Develop a predictive statistical model for stock management in clinical trials

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Outline

I. Context

II. Model

   i. General principles

   ii. The recruitment process

   iii. The visit process

   iv. The withdrawal process

   v. Predictions

III. Case study

   i. A finished study

   ii. Results

IV. Discussion

Context

1 TU = 1 packaged drug

Study budget for TU supplies
(Pilot Ph II Onco)

32%

Deterministic forecasting tools

Spreadsheets

Probabilistic forecasting tool for TU demand over time

Average waste in TUs for a clinical study (Ph II – III)
(Benchmark)

70%

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Model

General principles

3 successive processes:

I. The **recruitment** process

II. The **visit** process

III. The **withdrawal** process

The Bayesian methodology takes into account parameter uncertainty in estimating the predictive distribution

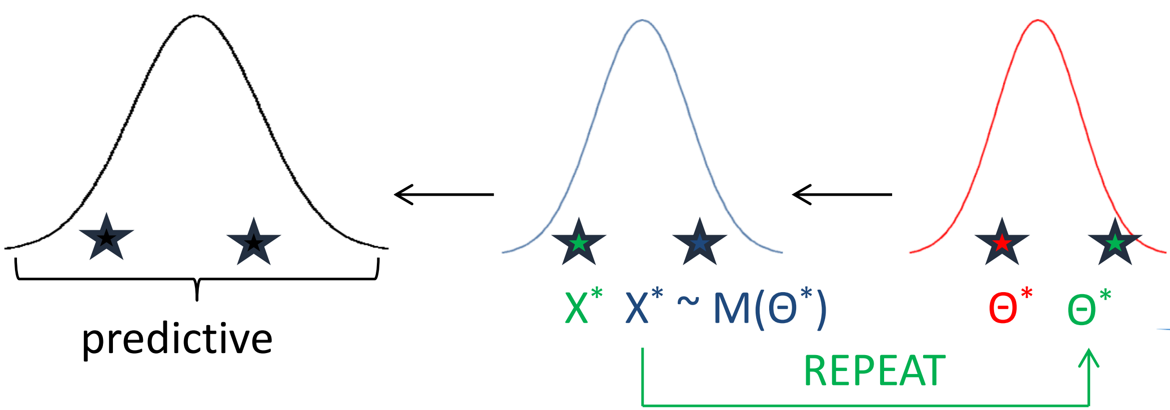
In a **Bayesian** framework:

→ **MCMC** estimation of the posterior

Total data = Observed data + Available data

posterior likelihood prior

Allows **prediction**:



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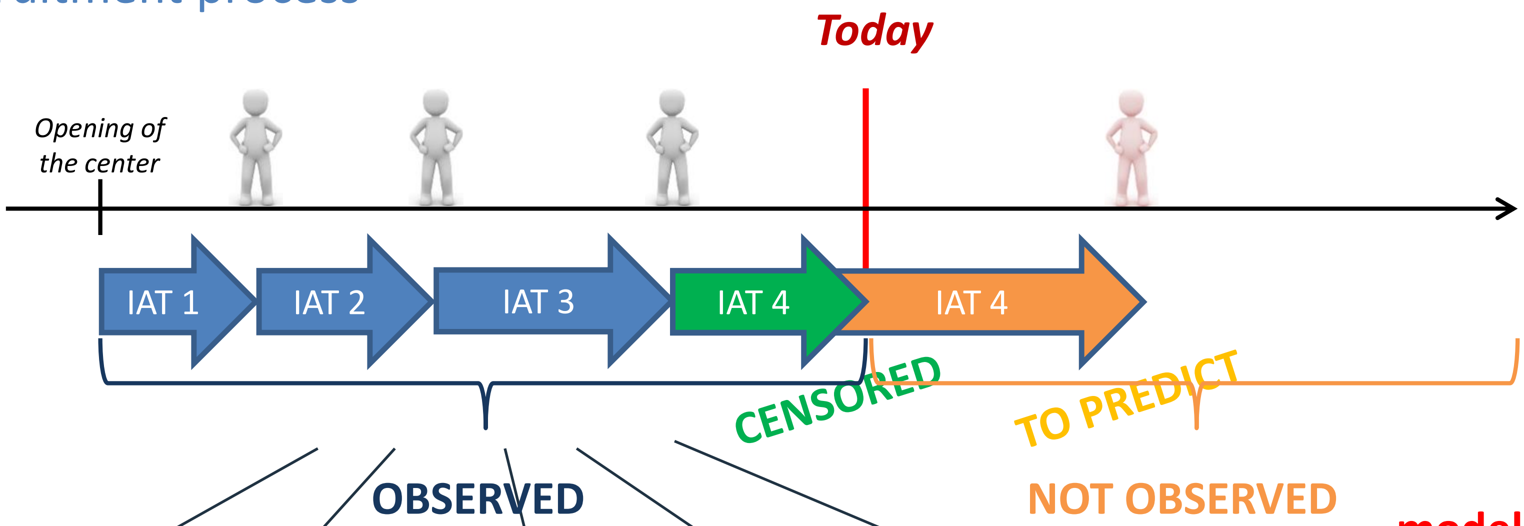
Model

The recruitment process



To predict new IAT:

exponential	Weibull	Gompertz	log-normal	log-logistic	…
constant accrual rate	"default choice"	"cure fraction"	yet another	yet another	

