Poisson-gamma model for patients' recruitment in clinical trials: Investigations on boundaries of relevancy by simulation studies.

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Workshop "Modélisation et simulation d'essais cliniques"

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1. Cohort study
2. Recruitment model
3. Robustness investigations

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1. Cohort study
   - Cohort definition
   - Recruitment process
2. Recruitment model
3. Robustness investigations

Definitions

Epidemiological cohort : Medical follow-up of a target population.

It is divided in three phases.

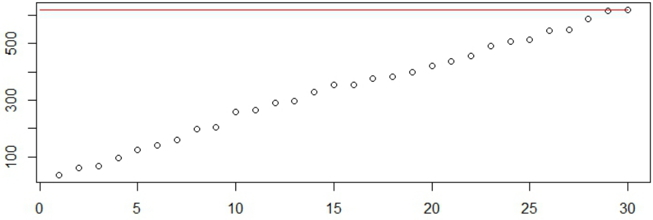
- **Recruitment :** By means of investigator centres, the necessary sample size of the study N is recruited.
- Follow-up : Monitoring of patients' state through medical visits.
- Analysis : Statistical test run on the data collected.

Introduction

Given the necessary sample size of the study N.

The recruitment process aims to reach *N* by means of several investigator centres.

The variable of interest is the duration of the recruitment.



1. Cohort study

2. Recruitment model
   - Notations
   - Poisson-gamma model

3. Robustness investigations

Notations

Global parameters :

- N : number of patient to recruit.
- C : number of investigator centres.

Model parameters :

- (α, β) : parameters of the gamma distribution.
- λ_i : the rate of the poisson process for centre i.
- t_1 : the interim time of observation.

Observations :

- k_i : recruitment of centre i at time t_1.
- τ_i : the duration of activity of centre i up to t_1.

Gamma distribution parameters

Theorem

At time t_1, the maximisation of the likelihood function gives us $(\hat{\alpha}, \hat{\beta} = 1/\hat{\mu})$.

$$M_C^{\Gamma}(\alpha,\mu) = \alpha \ln(\frac{\alpha}{\mu}) - \ln\Gamma(\alpha) + \frac{1}{C}\sum_{i=1}^{C}\left[\ln\Gamma(\alpha+k_i) - (\alpha+k_i)\ln(\frac{\alpha}{\mu}+\tau_i)\right].$$

They are the a-priori parameters of the bayesian estimation.

Inclusion process estimation

Bayesian reestimation

Theorem

The density of $\lambda_i | (N_i(t_1) = k_i)$ *is :*

$$p_\theta^{t_1}(x) = \frac{\mathbb{P}[N_i(t_1) = k_i \,|\, \lambda_i = x] p_\theta(x)}{\mathbb{P}[N_i(t_1) = k_i]}$$
$$= M e^{-(\beta+\tau_i)x} x^{k_i+\alpha-1} \mathbb{1}_{x>0}$$

This is a Gamma distribution with parameters $(\alpha + k_i, \beta + \tau_i)$.

Inclusion process estimation

Approximation of the global rate

We consider $\forall i = 1, \ldots, C$:

- $m_i = \mathbb{E}[\lambda_i] < \infty$
- $\sigma_i^2 = \mathbb{V}[\lambda_i] < \infty$

The gamma disribution parameters of the global rate Λ are :

$$A = \frac{m^2}{\sigma^2} \quad et \quad B = \frac{m}{\sigma^2};$$

with

$$m = \sum_{i=1}^{C} m_i, \quad \sigma^2 = \sum_{i=1}^{C} \sigma_i^2$$

Inclusion process estimation

Expected duration

Theorem

Given :

- $\tilde{N}$ *a doubly stochastic process with rate* $\Lambda = \sum_{i=1}^{C} \lambda_i$.
- *The expected duration* $\tilde{T} = \inf_{t \geq 0}\{\tilde{N}(t) = N\}$.

