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Using Poisson–gamma model to evaluate the duration of recruitment process when historical trials are available

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At the design of clinical trial operation, a question of a paramount interest is how long it takes to recruit a given number of patients. Modelling the recruitment dynamics is the necessary step to answer this question. Poisson–gamma model provides very convenient, flexible and realistic approach. This model allows predicting the trial duration using data collected at an interim time with very good accuracy. A natural question arises: how to evaluate the parameters of recruitment model before the trial begins? The question is harder to handle as there are no recruitment data available for this trial. However, if there exist similar completed trials, it is appealing to use data from these trials to investigate feasibility of the recruitment process. In this paper, the authors explore the recruitment data of two similar clinical trials (Intergroupe Francais du Myélome 2005 and 2009). It is shown that the natural idea of plugging the historical rates estimated from the completed trial in the same centres of the new trial for predicting recruitment is not a relevant strategy. In contrast, using the parameters of a gamma distribution of the rates estimated from the completed trial in the recruitment dynamic model of the new trial provides reasonable predictive properties with relevant confidence intervals.

Keywords: clinical trials; recruitment time; trial feasibility; Bayesian statistics; Cox process

1. Introduction

The question of evaluating the feasibility of recruitment in clinical trials is of a paramount interest. However, till now, traditional techniques used by pharmaceutical companies are based on deterministic models and various ad hoc techniques that yield to simplistic approximate results. The problem of predicting patients recruitment and evaluating the recruitment time in clinical trials has been given much attention during the past years. Using a Poisson process to describe the recruitment process is now an accepted approach [1–4]. However, in real trials, the recruitment rates vary between different centres. To address this issue, Anisimov and Fedorov [5] proposed to use a doubly stochastic Poisson processes to take into consideration the variation in recruitment rates between different centres. This model, called as a Poisson–gamma model, assumes that the patients arrive at different centres according to Poisson processes with the rates viewed as the independent gamma distributed random variables. This assumption reflects some prior knowledge about the type of the distribution of the rates in the population of the centres and can be considered within the Bayesian paradigm, as well. In [5], the procedure of parameters' estimation and adjustment at interim time using the Bayesian re-estimation of parameters and predicting the remaining

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recruitment time have been suggested. In [6, 7], the technique for forecasting recruitment process over time at any stage of the trial has been developed; in particular, in [7], the model where the centres initiation delays follow a uniform distribution was considered. Some practical applications to predicting and re-projecting recruitment process over time and verification of the technique for real trials are considered in [7, 8].

However, it is harder to investigate the feasibility at the initial stage as there are no data available to calibrate the model. In [9], authors discuss the use of data from many trials (meta-analysis) and propose to use for prior estimates of the parameters of a Poisson–gamma model [5] for recruitment prediction at the initial stage the estimates from different but somehow similar trials. They conclude that the huge variability in recruitment rates yields most of the time to inconclusive results.

Consider the following framework: predicting recruitment for a clinical trial, which is similar to a completed trial involving a collaborative group of investigators working on the same disease. The aim is to exploit the recruitment data of the completed trial to estimate the duration of the recruitment of the new trial. We consider two approaches on how to estimate the rates of the centres, which are common (the same) in both trials (called shared centres in the sequel). This distinction between shared and unshared centres is the main difference with the strategies developed in [9]. The first approach: for each shared centre, the rate estimated from the completed trial is used as the rate in the new trial. The second one: the parameters of the gamma distribution of the rates in shared centres estimated from data of the completed trial are used as parameters of the gamma distribution of the rates of the new trial. It can be expected that the shared centres for similar trials should have similar statistical behaviour of recruitment; therefore, the parameters of recruitment model should be similar. On contrary, unshared centres may have very different recruitment performance.

The assumption we aim to validate is that the second approach provides more relevant results compared with the first one. Indeed, the rates in similar trials on average are more or less similar but not necessary for the same centres. Therefore, it is not relevant to plug-in the estimated rates from one trial to another but use the same distribution. In order to show this, we use the recruitment datasets of rather similar trials (Intergroupe Francophone du Myélome (IFM) 2005, IFM 2009 and IFM 2014) . Trials IFM 2005 and IFM 2009 are completed; thus, the aforementioned assumption can be easily verified. The recruitment of trial IFM 2014 is in progress, and we apply our methodology to predict its duration of recruitment considering the list of centres involved in IFM 2014 trial, which had been known since the beginning of recruitment.

The paper is organized as follows. Section 2 presents the different trials, which allow us to discuss and compare our strategies. Section 3 is devoted to the method used in the paper. This section splits in three parts: first, the parameters estimation strategy; second, the prediction strategy; and third, a discussion on how to deal with centres opening dates. The prediction involves Monte Carlo simulation and analytic modelling for different scenarios described in this section. At designing state of the trial, the centres are not opened yet, and the opening dates are unknown. This issue is discussed in this section. The results are discussed in Section 4 using two ideas: the comparison of the rates and the comparison of predictive performances. Section 5.2 is an application of the machinery to predict the duration of IFM 2014 trial. Finally, in concluding Section 6, some recommendations on how to make use of such techniques are written.

