Models for patients' recruitment

Workshop "Modélisation et simulation d'essais cliniques"

Cancéropôle Grand Sud-Ouest

Bordeaux • Limoges • Montpellier • Nîmes • Toulouse

Thuesday 09 April 2015

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Research granted by IRESP

- Clinical trials is one of the main elements of the marketing authorization of a new drug
- Such a request has to follow a protocol specifying
  - Patients inclusion and exclusion criteria
  - Statistic analysis plan especially :
    - which test is used
    - what are the type I and type II risks
    - **necessary sample size** N
- In order to recruit these N patients, several investigators centres are involved

Definition

The **recruitment period** is the duration between the initiation of the first of the C investigator centres and the instant $T(N)$ when the N patients are included.

- N is fixed but $T(N)$ is a random variable

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Motivation of those investigations

- **Why a model of recruitment period ?**
  - The duration of the recruitment period is very **hard to control**
  - A clinical trial is **expensive**
    - $ 150.000.000 : Average out-of-pocket clinical cost for each new drug
  - Pharma-Companies need tools to **be able** to decide :
    - to overpass the targeted duration of the trial T_R
    - stop the trial if it is too long

- **What a model of recruitment for ?**
  - To develop tools for the study the feasibility of a clinical trial
    - based on the estimation of $T(N)$ (punctually and by means of CI)
  - To Detect critical point in the recruitment
  - To define decision rules on the recruitment process to reach T_R
    - based on the estimation of the recruitment rate
    - based on the estimation of the number of centre to open

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- **How to model the recruitment period ?**
  - Analogy with queueing theory

Queueing theory		**Clinical research**
Storage capacity	$\longleftrightarrow$	target population or cohort
Server	$\longleftrightarrow$	None
Exit process	$\longleftrightarrow$	Drop-out patients
Entry process	$\longleftrightarrow$	Recruitment

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The recruitment process model

Consider a multicentric trial involving C investigator centres

- N : number of patients to be recruited
- T_R : expected duration of the trial
- $\mathcal{N}_i$: the recruitment process for centre i

  $\Longrightarrow$ **modelled by a PP of rate** λ_i
- $\mathcal{N}$: the global recruitment process

  $\Longrightarrow$ **modelled by a PP of rate** $\Lambda = \sum \lambda_i$
- $T(N)$: the recruitment duration

  $\Longrightarrow$ **is the stopping time** $\inf \{t \in \mathbb{R} \,|\, \mathcal{N}(t) \geq N\}$
- T_1 an interim time
- $\mathcal{F}_{T_1}$ denote the history of the process up to T_1

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Theorem

- ***If λ is known (given by the investigator)*** *then*

  The ***feasibility of the trial*** *expresses by :*

$$\mathbb{P}\left[\mathcal{N}(T_R) \geq N \mid \mathcal{F}_{T_1}\right] = 1 - \sum_{k=0}^{N-N_1-1} \frac{1}{k!} \int_{\mathbb{R}^C} \left(\int_{T_1}^{T_R} (x_1 + \ldots + x_C)dt\right)^k e^{-\int_{T_1}^{T}(x_1+\ldots+x_C)dt} \prod_{i=1}^{C} p_\lambda^{T_1}(x_i)\, dx_i \quad (1)$$

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  Involving $p_\lambda^{T_1}$ the forward density of λ.

- ***If λ is unknown*** *then*
  - *$\hat{\lambda}$ an estimation of λ from the data collected on $[0, T_1]$*
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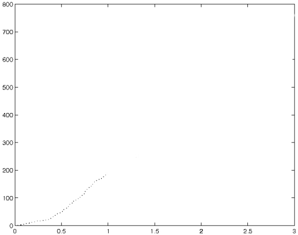