Conditionally to Λ, $\tilde{T}$ *follows a* $\Gamma(N, \Lambda)$ *distribution, therefore :*

$$\mathbb{E}[\tilde{T}] = N\frac{B}{A-1} \quad \text{si} \quad A > 1, \quad \mathbb{E}[\tilde{T}] = +\infty \quad \text{si} \quad 0 < A \leq 1$$

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1 Cohort study

2 Recruitment model

3 Robustness investigations
- Motivations
- Issues
- Simulations
- Analysis of variance
- Results

Model hypothesis

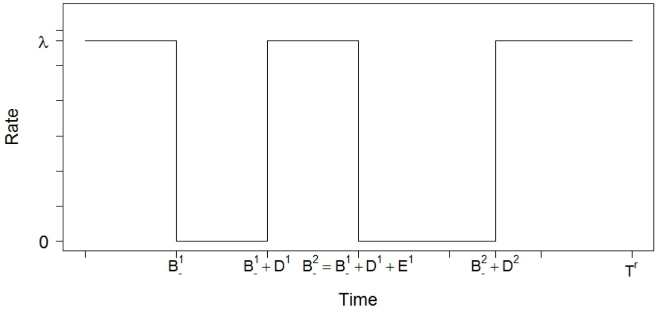
- C must be large enough (≥ 20).
- The recruitment rates must be constant over time.

On real data, the rates are rarely constant.

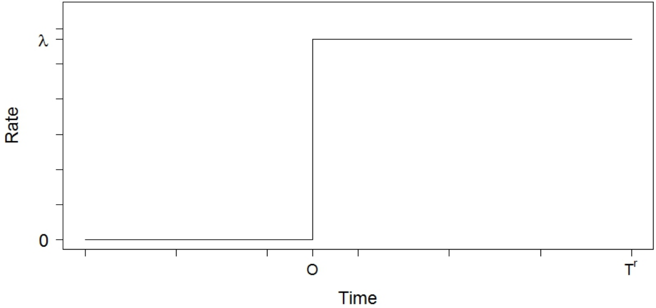
$\hookrightarrow$ cost/precision of its consideration.

Simulation study helps for the decision. It involves 20 centers to recruit 1000 patients.

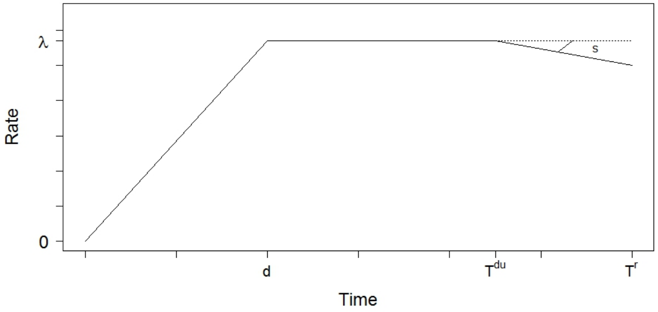
Scenario 1 : Breaks in recruitment process



Scenario 2 : Unknown opening dates



Scenario 3 : Rate changes over time



Inclusion process simulation

Data generation procedure :

- Generation of R global recruitment processes $\{N^r(t),\ 0 \leq t \leq T^r,\ 1 \leq r \leq R\}$.
- Given an interim time t_1 :
  - Estimation of (α, β) from data collected on $[0, t_1]$.
  - Calculation of the expected duration of the trial $T^r_{t_1}$ at t_1.
  - Measure of the performance of the model at interim time t_1 defined by :

$$E^r_{t_1} = \frac{T^r_{t_1} - T^r}{T^r}.$$

Processes generation

Simulation algorithm :

- Generation of the C rates $\sim$ Gamma(α, β) .
- Generation of the C recruitment dynamic.
- Aggregation of the C recruitment dynamics.
- Identification of the duration of the trial.
- Calculation of the relative error at $t_1 = 78$ and $t_1 = 104$ weeks.

Addition of the perturbations of the scenarios

Addition algorithm :

- Fix the modality of the factor condidered in the scenario.
- Perform 100 runs as follows :
  - Begin the processes generation.
  - Generate the factor's perturbations for each centre.
  - Shorten the global recruitments to 1000 patients.
  - Calculate the relative error at interim time $t_1 = 78$ and $t_1 = 104$ weeks.
- Calculate the average relative error at interim time t_1.