2. Description of the datasets

In order to investigate the relevancy of the models described next, the recruitment data of three Phase III clinical trials, enrolling young patients newly diagnosed with multiple myeloma, conducted by Toulouse hospital and the IFM are used. The IFM is a collaborative group of myeloma specialists from France, Belgium and Switzerland, which aims to optimize the effort of translational and clinical research on myeloma. The three trials are as follows:

- IFM2005-02 (NCT00430365): a phase III multicentre randomized, double blinded study comparing maintenance therapy using Lenalidomide to placebo after autologous stem cell transplantation in multiple myeloma patients up to 65 years. This study enrolled 614 patients between June 2006 and August 2008, thanks to the participation of 77 centres. The first centre was opened on 24/02/2006. The last patient was recruited on 26/08/2008. The duration of recruitment is thus 914 days. The study was published in 2012 [10].
- IFM2009 (NCT01191060): a phase III multicentre randomized, open-label study comparing conventional dose combination using Revlimid, Velcade and dexamethasone to high dose treatment with

Table I. Description of the recruitment of IFM 2005, IFM 2009 and IFM 2014 trials.

	IFM 2005	IFM 2009	IFM 2014
Trial duration (expected for 2014) in days	914	746	730
Total number of centres	76	67	47
Number of centres shared with 2005	–	50 (74%)	36 (77%)
Number of centres shared with 2009	50 (66%)	–	41 (87%)
Total number of patients	611	693	–
Number of patients recruited by centres shared with 2005	–	562 (81%)	–
Number of patients recruited by centres shared with 2009	543 (89%)	–	–

IFM, Intergroupe Francophone du Myélome.

autologous stem cell transplantation in de novo multiple myeloma patients up to 65 years. Seven hundred patients were enrolled between November 2010 and November 2012, thanks to the participation of 73 centres. The first centre was opened on 14/10/2010. The last patient was recruited on 29/10/2012. The duration of recruitment is thus 746 days.

- IFM2014-02 (NCT02197221): a phase III multicentre randomized, open-label study comparing the efficacy of a combined high-dose chemotherapy using melphalan and bortezomib versus melphalan alone followed by stem cell transplant in frontline multiple myeloma patients non-progressive after induction therapy. This study began in January 2015, and at this time, 47 centres were opened. The first centre was opened on 17/12/2014. The total number of patients planned to be enrolled is 300. This study is recruiting, and the expected duration is 730 days.

The main difference across the three trials come from the therapeutic scheme: autologous stem cell transplant was part of the overall study protocol for the IFM 2009 and IFM 2014 studies, whereas patients in the IFM2005-02 study were eligible only after transplantation. Hence, only transplant centres were opened for the IFM 2009 and 2014 studies. It is important to quote that some data have been removed from the datasets. Indeed, some dates of patients' arrival are missing, and some patients are written to be recruited before the opening date of the centre. These incoherent data generate inconsistency in the results; thus, some centres are removed. In detail, one centre is removed from IFM2005-02 involving three patients, and six centres are removed from IFM2009-02 involving seven patients.

The data used for this study are presented in Table I. The proportion of centres shared between the different trials and the number of patients recruited by the shared centres are given. For instance, in IFM 2005, the proportion of patients recruited by the shared centres was 89%, and in IFM 2009, this proportion was 80% (the shared centres recruit most of the patients).

3. Method

Consider a completed clinical trial. We aim to use the historical recruitment data collected from this trial to design a new trial under similar conditions. The parameters related to the historical completed trial are upper-indexed by 'h', and the parameters of the new trial will be upper-indexed by 'n'. Denote by C^h the number of recruitment centres involved in the historical trial, by N^h the number of recruited patients and by T^h the duration of the recruitment in the trial. To design the new trial, denote by C^n the number of recruitment centres involved, by N^n the number of patients to be recruited and by T^n the duration of the trial, which is unknown. The objective is to estimate the quantity T^n. Finally, denote by λ_i^h (respectively λ_i^n), the recruitment rate of the ith centre of the historical (respectively new) trial.

3.1. Estimation of the recruitment rate of the completed trial

The estimation of the recruitment rates in the centres involved in the completed trial can be obtained by two approaches: a frequentist approach and a Bayesian approach.