→ **Inverse probability method (IPM)**

model selection or model averaging

The recruitment rate may vary between two centres

frailty model

$$h(t) = h_0(t)\, u$$
$$U \sim \mathrm{Gam}(\theta)$$

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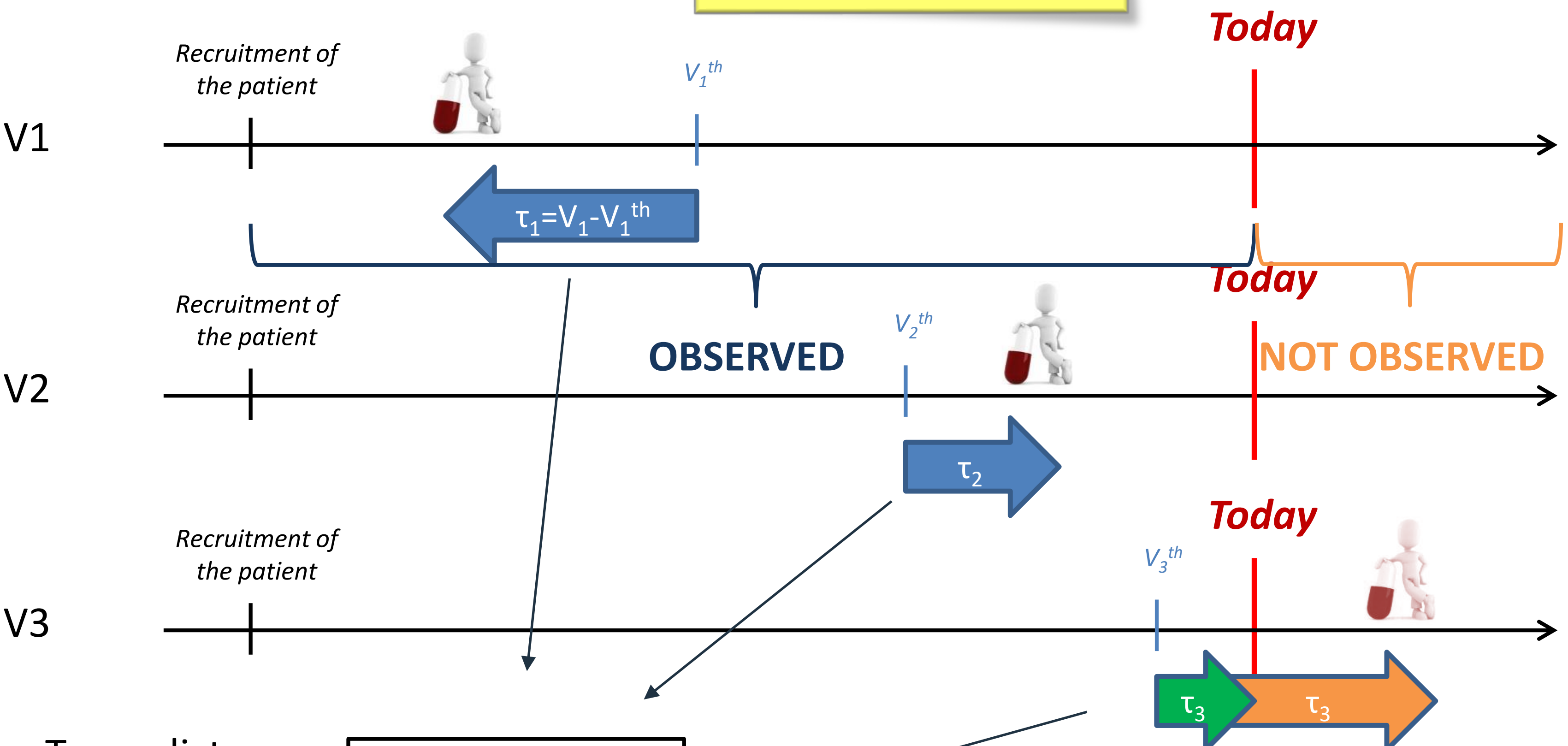
Model

The visit process

Visits are in time windows centered around the theoretical date

For a given patient:



To predict new τ: normal model $N(\mu,\sigma)$

→ **Truncated normal distribution**

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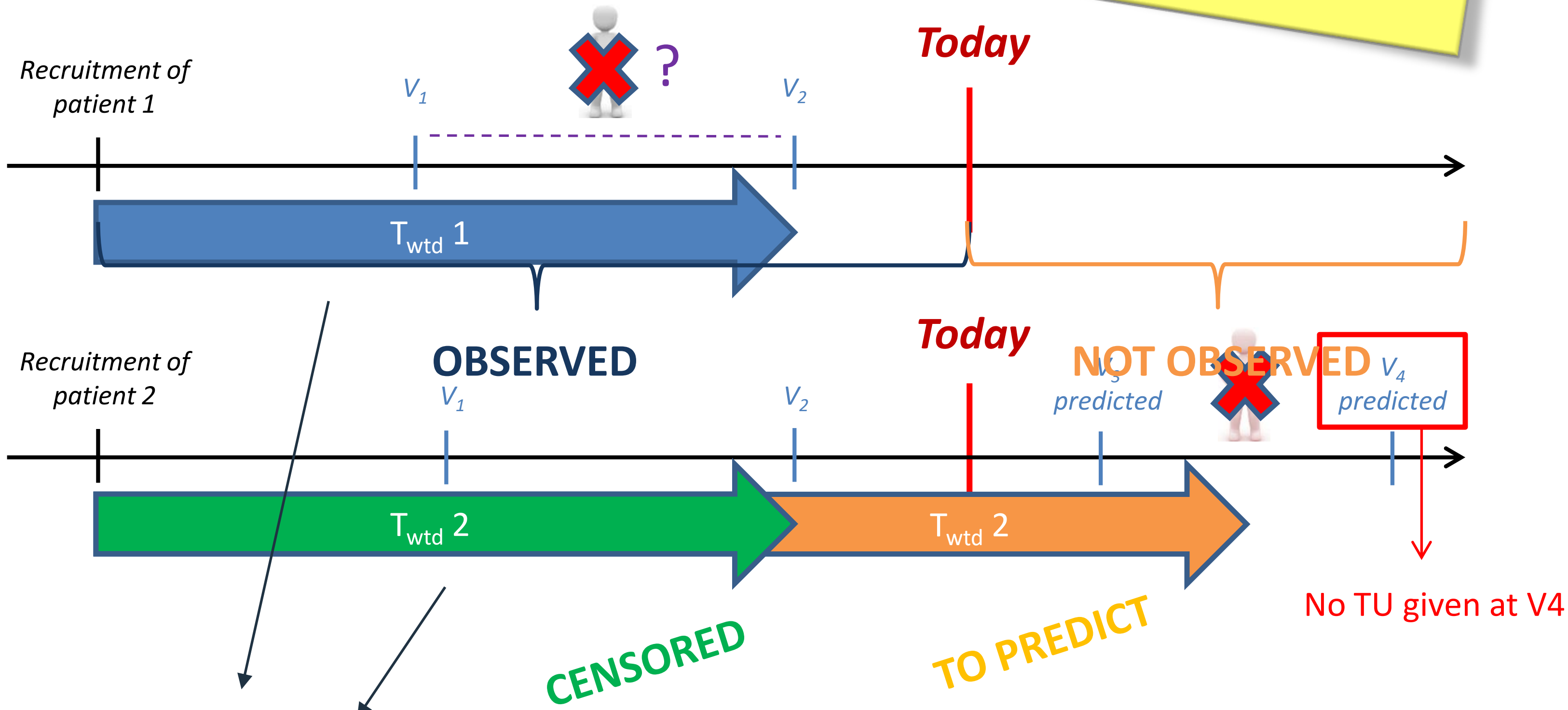
Model