Scenario 1 : Breaks

Factors' modalities :

- **Number** : 1, 2 and 3 breaks.

  Simulation by an exponential random sampling.

- **Duration** : 0, 2, 4, 8, 12, and 24 weeks.

  Simulation by a multinomial random sampling with 7 different event probabilities.

Scenario 2 : Opening dates

Factor's modalities :

Values : 0, 1, 2, 4, 8, 12, 16, 20 and 24 weeks.

Simulation by a multinomial random sampling with 10 different event probabilities.

Scenario 3 : Rate changes

Factors' modalities :

- **Start-up :** 0, 2, 4 and 8 weeks.
  Simulation by a multinomial random sampling with 5 different event probabilities .
- **Drying-up start :** 108 and 120 weeks.
  Equiprobably shared between all the simulations.
- **Drying-up slope :** 0, 0.05, 0.1 and 0.2.
  Simulation by a multinomial random sampling with 5 different event probabilities .

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Conducted analysis

The variable of interest is the relative error made defined as :

$$\mathrm{E} = \frac{\hat{T} - T_{\text{real}}}{T_{\text{real}}}$$

For each scenario, the impact of the factors is studied by an ANOVA.

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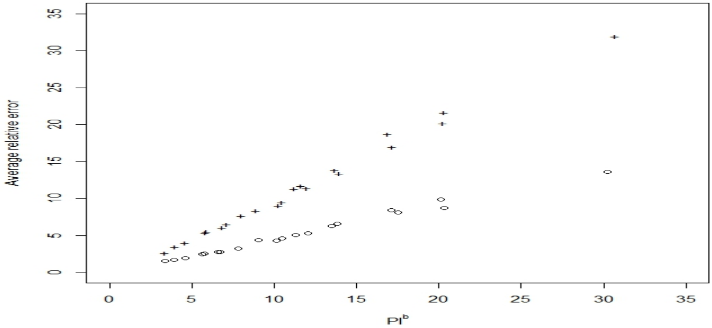
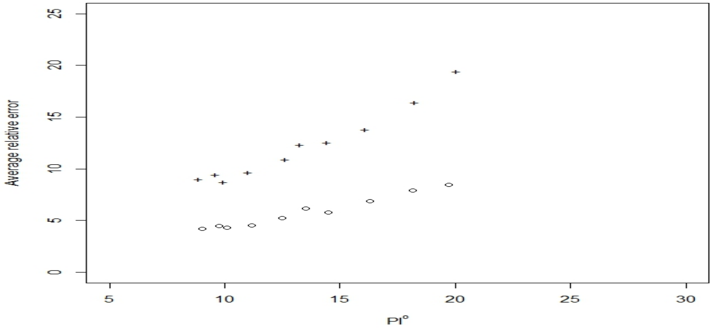
Breaks

Average relative error the expected trial duration from data collected at $t_1 = 78$ weeks, '**+**' and $t_1 = 104$ weeks, '**o**' as a function of PI^b.



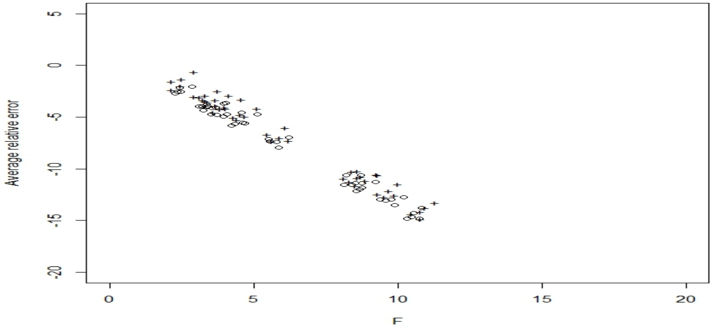
Opening dates

Average relative error the expected trial duration from data collected at t_1 = 78 weeks, '**+**' and t_1 = 104 weeks, '**o**' as a function of PI^o.



Rate changes

Average relative error the expected trial duration from data collected at t_1 = 78 weeks, '**+**' and t_1 = 104 weeks, '**o**' as a function of F.



Thank you for your attention

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