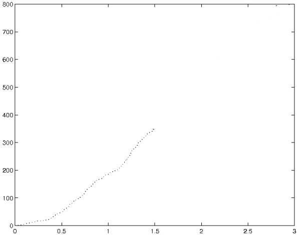
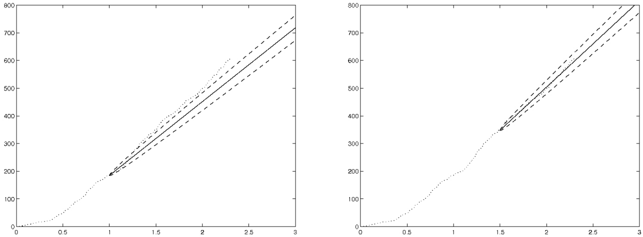


FIGURE: On going study at 1 year (on the left) and at 1.5 year (on the right)

- Dots : Real data used to calibrate the model



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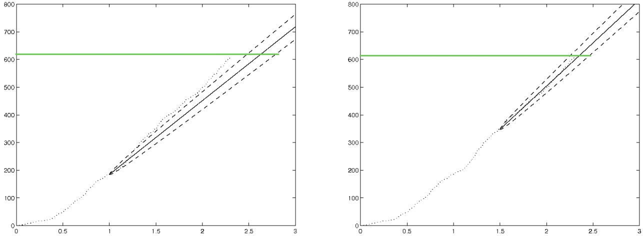

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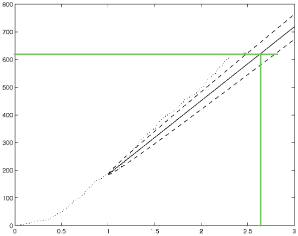

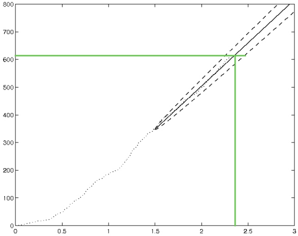

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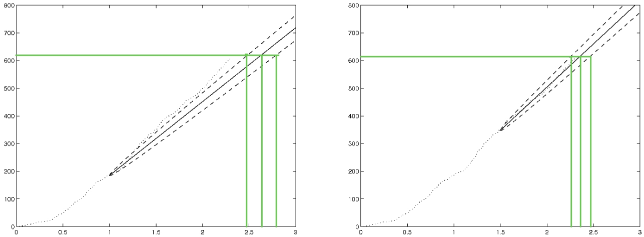

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Limit of this approach

Problem 1 : If p estimations are needed to describe $\mathcal{N}_i$, $C \cdot p$ estimation are needed to describe $\mathcal{N}$

When C large, this is not relevant

Problem 2 : If centre i has not recruited before T_1, then $\hat{\lambda}_i = 0$ and the model does not authorize centre i to recruit later

Empirical Bayesian model

Ones considers

$$(\lambda_1, \ldots, \lambda_C)$$

is a sample of size C distributed by a certain distribution $\mathcal{L}(\theta)$

Instead of estimate C values of λ, one estimates θ

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  - Rates are $\Gamma(\alpha, \beta)$ distributed.
  - Distribution of T is explicit.

- **Π-Poisson model** (Mijoule, Savy and **Savy** (2012))
  - Rates are Pareto-(x_m, k_p) distributed.
  - 20% of centres recruit 80% of patients.
  - Distribution of T is no more explicit (Monte Carlo Simulation).

- **$\mathcal{U}\Gamma$-Poisson model** (Mijoule, Savy and **Savy** (2012))
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- **Objectives :**
  - $N = 610$ patients
  - $T_R = 3$ years
  - $C_R = 77$ investigators centres
- **On-going studies :** after 1 year, after 1.5 year and after 2 years
- **The estimated duration** of the trial

The model	Time 1	Time 1.5	Time 2
Constant intensity	3.30	2.63	2.44
Γ-Poisson model	3.31	2.63	2.44
Π-Poisson model	2.63	2.39	2.36
$\mathcal{U}\Gamma$-Poisson model	2.60	2.34	2.36

- **Effective duration** of the trial : **2.31 years**
  - The end of the trial was predicted with an error of **15 days, 10 mouths** before the expected date
  - **56 centres** would be enough for ending in 3 years.