Frequentist approach. Consider the ith centre of the completed trial. Assume that n_i^h patients have been recruited since the time γ_i^h of opening the centre. Denote by $\tau_i^h = T^h - \gamma_i^h$ the duration of recruitment in this centre. Then, the maximum likelihood point estimator of the rate for centre i:

$$\widehat{\lambda}_i^h = \frac{n_i^h}{\tau_i^h}.$$

Population approach. As different centres recruit differently, a Poisson–gamma model [5, 6] can be used to model the variation of the rates. The rates λ_i^h are viewed as a sample from a gamma distributed population with some unknown parameters $\left(\alpha^h, \beta^h\right)$ (shape and rate). The p.d.f. of a $\mathrm{Ga}\left(\alpha^h, \beta^h\right)$ distribution is given by

$$f\left(x; \{\alpha^h, \beta^h\}\right) = \frac{e^{-\beta^h x} x^{\alpha^h - 1} \left(\beta^h\right)^{\alpha^h}}{\Gamma(\alpha^h)} \mathbf{1}_{\{x>0\}},$$

where $\Gamma(x) = \int_0^\infty t^{x-1} e^{-t} dt$. The re-parametrized version of this distribution in terms of shape and mean parameters $\left(\alpha^h, \mu^h\right)$, where $\mu^h = \alpha^h / \beta^h$,

$$f\left(x; \{\alpha^h, \mu^h\}\right) = \frac{e^{-\alpha^h x/\mu^h} x^{\alpha^h - 1} \left(\alpha^h\right)^{\alpha^h}}{\Gamma(\alpha^h)(\mu^h)^{\alpha^h}} \mathbf{1}_{\{x>0\}} \tag{1}$$

is preferred. Indeed, as pointed out in [6], the estimation of μ^h is more stable than the one of β^h. For the sake of simplicity, the re-parametrized gamma distribution will be denoted by $\mathrm{Ga}(\alpha^h, \mu^h)$. The parameters $\left(\alpha^h, \mu^h\right)$ can be estimated using maximum likelihood procedure as in [5]. The log-likelihood function is expressed as

$$\begin{aligned} \mathcal{L}\left(\alpha^h, \mu^h\right) = & \sum_{i=1}^{C^h} \ln\left(\Gamma\left(\alpha^h + n_i^h\right)\right) - C^h \ln\left(\Gamma\left(\alpha^h\right)\right) + C^h \alpha^h \ln\left(\alpha^h\right) + \\ & - \sum_{i=1}^{C^h} n_i^h \ln\left(\mu^h\right) - \sum_{i=1}^{C^h} \left(\alpha^h + n_i^h\right) \ln\left(\alpha^h + \mu^h \tau_i^h\right) + \mathrm{Const.} \end{aligned} \tag{2}$$

Indeed, considering N, a Poisson random process with intensity $\mathrm{Ga}(\alpha, \mu)$- distributed, we have

$$\mathbb{P}\left[N_t = n\right] = \frac{\Gamma(\alpha + n)}{\Gamma(\alpha)} \frac{\alpha^\alpha \mu^{-n}}{(\alpha + \mu t)^{\alpha + n}} \frac{t^n}{n!}, \quad n = 0, 1, \ldots.$$

Moreover, the Gaussian asymptotic distribution of the estimator of the parameters $\left(\alpha^h, \mu^h\right)$ can be exploited. This is related to the Fisher information matrix. Details on the Fisher information matrices below are relegated in the Appendix section. Denote

$$\mathrm{F}^{C_g^h} = \sum_{i \in C_g^h} \mathrm{J}_i^h\left(\alpha^h, \mu^h\right),$$

where $\mathrm{J}_i^h\left(\alpha^h, \mu^h\right)$ is the Fisher information matrix for a centre i that is described in the Appendix. Consider the asymptotic matrix $\mathrm{F}_g^h = \lim_{C_g^h \to \infty} \frac{1}{C_g^h} \mathrm{F}^{C_g^h}$. Then, the variance–covariance matrix of the asymptotic distribution of (α^h, μ^h) is $[\mathrm{F}_g^h]^{-1}$. The $(1-\delta)$-confidence region of (α^h, μ^h) is thus the set

$$\left\{ \theta \in \mathbb{R}^2; \left(\theta - \left(\alpha^h, \mu^h\right)\right)^T \mathrm{F}_g^h \left(\theta - (\alpha^h, \mu^h)\right) \leq \frac{\chi_2^2(\delta)}{C_g^h} \right\}, \tag{3}$$

where $\chi_2^2(\delta)$ is the δ-quantile of a chi-squared distribution with two degrees of freedom.

3.2. Comparison of the recruitment rates

In order to compare the recruitment dynamics of two clinical trials, the centres are split in two categories:

- **Shared centres.** Denote $\mathcal{C}_s^h$ (respectively $\mathcal{C}_s^n$) the set of centres of the historical (respectively new) trial shared between both trials. Finally, C_s^h (respectively C_s^n) denotes its cardinality. Obviously $C_s^h = C_s^n$.

