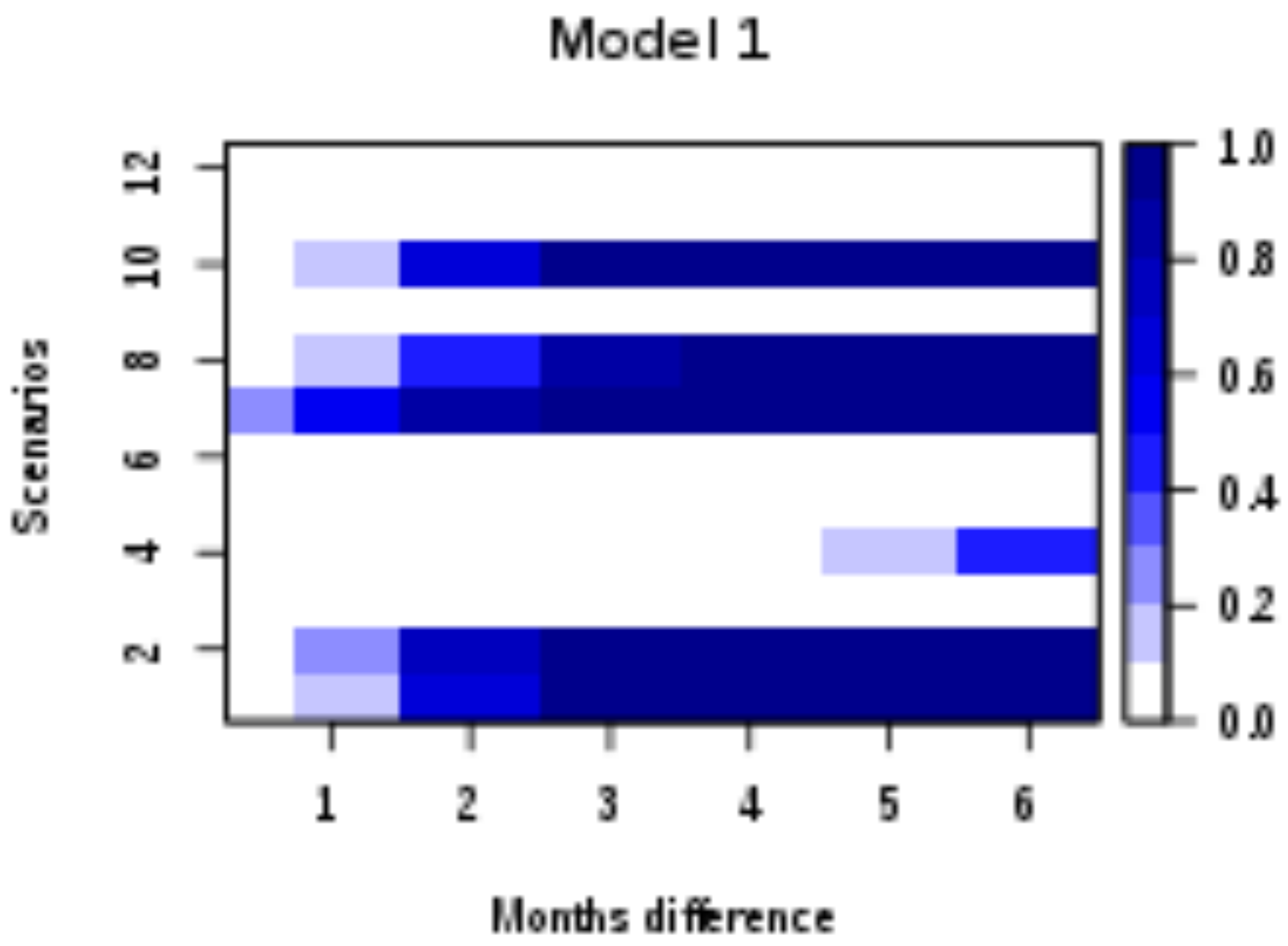
Models

Distribution	Treatment	Lag	Implementation	
Exponential	Unblinded	✗	Analytical	
Exponential	Unblinded		Analytical	Bagiella & Heitjan
Exponential	Blinded	✗	Analytical	
Exponential	Blinded		Analytical	
Weibull	Unblinded	✗	Hamiltonian Monte Carlo	
Weibull	Unblinded		Hamiltonian Monte Carlo	Ying & Heitjan
Weibull	Blinded	✗	Hamiltonian Monte Carlo	Servier Approach
Weibull	Blinded		Hamiltonian Monte Carlo	