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Constant intensity	3.30	2.63	2.44
Γ-Poisson model	3.31	2.63	2.44
Π-Poisson model	2.63	2.39	2.36
$\mathcal{U}\Gamma$-Poisson model	2.60	2.34	2.36

- **Effective duration** of the trial : **2.31 years**
  - The end of the trial was predicted with an error of **15 days, 10 mouths** before the expected date
  - **56 centres** would be enough for ending in 3 years.

- **Objectives :**
  - $N = 610$ patients
  - $T_R = 3$ years
  - $C_R = 77$ investigators centres
- **On-going studies :** after 1 year, after 1.5 year and after 2 years
- **The estimated duration** of the trial

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Real case study : n=629 patients, N=91 centres

Data : $\vec{v} = (v(0), v(1), v(2), ...)$ where $v(j)$ is number of sites recruited j patients.

$$\vec{v} = (7, 11, 8, 8, 9, 8, 9, 7, 2, 4, 1, 3, 3, 4, 0, 0, 2, 1, 1, 2, 1, 0, 0, ..)$$

- **Real data :** step-wise green line
- **Fitted mean number of sites recruited j pts (theoretical) :** solid blue line
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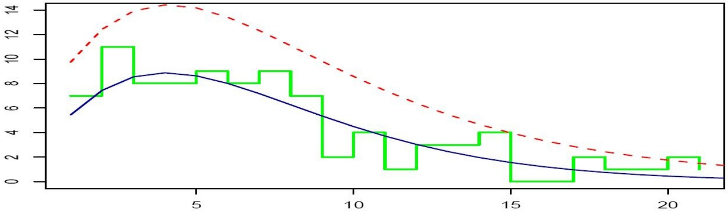

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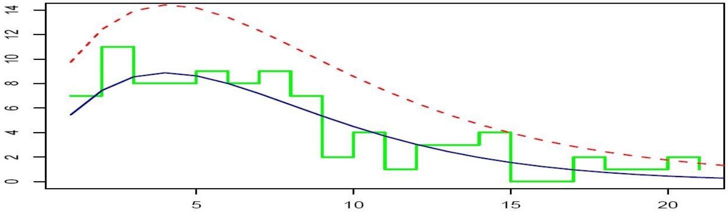

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Models investigated in (Anisimov, Mijoule, **Savy** (in progress))

- **Drop-out at the inclusion**

  modelled by a probability p_i in centre i

  $(p_1, \ldots, p_C)$ sample having a beta distribution
- **Drop-out during the screening period**

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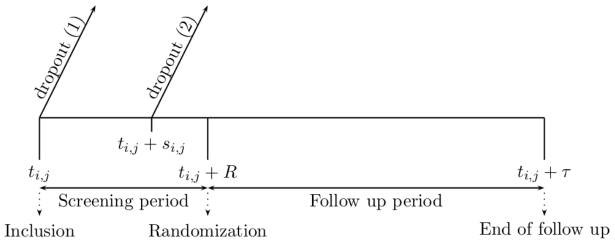

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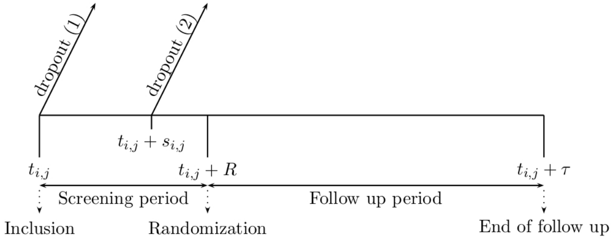

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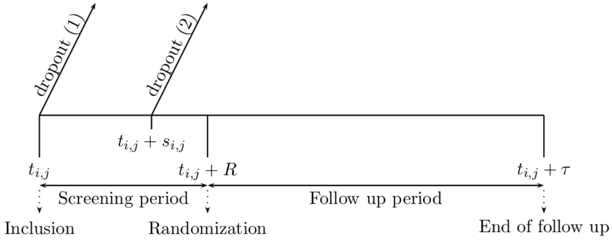