- **Unshared centres.** Denote $\mathcal{C}_u^n$ the set of centres, which are involved in the new trial but not in the historical one and denote C_u^n its cardinality. Finally, denote $\mathcal{C}_u^h$ the set of centres, which are involved in the historical trial but not in the new one and denote C_u^h its cardinality.

In the sequel, the parameters related to the shared centres trial are under-indexed by 's', the parameters of the unshared centres will be upper-indexed by 'u' and the parameters related to the set of all centres are under-indexed by 'g'. Moreover, the indexes of sums will be written by sets while summing over a specified set of centres.

3.2.1. Frequentist approach. To illustrate the comparison of the estimated rates of centres, an analysis of the relationship between rates in both trials (historical and new) is made by plotting the pairs of the estimated rates in different centres $\left\{(\widehat{\lambda}_i^h, \widehat{\lambda}_{j(i)}^n), i \in \mathcal{C}_s^h\right\}$, where $j(i) \in \mathcal{C}_s^n$ is the index of the shared centre i in the new trial. The conclusion follows by means of a least distance linear regression analysis and a comparison of the regression line with $y = x$.

3.2.2. Population approach. By considering a population approach, thanks to the asymptotic normality of the distribution of the estimators of α and β, it is possible to perform Wald's test to compare the parameters of the gamma distribution $\left(\alpha_s^h, \mu_s^h\right)$ estimated from the set of shared centres (from the centres in $\mathcal{C}_s^h$) and (α_s^n, μ_s^n) estimated from the set of shared centres (from the centres in $\mathcal{C}_s^n$).

The comparison is enriched by the comparison of $\left(\alpha_g^h, \mu_g^h\right)$ estimated from the complete set of all centres $\mathcal{C}_g^h = \mathcal{C}_s^h \cup \mathcal{C}_u^h$ and $\left(\alpha_g^n, \mu_g^n\right)$ estimated from the complete set of all centres $\mathcal{C}_g^n = \mathcal{C}_s^n \cup \mathcal{C}_u^n$.

Notice that the comparison of $\left(\alpha_u^h, \mu_u^h\right)$ estimated from the set restricted to the unshared centres (from the centres in $\mathcal{C}_u^h$) and $\left(\alpha_u^n, \mu_u^n\right)$ estimated from the set restricted to the unshared centres (from the centres in $\mathcal{C}_u^n$) may be meaningless if the number of these centres is small (less than 20) or if the selection of these centres is not due to randomness. Indeed, the unshared centres are often those that do not recruit enough patients. Thus, the distribution of recruited patients can be described by the tail of a gamma distribution, which is not gamma distributed.

3.3. Prediction of the duration of recruitment for the new trial

Assume that the values γ_i^n are known. In the framework of a Poisson–gamma model, the predictive patients' recruitment process is defined by the values of the enrolment rates in different centres. The evaluation of these values is the core of the method. The aim of this paper is to make recommendations on the procedure to choose and thus to verify the consistency of the parameters taking into account what happened in the completed trial. To estimate the duration of the new trial, we need to evaluate the global recruitment rate:

$$\Lambda^n = \sum_{i \in \mathcal{C}_s^n} \lambda_i^n + \sum_{i \in \mathcal{C}_u^n} \lambda_i^n,$$

where λ_i^n denotes the recruitment rate in centre i in the new trial. This parameter is unknown at the step of the planning process, and usually, the values λ_i^n are given by the investigators of each centre. Here, the data of the completed trial can be exploited to rationally evaluate the rates for the new trial. In this section, the durations of centres initiation γ_i^n for the new trial are supposed to be given.

- For shared centres, different scenarios can be explored exploiting the information from historical trial by considering
  - Assumption S1: λ_i^n deterministic and equal to the value estimated from historical trial $\widehat{\lambda}_i^h$,
  - Assumption S2(g) (respectively Assumption S2(s)): λ_i^n distributed according to a gamma distribution of parameters $\left(\hat{\alpha}_g^h, \hat{\mu}_g^h\right)$ (respectively $\left(\hat{\alpha}_s^h, \hat{\mu}_s^h\right)$).
- For unshared centres, the issue is much more difficult. There is no information on these centres, and different assumptions have to be carried out. Each assumption can be linked with a model for the rate. Notice that it is meaningless to consider parameters specific to $\mathcal{C}_s$ because it is exactly the sub-sample we do not consider. The sub-samples of relevancy are thus $\mathcal{C}_u$ and $\mathcal{C}_g$. That explains the choice of the assumptions investigated.
  - Assumption U1(g) (respectively Assumption U1(u)): Not accounting for variability between centres. λ_i^n is chosen deterministically and equal to the average over all the values of the recruit-

ment rates of historical trial $\frac{1}{C_g^h}\sum_{k\in\mathcal{C}_g^h}\widehat{\lambda}_k^h$ (respectively the average value of the recruitment rates over the unshared centres of historical trial $\frac{1}{C_u^h}\sum_{k\in\mathcal{C}_u^h}\widehat{\lambda}_k^h$).