Simulation Study

Results

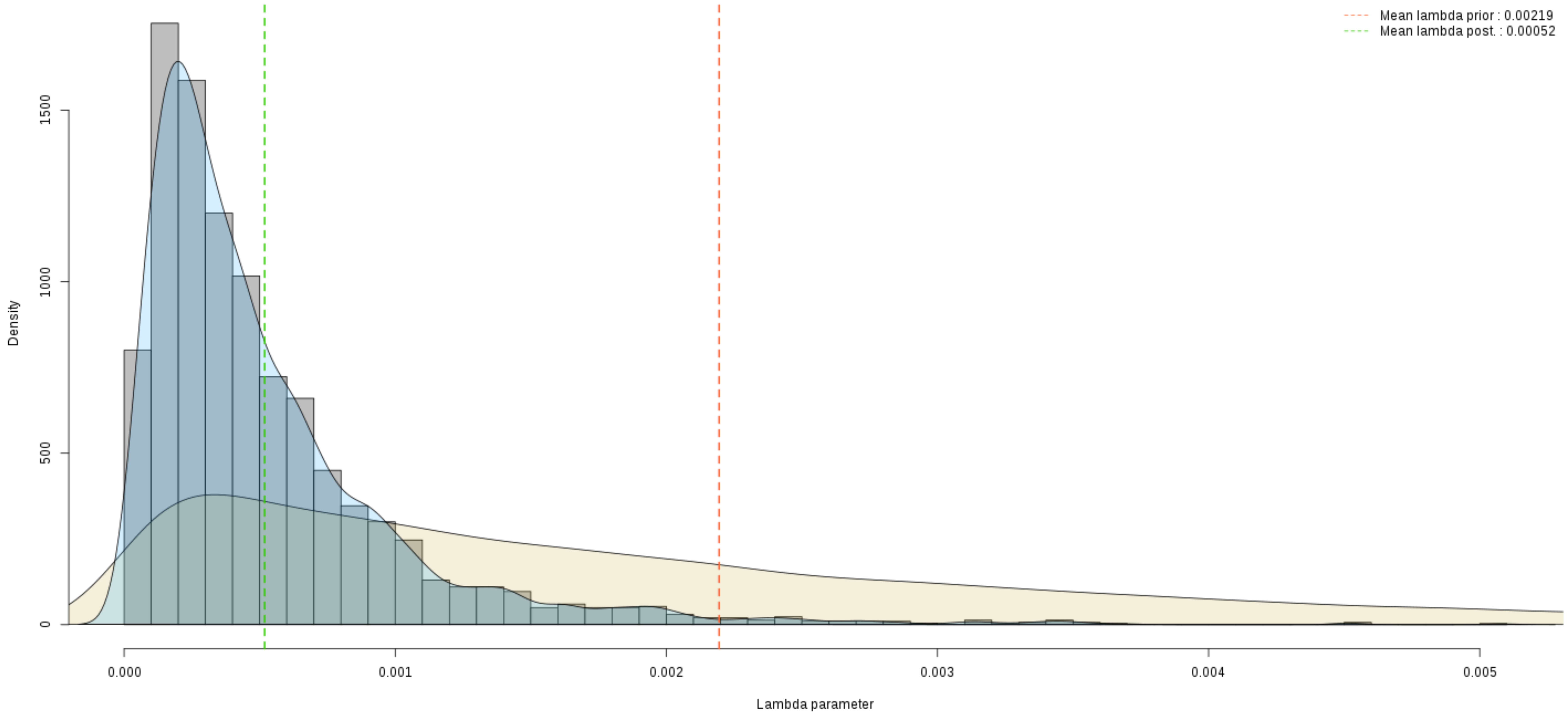
- Repeat each simulation 1,000 times
- Evaluation criterion: difference in month between the target date & the predicted date of the X^{th} event



- Heatmap produced with different cut-off & different probability thresholds

Case Studies

Phase II



Case Study

Parameters calcul

Example:

$$median = \frac{median_{trt} + median_{ctrl}}{2} = \frac{\frac{median_{ctrl}}{HR} + median_{ctrl}}{2} = 315\ days$$

$$\mathbb{E}(\lambda) = \frac{log(2)}{median} = 0.0022$$

Scale notation: $\lambda \sim \Gamma(1{,}0.0022)$

Rate notation: $\lambda \sim \Gamma\left(1, \frac{1}{0.0022}\right) = \Gamma(1{,}455)$