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- The recruitment dynamic is $\Gamma(\alpha, \beta)$-Poisson.
- Drop-out process is directed by p a constant or $B(\psi_1, \psi_2)$.
- T_1 is an interim time.
  - τ_i the **duration of activity** of centre i up to T_1 (assume $\tau_i \geq R$)
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Theorem ((Anisimov, Mijoule, **Savy** (in progress)))

Given data $\{(n_i, r_i, \tau_i), 1 \leq i \leq C\}$, the log-likelihood function writes :

$$\mathcal{L}_1(\alpha, \beta, p) = \mathcal{L}_{1,1}(\alpha, \beta) + \mathcal{L}_{1,2}(p)$$

- *Notice the separation of the log-likelihood function (processes independent)*
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Given data $\{(n_i, r_i, \tau_i, \nu_i),\ 1 \leq i \leq C\}$, the predicted process of the number of randomized patients in centre i, $\{\widehat{\mathcal{R}}^i(t),\ t \geq T_1 + R\}$, expenses as

$$\widehat{\mathcal{R}}_i(t) = r_i + \mathrm{Bin}(\nu_i, \widehat{p}) + \Pi_{\widehat{p}\,\widehat{\lambda}_i}(t - T_1 - R).$$

$$\widehat{p} = \Big(\sum_{i=1}^{C} n_i\Big)^{-1} \sum_{i=1}^{C} r_i \quad \textit{and} \quad \widehat{\lambda}_i = \mathrm{Ga}(\widehat{\alpha} + n_i, \widehat{\beta} + \tau_i)$$

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Consider a clinical trial such that for centre i,

- The inclusion process $\mathcal{N}_i$ is modelled by a **PP(λ_i)**
- The probability for a patient to be screening failure is p_i

- $\mathcal{F}_i(t)$: the number of screening failure at time t for center i
  - $\Rightarrow$ modelled by a **PP($p_i\lambda_i$)**
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Improvement of patient recruitment' models

An additive model for cost

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- The duration of the trial is the stopping time

$$T(N) = \inf_{t \geq 0} \{\mathcal{R}(t) \geq N\}$$

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Theorem ((Mijoule, Minois, Anisimov, **Savy** (2014)))

- *Assume* $(\lambda_i)_{1\leq i\leq C}$ *and* $(p_i)_{1\leq i\leq C}$ ***are known***

$\Longrightarrow$ ***we have an explicit expression of*** $\mathcal{C}$

- *Assume* $\lambda_i \sim \Gamma(\alpha,\beta)$ *and* $p_i \sim B(\psi_1,\psi_2)$
- *Consider an interim time* T_1, *and consider that the i-th centre has*
    - *screened* n_i *patients*
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$\Longrightarrow$ ***we can compute*** $\mathcal{C}$ ***by means of Monte Carlo simulation***

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Theorem ((Mijoule, Minois, Anisimov, **Savy** (2014)))

- *Assume $(\lambda_i)_{1\leq i\leq C}$ and $(p_i)_{1\leq i\leq C}$* ***are known***

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Assume the closure of centre j, denote

- $T^j(N)$ the duration of the trial without centre j
- $\mathcal{C}^j(t)$ the cost of the trial at time t without centre j

- By means of Monte Carlo simulation we are able to evaluate the variation of cost due to centre j closure :

$$\Delta\mathcal{C}_j = \mathbb{E}\left[\mathcal{C}(T(N)) - \mathcal{C}^j(T^j(N))\right]$$

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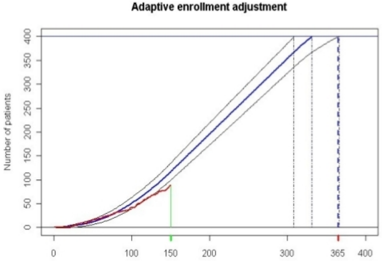
Study design : Sites : 70, patient's target : 400, enrolment duration :1 year
Sites initiated in 5-month period,
half of sites will be closed in two months before the end of enrolment