The withdrawal process

Beware of interval censoring: withdrawal date usually reported at the following visit date



To predict new T_{wtd}:

exponential model $E(\lambda)$

→ **Inverse probability method (IPM)**

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Predictions

Layout

1) <u>Predict **recruitment dates**</u>

→ For all participating centres

→ Sort all the dates of pooled centres

⚠ If the centre is not yet open, predict an **opening date** first

2) <u>Predict **visit dates**</u>

→ For observed and predicted patients

3) <u>Predict **withdrawal dates**</u>

→ For observed and predicted patients

We repeat the procedure 1000 times to get predictive intervals

→ **« Patient TU demand over time »**

→ Corresponds to a blind number of TU

Predictions

The IRS algorithm

An IRS algorithm is study specific

« Patient TU demand over time »

IRS algorithm

- Manage patient randomization
- Monitor TU delivery to the centers

« Centre TU need over time »

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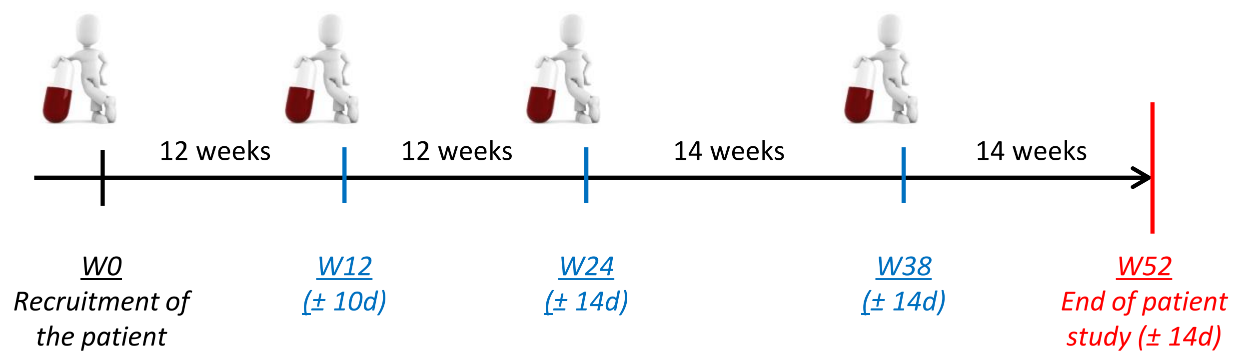
Case study

A finished study

A finished study is chosen so that we can compare our predictions with the reality

- A 52-week international, multi-centre, randomized, double-blind, placebo controlled phase II study
- 500 patients, 4 treatment arms, 88 centres, 11 countries
- TU = 450 €, TU budget = 2 millions €, overage = 60%
- IRS managed trial (stratification by region)



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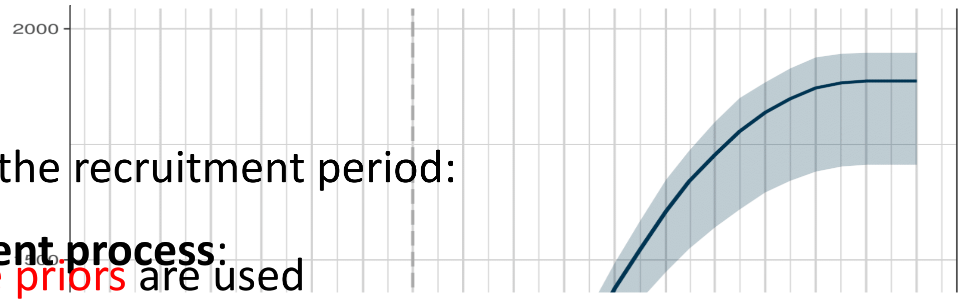
Case study

Use of ongoing data



Goodness-of-fit:

Cutoff at mid-point of the recruitment period:

- For the **recruitment process**:

⟶ Non-informative priors are used

⟶ Bayesian Model Averaging

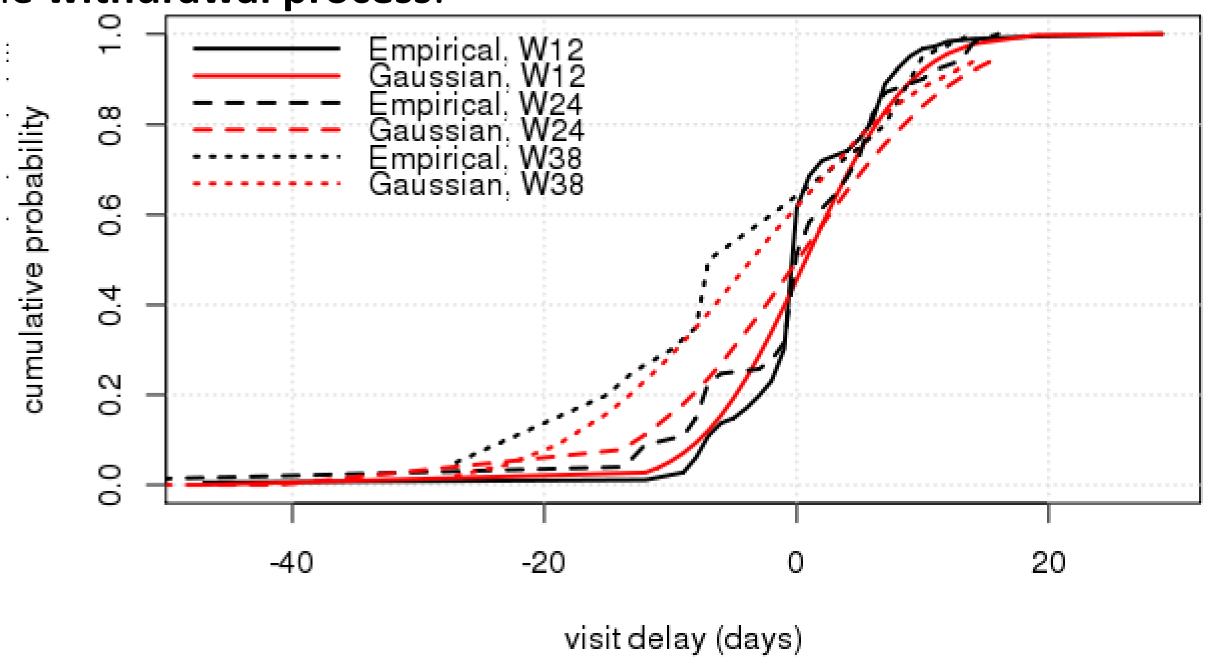
- For the **visit process**:

Nb of TU de

- For the **withdrawal process**:

an

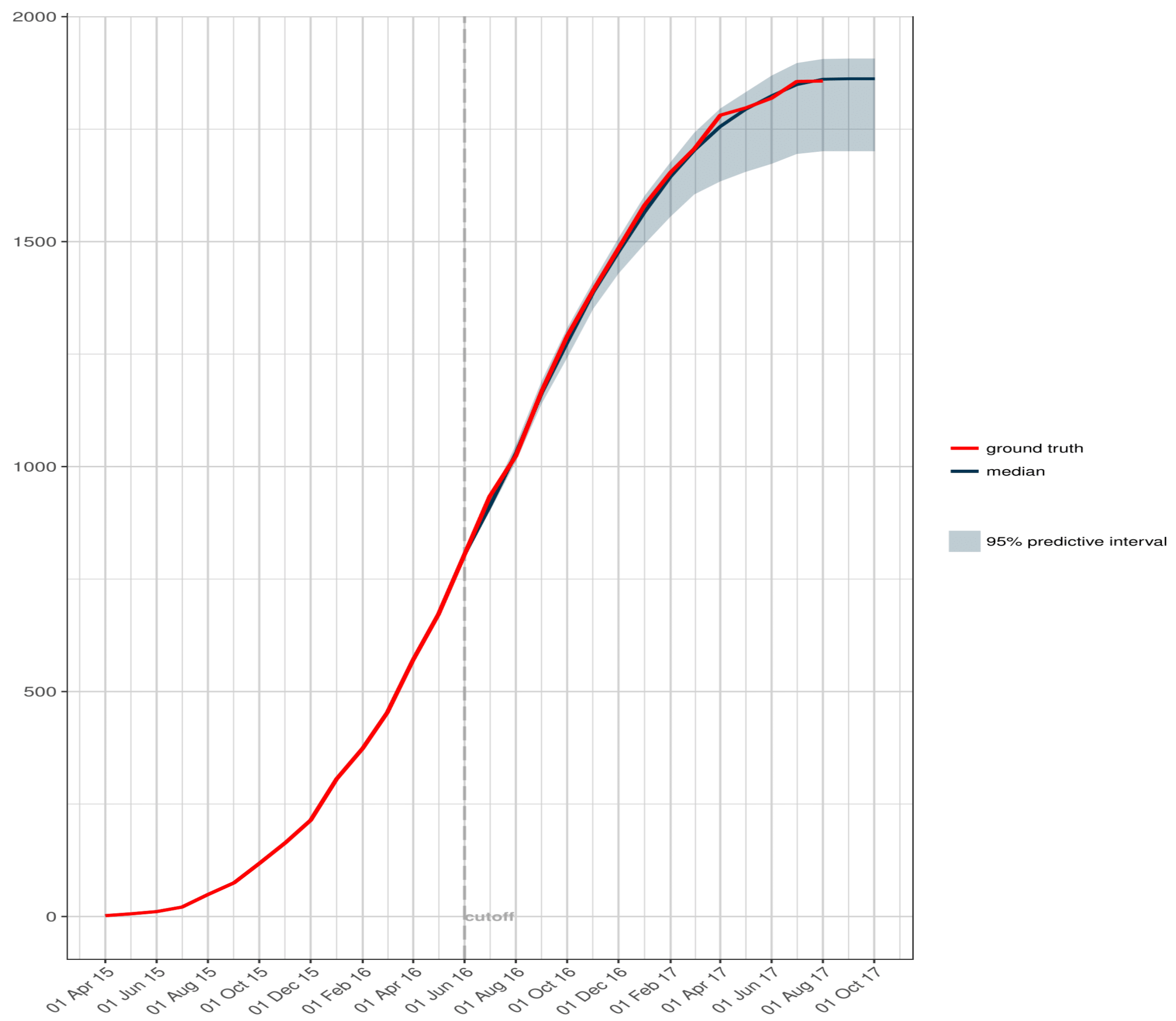
predictive interval



Case study

Use of ongoing data

Nb of TU demand



Cutoff midpoint +2 months

Case study

At the beginning of the study

No observed data, so we use feasibility data

Feasibility data are preliminary targets given by the participating countries, often with an added margin

- For the **recruitment process**:

exponential model
E(λ)