Case Study

Phase III

Phase III in oncology

Recruitment: 320 patients (FVFP: 20/04/2011)

Target: 216 events (completion target event : 09/05/2018)

Primary outcome: Progression Free Survival

Design hypotheses: $median_{ctrl} = 2.8 \text{ months}, \quad HR = 0.65$

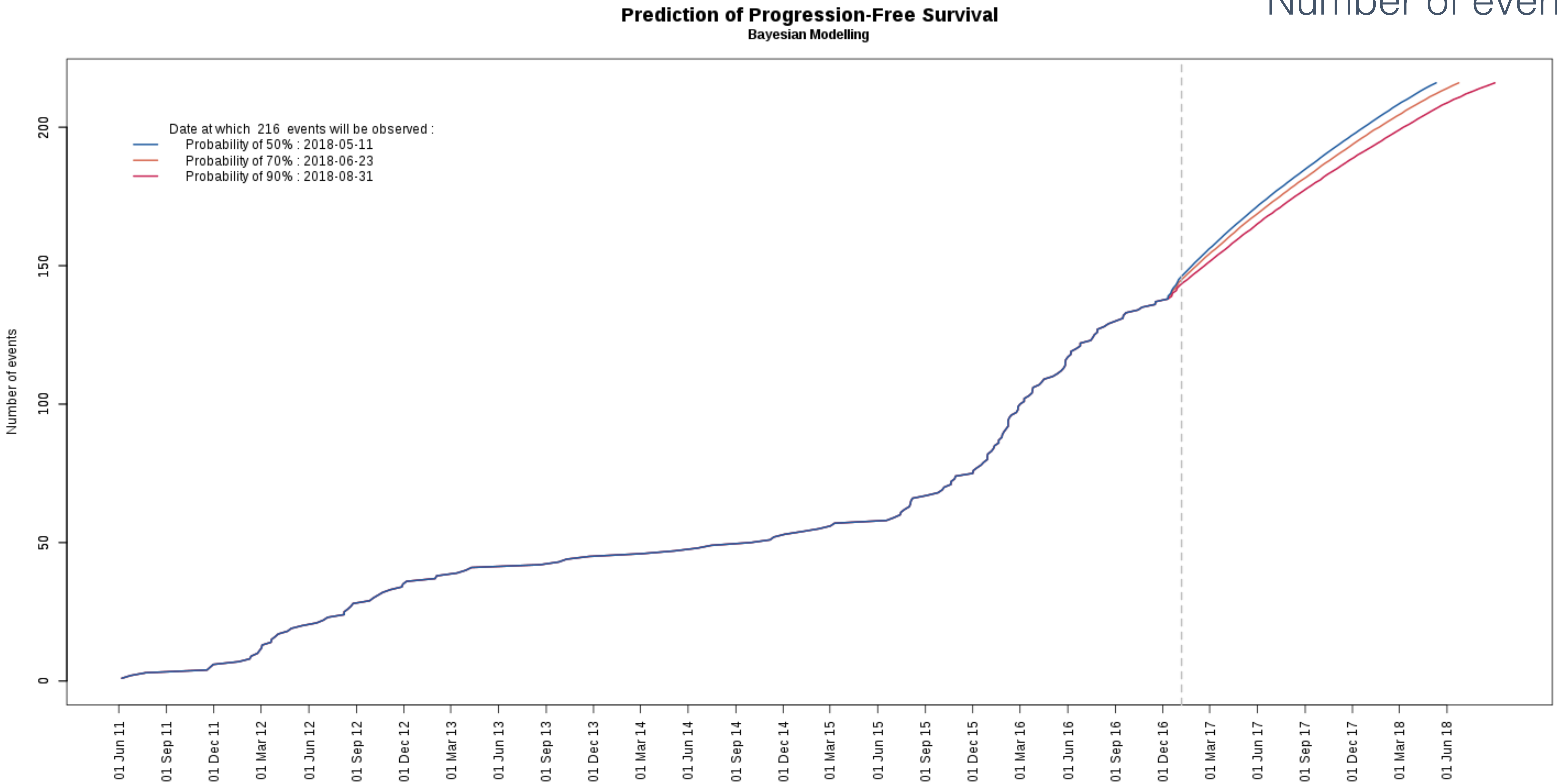
Drop-out rate:

Case Study

Phase III

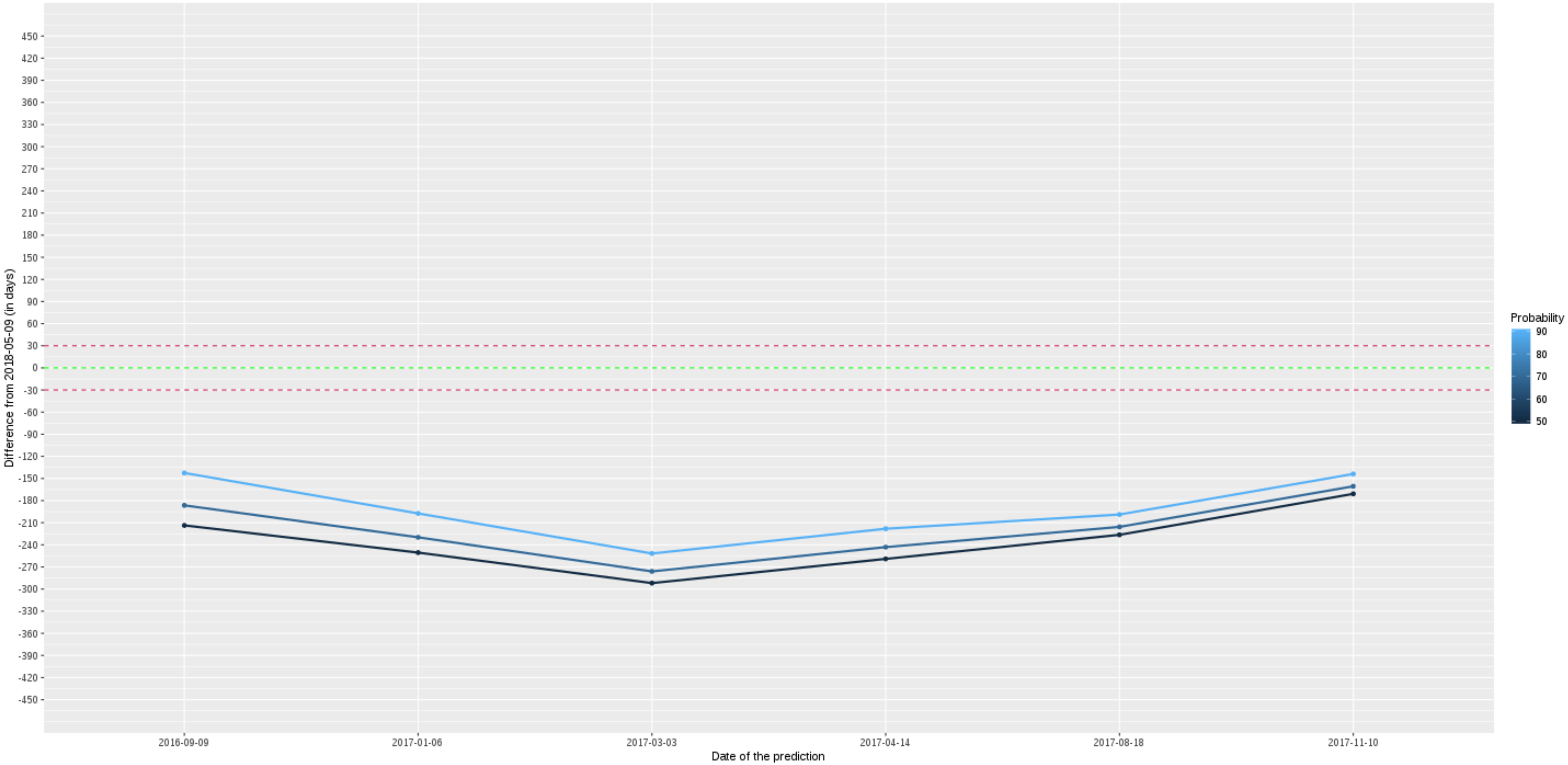
Cut-off: 09/09/2016

Number of events: 128



Case Study

Phase III – Ying & Heitjan Algorithm



Case Study

Phase III – Servier Approach