- Assumption U2: Accounting for variability between centres. λ_i^n is chosen randomly from a gamma distribution with parameters $\left(\hat{\alpha}_g^h, \hat{\mu}_g^h\right)$. Notice that it is relevant to make use of a gamma distribution of parameters $\left(\hat{\alpha}_u^h, \hat{\mu}_u^h\right)$, but in practice, there are not so much values, and the estimation of these parameters are poor. That explains our choice not to investigate that model.
- Assumption U3(L) (respectively Assumption U3(M), Assumption U3(H)): Accounting for variability between centres by choosing λ_i^n randomly from a gamma distribution with parameters $\left(\hat{\alpha}_g^h, \hat{\mu}_g^h\right)$ restricted to a pre-specified sub-distribution for instance $[0, q_1]$ (respectively $[q_1, q_2]$, $[q_2, +\infty]$), where q_1 and q_2 are the 1/3-fractiles. By this means, the rates are restricted to low (respectively medium and high) potential of recruitment.

The global recruitment process $X^n(t)$ for the new trial is modelled by a doubly stochastic Poisson process with random cumulative rate given by the function:

$$\Sigma^n(t) = \sum_{i\in\mathcal{C}_g^n} \lambda_i^n \max(t - \gamma_i^n, 0),$$

where the rates λ_i^n depend on the choice for the rates of shared and unshared centres.

The main criterion to compare scenarios is an error in the estimation of the expected trial duration. This duration can be computed by means of Monte Carlo simulation and by means of analytic formulae. Both computations are presented in the next discussion.

3.3.1. Monte Carlo approach. For a given scenario of the choice for the rates of shared centres and an assumption for the rates of unshared centres, perform the following algorithm:

1 Generate the values of the λ_i^ns from the distribution related to a chosen scenario.
2 Generate by means of `R` package `NHpoisson` the sample path of a non-homogeneous Poisson process X^n with rate function Σ^n. This sample path has to be generated on a bounded interval. The interval $[0, 3T^n]$ can be considered. Indeed, for realistic scenarios, the length $3T^n$ of simulated path with very high probability will cover the recruitment time.
3 Identify the simulated recruitment time $\tilde{T}^n$ as the first time such that $X^n_{\tilde{T}^n} \geq N^n$.

This algorithm is performed 5000 times, which yields to a simulated sample $\{\tilde{T}_j^n,\ j = 1, \ldots, 5000\}$ allowing the evaluation of the expected duration of the recruitment:

$$\widehat{T}^n_{\mathrm{MC}} = \frac{1}{5000}\sum_{j=1}^{5000} \tilde{T}_j^n,$$

together with its 95% confidence interval $[\tilde{T}^n_{(125)}; \tilde{T}^n_{(4875)}]$, where $\{\tilde{T}^n_{(j)},\ j = 1, \ldots, 5000\}$ is the sorted sample associated to $\{\tilde{T}_j^n,\ j = 1, \ldots, 5000\}$. The number of Monte Carlo runs (here 5000) is arbitrary but has to be sufficiently large for the results to be relevant.

3.3.2. Analytic approach. The average recruitment duration is estimated by

$$\widehat{T}^n_{\mathrm{A}} = L^n + \frac{N^n - \mathbb{E}\left[\Sigma(L^n)\right]}{\sum_{i\in\mathcal{C}_g^n}\mathbb{E}\left[\lambda_i^n\right]}, \tag{4}$$

where $L^n = \max(\gamma_i^n)$ and assuming that, for any i, γ_i^n is given. Moreover, for rather large C^n ($C^n > 10$), $[T_*(\delta, N^n), T^*(\delta, N^n)]$ can serve as a predictive $(1-\delta)$-confidence interval of T^n, where $T_*(\delta, N^n)$ (resp. $T^*(\delta, N^n)$) is a solution in the variable t of the equation

$$\mathbb{E}\left[\Sigma^n(t)\right] + z_{1-\delta/2}\sqrt{\mathbb{E}\left[\Sigma^n(t)\right] + \mathbb{V}\left[\Sigma^n(t)\right]} = N^n \qquad \left(\text{resp. } \mathbb{E}\left[\Sigma^n(t)\right] - z_{1-\delta/2}\sqrt{\mathbb{E}\Sigma^n(t) + \mathbb{V}\Sigma^n(t)} = N^n\right).$$

The proof of this statement and the expressions of $\mathbb{E}\left[\Sigma^n(t)\right]$ and $\mathbb{V}\left[\Sigma^n(t)\right]$ for each setting are relegated to the Appendix section.

3.4. Prediction of the duration of recruitment for the new trial accounting for delay in opening centres

The main issue at the designing stage comes from the opening dates of the centres (γ_i^n), which are unknown values. This is a special case of the question of break in recruitment dynamic investigated in [11]. As a consequence of the results [11], the delay in recruitment has been considered in the estimation of the recruitment rates from IFM 2005 and IFM 2009 trials; thus, delay must be considered to obtain a consistent estimation of IFM 2014 trial duration.