⟶ **Inverse gamma distributions** are constructed as priors for λ and θ

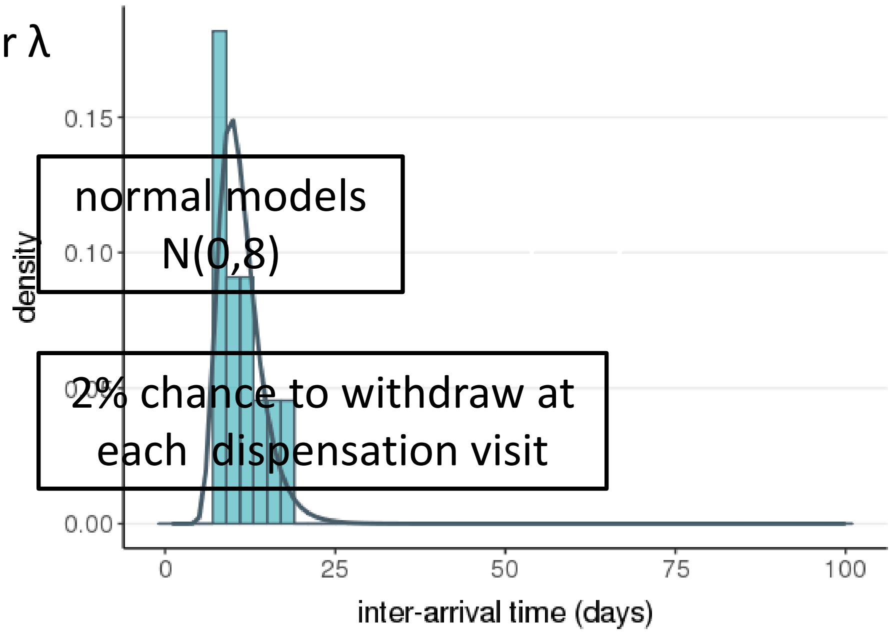
- For the **visit process**:

Goodness-of-fit:

normal models
N(0,8)

- For the **withdrawal process**:

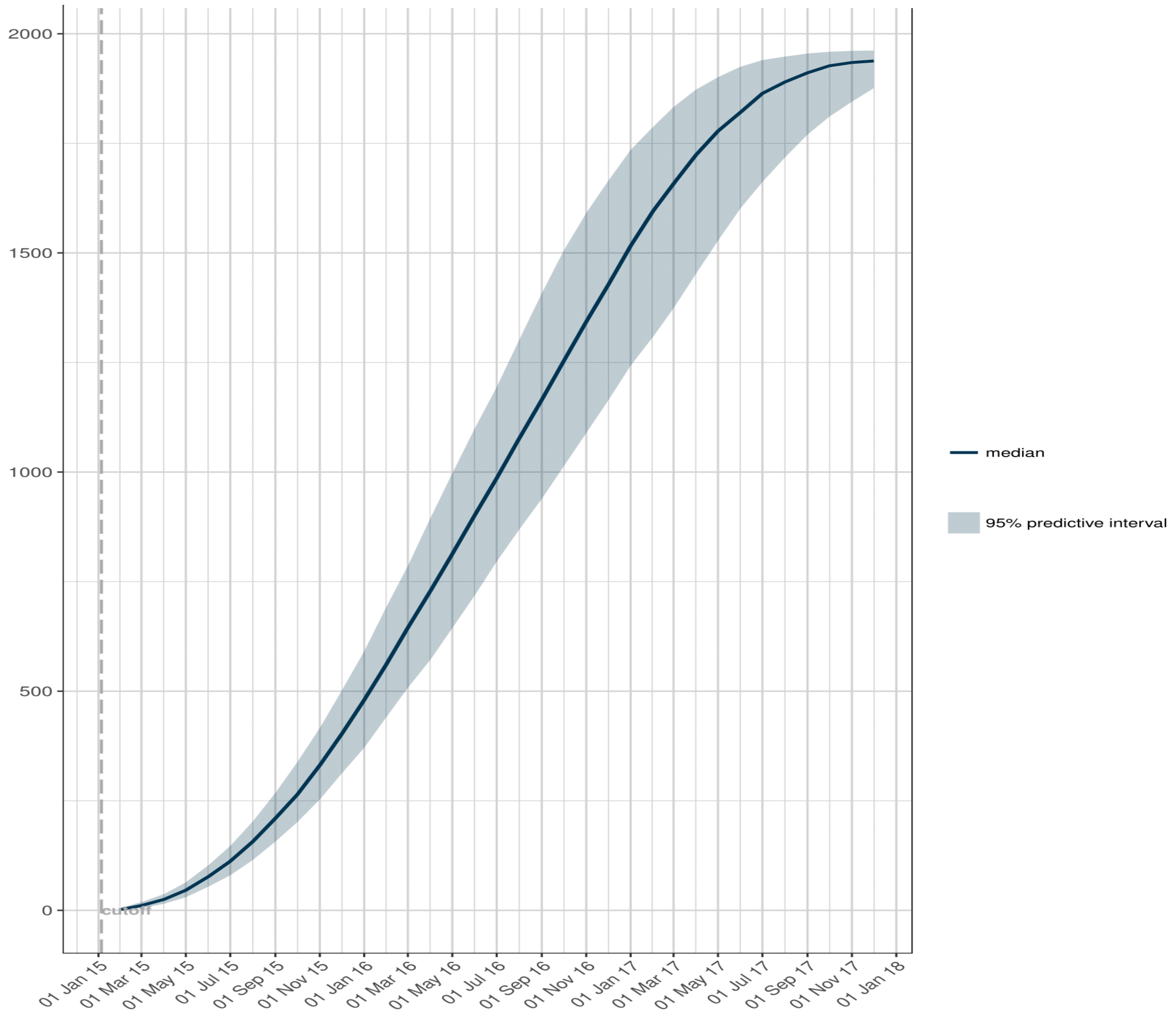
2% chance to withdraw at each dispensation visit



Case study

At the beginning of the study

Nb of TU demand



<u>Cutoff beginning</u>

Case study

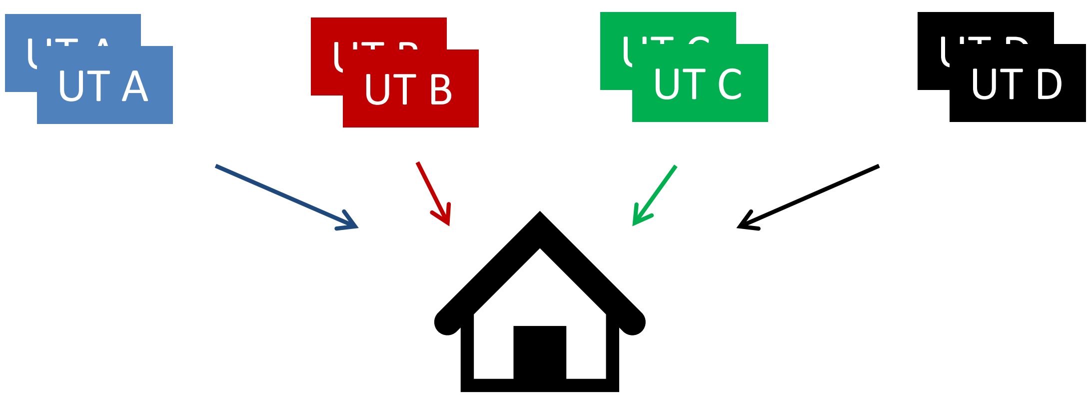
Modelling of the IRS algorithm

→ For each of the 1000 patient TU demand predictions, simulate randomization

Each day the system checks if there is sufficient stock for the next 21 days

IRS algorithm:

