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"
1 Cohort study
2 Recruitment model
3 Robustness investigations

Investigations on boundaries of relevancy by simulation studies.
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 patientsʼ 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 patients to recruit.
- $C$: number of investigator centres.

Model parameters:
- $(\alpha, \beta)$: parameters of the gamma distribution.
- $\lambda_i$: 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 $t_1$.
- $\tau_i$: the duration of activity of centre $i$ up to $t_1$. 
Poisson-gamma model

Gamma distribution parameters

**Theorem**

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

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

*They are the a-priori parameters of the bayesian estimation.*
Inclusion process estimation

Bayesian reestimation

Theorem

The density of \( \lambda_i \mid (N_i(t_1) = k_i) \) is:

\[
p_{\theta}^{t_1}(x) = \frac{\mathbb{P}[N_i(t_1) = k_i \mid \lambda_i = x] p_\theta(x)}{\mathbb{P}[N_i(t_1) = k_i]}
\]

\[
= Me^{-(\beta + \tau_i)x} x^{k_i + \alpha - 1} \mathbb{1}_{x > 0}
\]

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 distribution parameters of the global rate $\Lambda$ are:

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

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

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

2 Recruitment model

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

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

On real data, the rates are rarely constant.

$\rightarrow$ 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

![Graph showing rate over time with a step function change at time T]
Scenario 3: Rate changes over time

The graph illustrates the change in rate over time, with time periods denoted as $d$, $T^{du}$, and $T^r$. The rate function shows an upward trend from $d$ to $T^{du}$, followed by a decrease from $T^{du}$ to $T^r$. The function is not explicitly defined, but the graph provides a visual representation of the rate changes.
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 \( (\alpha, \beta) \) 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 $\sim \text{Gamma}(\alpha, \beta)$.
- 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 considered 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.
Conducted analysis

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

\[ E = \frac{\hat{T} - T_{\text{real}}}{T_{\text{real}}} \]

For each scenario, the impact of the factors is studied by an ANOVA.
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 $\text{PI}^b$.

![Graph showing average relative error as a function of PI]

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Summary
- Cohort study
- Recruitment model
- Robustness investigations

Results
- Investigations on boundaries of relevancy by simulation studies.

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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 $\Pi^0$. 

![Graph showing average relative error as a function of $\Pi^0$.]
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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