In order to account for delay in the recruitment, the 'uniform' strategy introduced in [7] and in [12] consists in considering γ_i^n as a random variable uniformly distributed on $[0, L^n]$, where $L^n = \max(\gamma_i^h)$, where these dates for different centres are independent. Notice that an analytic approach is considered in [7], but as both approaches provide very similar results (see results in Section 4.2), to shorten the paper, only Monte Carlo simulation is performed. For each simulation run, the opening date and the rate of each centre are randomly generated.

4. Results

In order to investigate the performance of the methods introduced in Section 3, the trial IFM 2005 is considered as the historical trial and IFM 2009 as new trial. Duration of this new trial is estimated, and this estimation is compared with the true trial duration, which is known as this trial is completed. The same strategy is applied considering IFM 2009 as the historical dataset and IFM 2005 as the new one.

4.1. Comparison of the rates

4.1.1. Frequentist approach. For predicting enrolment rates of the new trial, it can be used a natural idea: in each centre, estimate the rate in the historical trial using the frequentist approach (ratio of the number of enrolled patients to the enrolment time) and then use this estimator as the predictor of the rate in this centre for the new trial. In spite of simplicity of this approach, there are some cons.

Figure 1 is the plot of the least distance linear regression explained in Section 3.2.1. The regression equation is

$$\widehat{\lambda}_i^n = 1.36\ \widehat{\lambda}_i^h - 0.001.$$

There is rather high positive correlation between the rates for the new and historical trials. The positivity of the slope allows us to say that generally the centres, which enrol on average many patients in the first trial may also enrol many patients in the second one and vice versa. However, the comparison of the slope to 1 and the intercept to 0 is not significant. Moreover, it is easily seen on the graph that the regression is directed by the large values of the rates that are not numerous, but for small values of the rates, there is a large variation near regression line. This means, for the vast majority of centres, there is no statistically significant dependence between the rates of both trials. In addition, as we do not know the rates for the new trial, we cannot estimate the slope and intercept; thus, this is a problematic question, which regression coefficients to take for creating predictors of the new rates.

Note also that in centres that did not recruit any patients, the frequentist estimators are zeros. Nevertheless, it is clear that the predicted rates in general are not zeros. However, in large trials, the number of centres that did not recruit any patients can be rather significant (up to 20–30% in oncology trials). Therefore, using the frequentist approach in such centres will lead to underestimation of the global enrolment rate and therefore overestimation of the recruitment time. Another point is that if potentially we can use

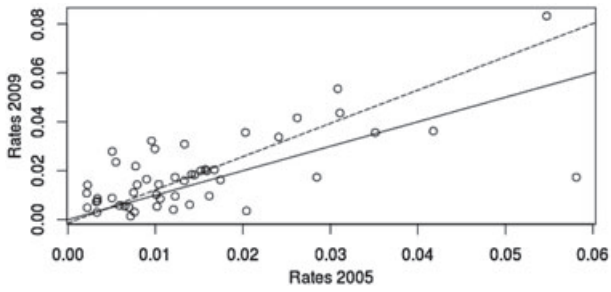

Figure 1. Rates of IFM 2009 trial as a function of rates of IFM 2005 trial. Dotted line, least distance regression line; plain line, line $y = x$.

Table II. Recruitment parameters for each category of centres.

Parameters	Historical dataset: / New dataset:	IFM 2005 / IFM 2009	IIFM 2009 / IFM 2005	*p*-value Wald's test
Global	Number of centres (new)	67	76	
	Number of centres (hist.)	76	67	
	Recruited (hist.)	611	693	
	$\frac{1}{C^h}\sum_{i=1}^{C^h}\widehat{\lambda}_i^h$	0.012	0.017	0.62
	Bounds	[0.002 ; 0.016]	[0.003 ; 0.033]	
	α_G	1.75 ± 0.71	1.99 ± 0.84	0.57
	μ_G	0.012 ± 0.027	0.017 ± 0.035	0.7
Shared	Number of centres (hist.)	50	50	
	Recruited (hist.)	543	562	
	$\frac{1}{C^{h,s}}\sum_{i=1}^{C^{h,s}}\widehat{\lambda}_i^h$	0.015	0.018	0.77
	Bounds	[0.003 ; 0.031]	[0.003 ; 0.034]	
	α_S	2.15 ± 1.02	2.15 ± 1.03	0.7
	μ_S	0.015 ± 0.038	0.017 ± 0.042	0.85
Unshared	Number of centres (hist.)	26	17	
	Recruited (hist.)	68	131	
	$\frac{1}{C^{h,u}}\sum_{i=1}^{C^{h,u}}\widehat{\lambda}_i^h$	0.005	0.013	0.46
	Bounds	[0.002 ; 0.009]	[0.002 ; 0.023]	

Bounds denote the 84% empirical quantiles (which corresponds more or less to a standard deviation) of the historical rates. Parameters of the gamma distribution for the new trial estimated from the historical data are explicited on the format (mean ± standard deviation). The third column considers IFM 2005 as historical data; the fourth column considers IFM 2009 as historical data. The last column is the *p*-value of Wald's test between both trials.
IFM, Intergroupe Francophone du Myélome.

this approach in the shared centres, the main question would be: which values to plug-in for the rates in the unshared centres as there are no historical data? These cons show that using the frequentist approach may not be a relevant strategy.