At the opening of the centre:



→ If resupply necessary, the system sends TU based on the demand for the next 60 days

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Discussion

- Regarding the use:
  - Decision support tool that gives data-driven predictions
  - Launching of the pilot phase
  - Enable TU order optimization
- Regarding the methodology:
  - Possible prior-data conflict
  - Model selection and model averaging shall be refined

THANK YOU

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Back-up

The Bayesian Framework

Bayes theorem:

$$\boxed{\underbrace{p(\theta|\text{data})}_{\text{posterior}} \propto \underbrace{p(\text{data}|\theta)}_{\text{likelihood}} \times \underbrace{p(\theta)}_{\text{prior}}}$$

Prediction:

$$\boxed{\underbrace{p(x^*|\text{data})}_{\text{predictive}} = \int \underbrace{p(x^*|\theta)}_{\text{model}} \times \underbrace{p(\theta|\text{data})}_{\text{posterior}} d\theta}$$

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Bayesian model averaging

$M = \{M_1, \ldots, M_k\}$ (finite) set of potential models

$$BIC_i \overset{M_i}{=} -2\log\hat{L} + f \times \log N \overset{M_i}{\approx} -2\log p(\mathcal{D})$$

$\hat{L}$ estimated owing to Laplace transformation of the frailty function

Bayes theorem: $$\boxed{p(M_i|\mathcal{D}) = \frac{p(\mathcal{D}|M_i) \times p(M_i)}{\sum_{j=1}^{k} p(\mathcal{D}|M_j)p(M_j)}}$$

$$p(\mathcal{D}|M_i) \approx \exp\left(-BIC_i/2\right) \longrightarrow \boxed{p(M_i|\mathcal{D}) \approx \frac{exp(-BIC_i/2)}{\sum_{j=1}^{k} exp(-BIC_j/2)}}$$

The inverse probability method

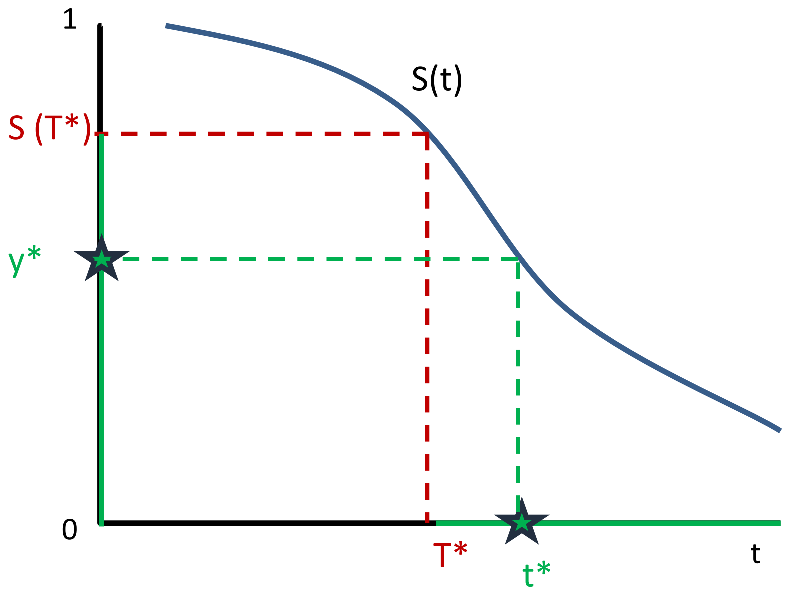
$$S(t) = e^{-A(t)}$$
$$A(t) = \int_0^t \alpha(x)dx$$

To generate t* > T*:

1) Draw y* from Y ~ U(0,S(T*))

2) Make the transformation

   $t^* = A^{-1}(-\log(y^*))$



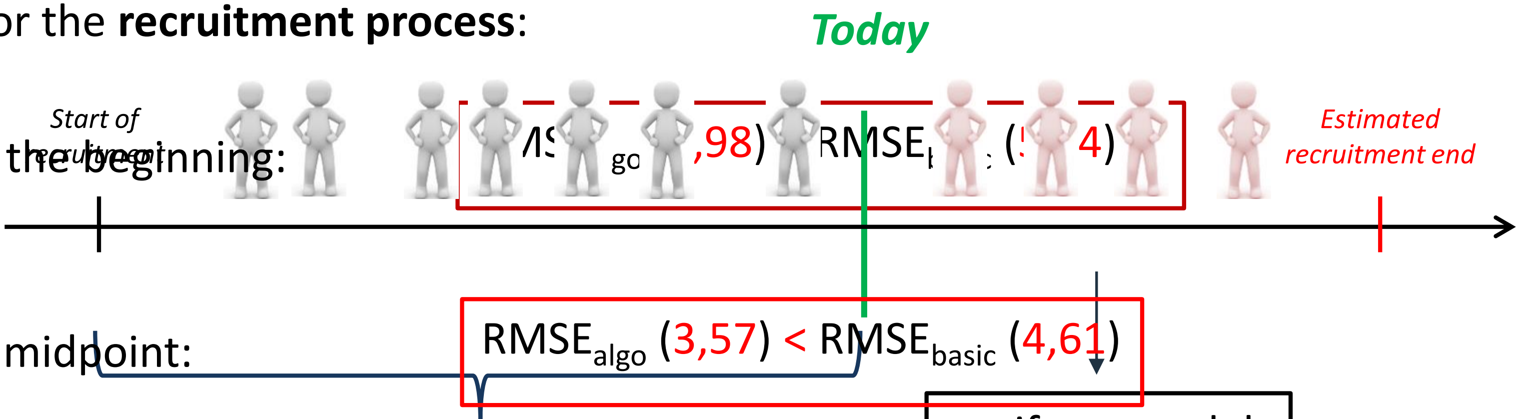
Case study

RMSE validation

$$RMSE = \sqrt{\sum_m \frac{(x_m^* - x_m^{reality})^2}{N_{months}}}$$

→ **RMSE validation** against a basic algorithm:

- For the **recruitment process**:



At the beginning: $RMSE_{algo}$ (…,98) < $RMSE_{basic}$ (…4)

At midpoint: $RMSE_{algo}$ (3,57) < $RMSE_{basic}$ (4,61)

uniform model

At midpoint +2 months: $RMSE_{algo}$ (3,07) < $RMSE_{basic}$ (4,09)

- For the **visit process**:

normal model
N(0,8)

- For the **withdrawal process**:

2% chance to withdraw
at each visit

Case study

Optimization of TU orders

1) Consider Tu order scenarios based on estimations of the Centre TU needs over time:

Scenario 1:	Scenario 2:	Scenario 3:	Scenario 4:
Orders done at each TU delivery	Orders done monthly	Orders done quarterly	Orders done biannually

2) Under the following assumptions:

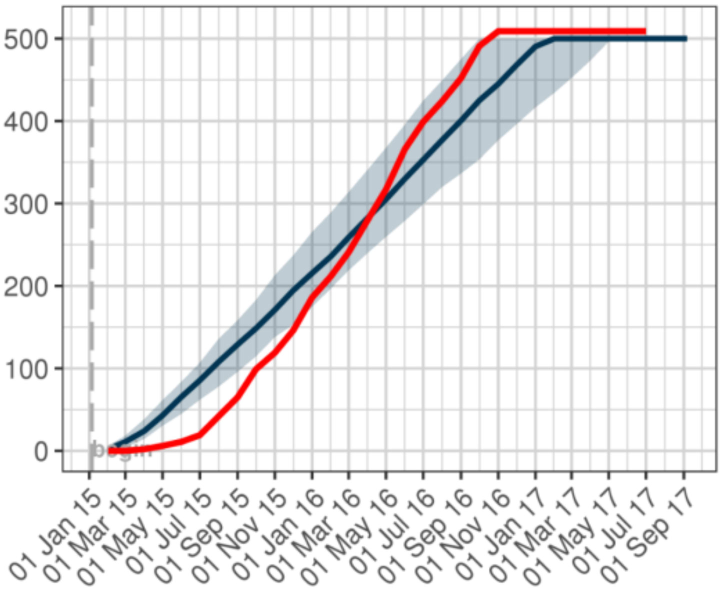
- TU ordered immediately available
- Expiry date of 1 year
- Cost of an order: 10 000 €

3) Compare the scenarios on 3 criteria:

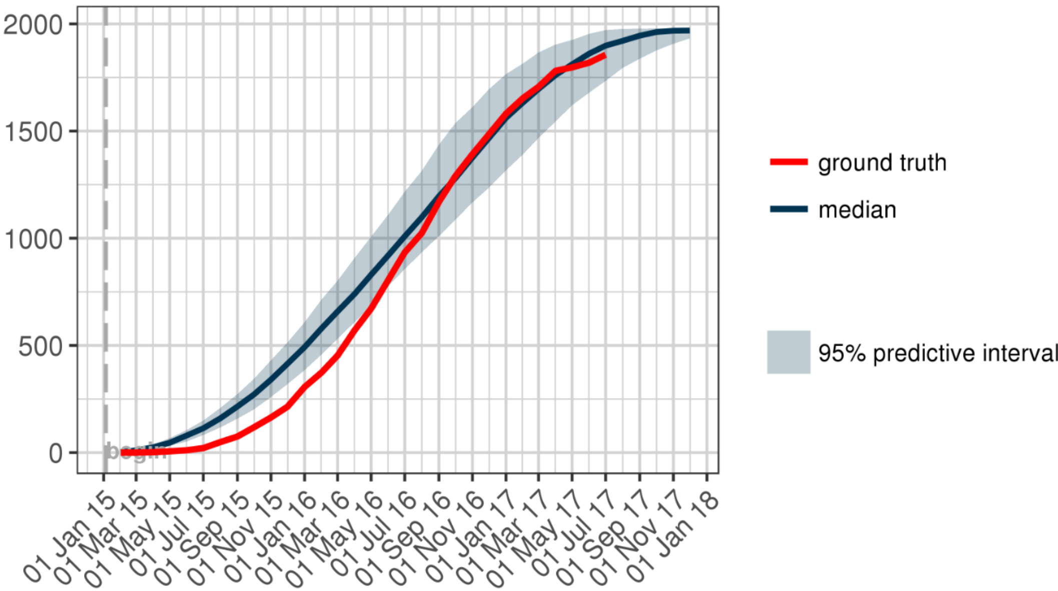
- The **number of missed visits**
- The **overage**
- The **total cost** (€)