- **Initial design :** to complete with 90% confidence.
  Predictive area : mean and confidence bounds.
- **Interim analysis after 150 days :** 88 pts recruited.
  Real enrolment is slower than predicted.
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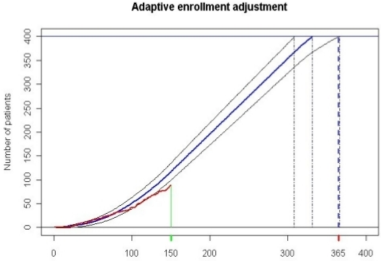

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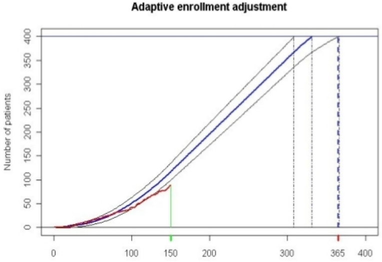

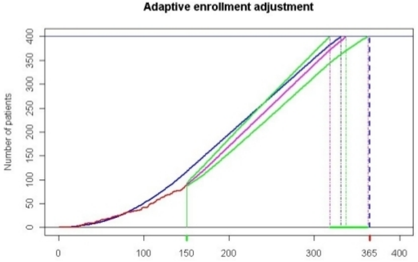

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- **Triggers for detecting outliers :**

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  Predicting future behavior and alarm unusual sites

  Create dynamic forecasts in future time intervals

  Opportunities for optimal decision-making (sites, costs, risks).

Current triggers for RBM usually use assumptions of **normality** and detect unusual behaviour within cohort using Mean and SD :

$$X > Mean(cohort) + K * SD(cohort), K = 1, 2, 3$$

Many of variables describing trial operation are **rather far from the normality**

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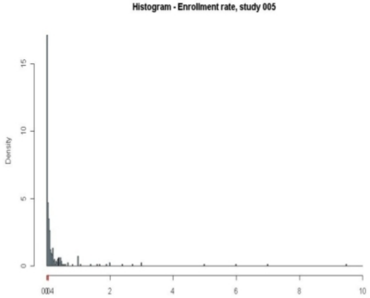

Histogram of the enrolment rate
(# of patients)/(site enrolment duration)

- far from normal distribution
- heavy tailed
- Adequate model : Poisson mixed with gamma

Histogram of time from Last Patient Enrolled till current time

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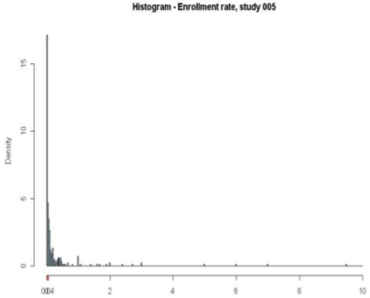

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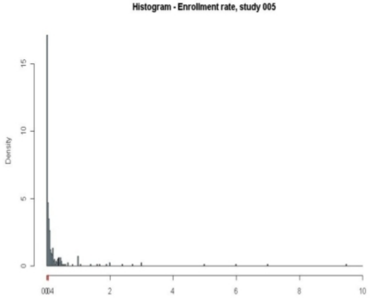
Decisions tools

Site performance and risk-based monitoring (Vladimir Anisimov)



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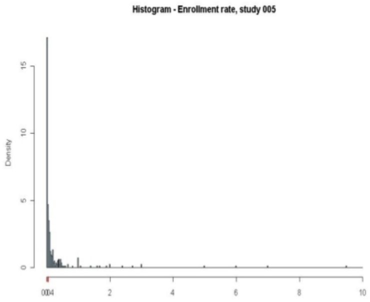

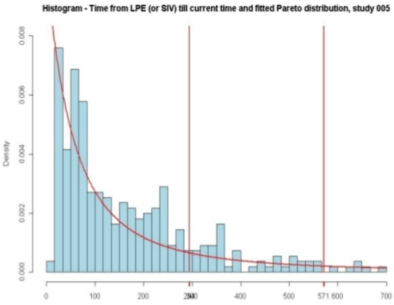

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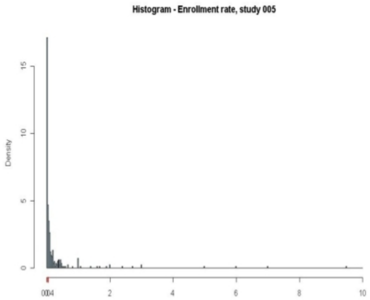