Therefore, we consider another population approach, which is based on the idea to use for the population of the rates in the new trial the parameters of a Poisson–gamma model estimated from the historical trial.

4.1.2. Population approach. The results of the estimation of the parameters of the Poisson–gamma model are collected in Table II. In order to facilitate the comparisons, Table II is completed by the mean values of historical rates as well as the empirical 84% quantiles (which corresponds more or less to a standard deviation) of these rates for each category of centres. It is important to notice that the historical means coincide with the estimated values of μ for each category; however, a Poisson–gamma model accounts for the variability in the rates.

Note that if to consider all centres or only shared centres, the 95% confidence intervals for parameters (α_s, μ_s) are very similar for IFM 2005 and IFM 2009. In order to complete this analysis, Figure 2 represents ellipses that are the plots of the 95% confidence region of the pairs of parameters given by Eqn 3. The parameters of the gamma distribution are heavily correlated; it is a well-known fact evoked in [5]. The ellipses overlap; this means that the parameters are very close. This overlap is more important for the shared parameters rather than the global parameters. This is coherent with our hypothesis: for the shared centres, the rates have practically the same distribution in both trials.

Considering the unshared centres, the behaviour is really different between 2005 and 2009. This can be explained by the choice of the centres. The centres with very low enrolment in the IFM 2005 trial were not transplant centres, and therefore, they could not be opened for the IFM 2009 trial. They are replaced by other centres without a priori on these recruitment rates. Thus, the values of the rates of centres unshared of 2009 trial are chosen without any assumption. The rates can be modelled by a standard gamma distribution fitted from the data. On the contrary, the centres unshared of 2005 are the ones taken off in 2009. For these centres, the rate cannot be modelled by a gamma distribution but by sub-distributions of the gamma distribution of the rates. For example, considering three classes, low/medium/high recruitment's

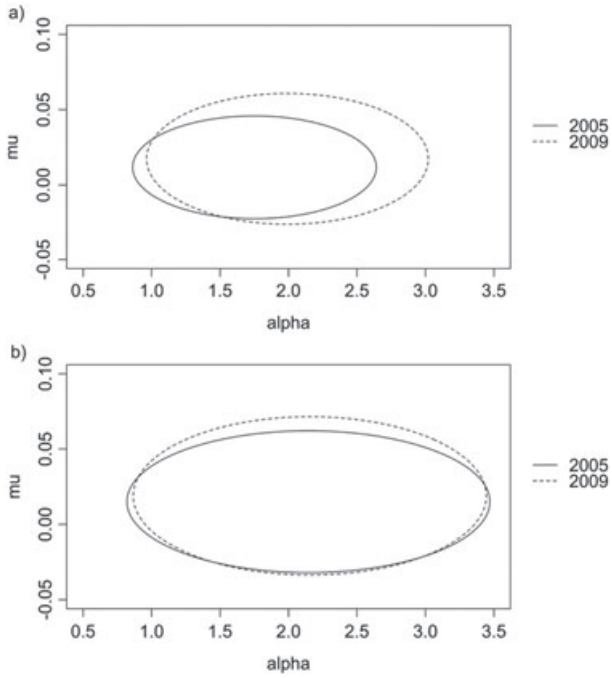

Figure 2. Plots of the 95% confidence regions for (α, μ). Sub-figure (a) global parameters, all centres are involved. Sub-figure (b) shared parameters, only shared centres are involved.

potential as for Assumptions U3(L), U3(M) and U3(H). Using the data from the unshared centres is so dependent on the assumptions made on these centres; thus, it is better not to use these data.

In order to validate these conclusions, Wald' tests are performed for each pair of parameters between the two studies $(\alpha_{X,2005}, \alpha_{X,2009})$, $(\lambda_{X,2005}, \lambda_{X,2009})$, $(\mu_{X,2005}, \mu_{X,2009})$ $X = G, S$, considering the asymptotic Gaussian distributions of the parameters. None of these comparisons are significant (Table II).

In conclusion, results of Section 4.1.1 indicate that plugging the historical rates into the new trial model is not convincing because these rates may be not the same. On the contrary, results of Section 4.1.2 allow us to say that the parameters of the distribution of the rates are not significantly different. That advocates in favour of the population approach.