Prediction with feasibility data

Nb of recruits



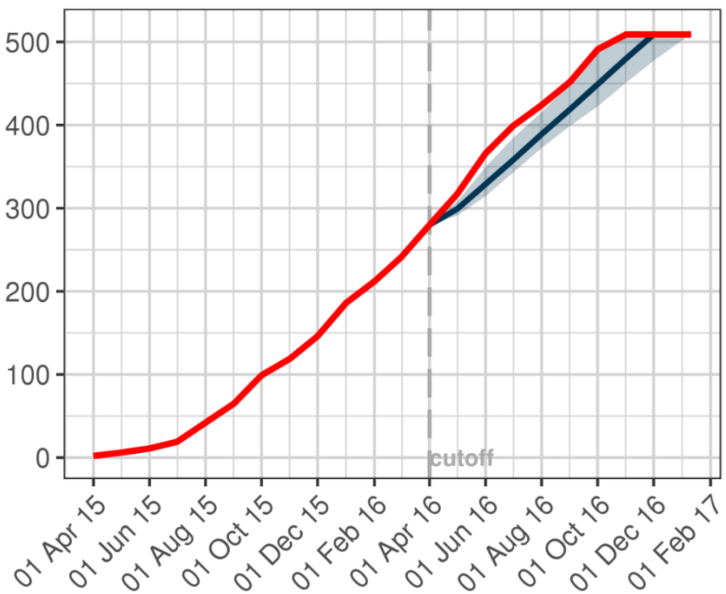
Nb of TU demand



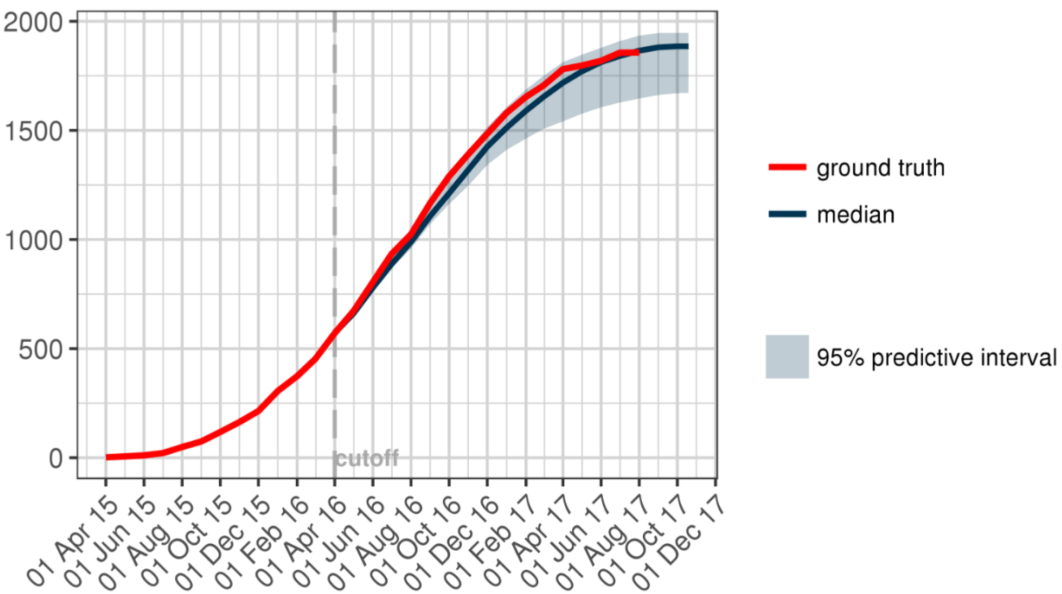
Cutoff beginning

Prediction with ongoing data

Nb of recruits



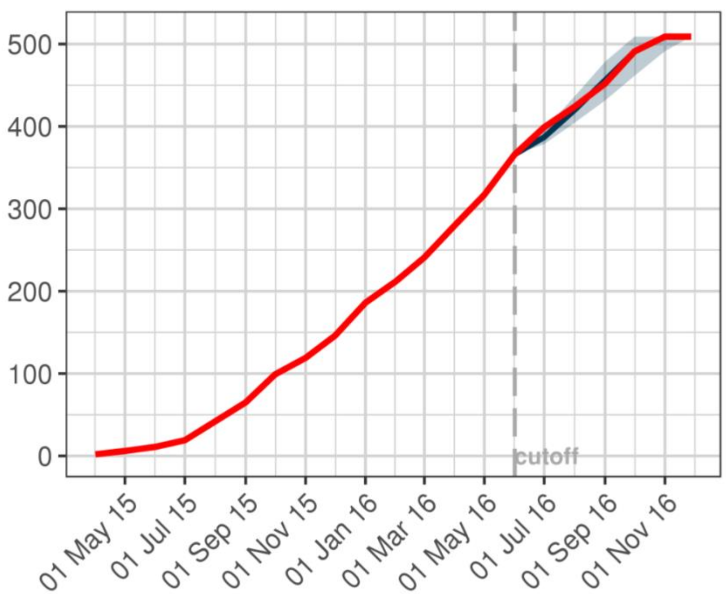
Nb of TU demand



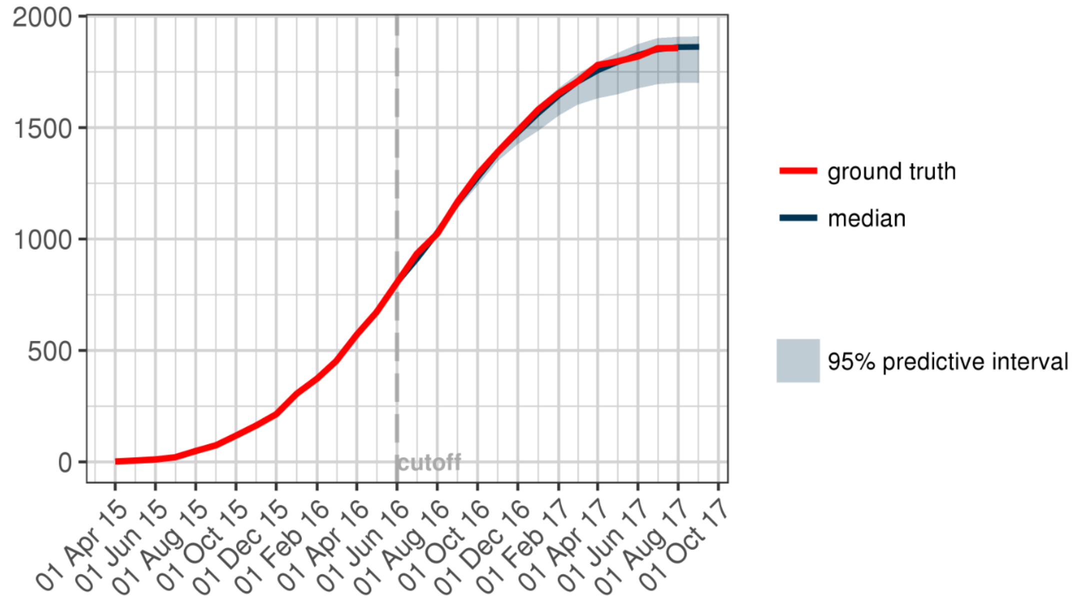
Cutoff midpoint

Prediction with ongoing data

Nb of recruits



Nb of TU demand



<u>*Cutoff midpoint +2 months*</u>

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