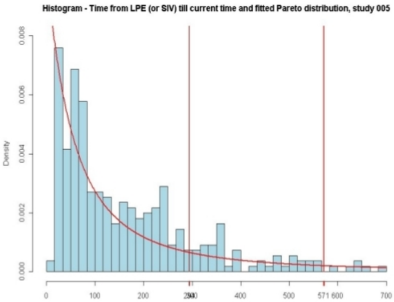

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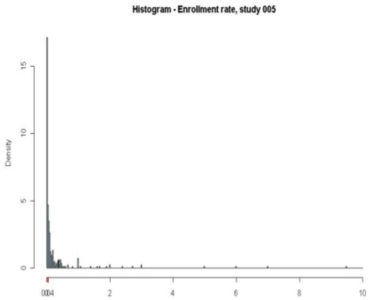

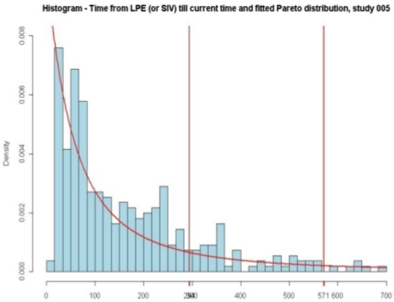

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Interim analysis, real case study, 330 active sites.

SID	# of patients	Enrolment duration		
1004	1	166		
1006	0	268		
1007	2	533		
1009	1	190		
1011	0	124		
1012	1	595		
1013	3	450		
1014	5	488		
1017	0	494		
1022	3	486		
1029	0	5		
1201	2	424		
1203	2	316		
1901	25	180		
1904	3	347		
1905	5	550		
1906	10	534		

Poisson-Gamma model of enrolment + Data-driven Bayesian re-estimation of rates
$\Longrightarrow$ **Predictive probabilities** for the next 4-month period

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1013	3	450	0.445	
1014	5	488	0.325	
1017	0	494	0.801	
1022	3	486	0.465	
1029	0	5	0.451	
1201	2	424	0.525	
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1006	0	268	0.716	0.926
1007	2	533	0.578	0.87
1009	1	190	0.485	0.785
1011	0	124	0.614	0.862
1012	1	595	0.705	0.933
1013	3	450	0.445	0.773
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Study design : Sites : 200, patient's target : 800, enrolment duration :1 year
4 visits in total, each after 60 days, Follow-up period L=180 days

- **Predictive number of follow-up patients**

  Mean, Low and Upper 90% bounds for a Region with 100 sites
- **Predictive number of Visits No. 3**

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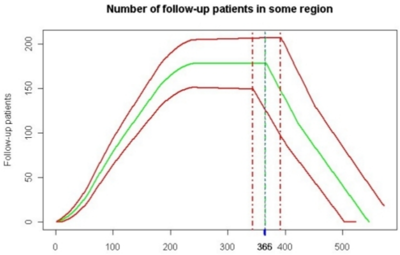

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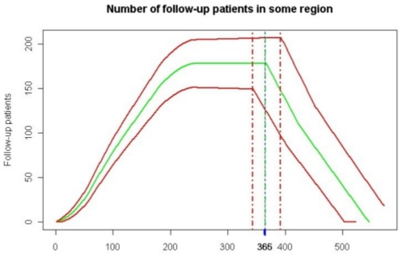

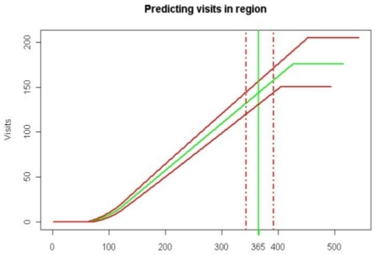

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- **Stéphanie Savy**
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