4.2. Prediction performances

It is important to notice that in this particular setting, the γ_i^n are observed for any i. This parameter has to be taken into consideration in order to be able to reach the true duration of the trial.

The results of the previous section encourage us to use the population approach and a Poisson–gamma model rather than to plug the historical rates for centres in the new trial. To provide the argumentation for this hypothesis, the performance of the model in terms of prediction of the recruitment time is evaluated. The results obtained by both Monte Carlo and analytic approaches are collected in Table III. This table presents the different scenarios investigated depending on the assumption made for the unshared parameters. For each scenario, three sub-scenarios are investigated depending on the choice for the rates of shared parameters: deterministic by plugging in the historical rate for each centre and random by considering the rate for each centre is a random variable $\mathrm{Ga}\left(\alpha_g^h, \mu_g^h\right)$-distributed and $\mathrm{Ga}\left(\alpha_s^h, \mu_s^h\right)$-distributed.

The expected duration together with its 95% confidence interval is estimated, and as the true duration of recruitment for the trial IFM 2009 is known, $\mathrm{T}^n = 746$ days, the performances of the prediction can be assessed by means of the relative error of prediction defined as

$$\widehat{\mathrm{RE}}_{\mathrm{MC}}^n = \frac{|\hat{T}_{\mathrm{MC}}^n - T^n|}{T^n} \qquad \text{resp.} \quad \widehat{\mathrm{RE}}_{\mathrm{A}}^n = \frac{|\hat{T}_{\mathrm{A}}^n - T^n|}{T^n}.$$

Figure 3 is a graphical summary of Table III and represents the 95% confidence interval for each scenario. Sub-plots are created for two different methods of computation (Monte Carlo on the top and Analytic on the bottom). The horizontal line characterizes the true duration time.

Table III. Expected duration of IFM 2009 using data of IFM 2005 trial for different assumptions on the unshared centres and different choices for shared centres. The real duration of the recruitment is $T^n = 746$ days.

Unshared	Shared	Monte Carlo approach			Analytic approach		
assumption	choice	Exp. Dur.	Standard deviation	Rel. Error	Exp. Dur.	Standard deviation	Rel. Error
	S1	915.62	29.81	0.23	881.24	28.31	0.18
U1(g)	S2(g)	1066.11	81.87	0.43	1046.39	81.35	0.40
	S2(s)	911.08	63.67	0.22	891.70	64.86	0.20
	S1	1019.02	33.27	0.37	980.33	32.07	0.31
U1(u)	S2(g)	1226.97	112.25	0.64	1194.61	108.40	0.60
	S2(s)	1017.32	80.43	0.36	990.32	81.66	0.33
	S1	913.39	42.02	0.22	876.82	40.83	0.18
U2	S2(g)	1062.97	99.82	0.42	1039.96	92.05	0.39
	S2(s)	906.39	66.92	0.21	887.29	71.17	0.19
	S1	1046.62	34.68	0.40	1001.70	33.77	0.34
U3(L)	S2(g)	1266.75	119.22	0.70	1227.61	115.76	0.65
	S2(s)	1035.85	84.44	0.39	1011.54	85.95	0.36
	S1	946.19	28.48	0.27	904.44	30.00	0.21
U3(M)	S2(g)	1106.62	85.01	0.48	1080.40	87.81	0.44
	S2(s)	943.10	64.90	0.26	914.82	68.98	0.23
	S1	785.55	23.45	0.05	763.80	30.61	0.02
U3(H)	S2(g)	898.92	55.91	0.20	880.28	62.47	0.18
	S2(s)	774.92	45.75	0.04	774.25	51.71	0.04

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First of all, notice that whatever the model chosen, the duration of trial is overestimated. That is not surprising. The clinical teams are mainly the same as type of studies is the same, so with time, they gain experience and improve the quality of recruitment. That phenomenon is called learning effect in the sequel. Notice that the results computed using Monte Carlo simulation and closed-form analytic expressions are, as expected, very close.

It is of a paramount interest to notice that whatever the assumption for unshared centres considered, the scenario with smaller relative error is the one involving the parameters estimated from the historical shared centres. The difference between S1 and S2(s) is not so large. That is not surprising because both these models have the same average rate. However, the 95% confidence interval is wider because of randomness in the recruitment rates, and this is on the benefit of Poisson model as pointed out by Senn [1]. Indeed, in this setting, to reach the smallest confidence interval is not an objective. The purpose is to offer an approximation along with its confidence interval, which we hope can cover the true value. Small confidence interval limitates this assumption and does not overcome the embedded bias. In practice, such small confidence interval may be unrealistic [1]. The more realistic choice for shared parameter is thus S2(s).

Putting a side the models involving the restricted rates (U3(L), U3(M) and U3(H)), given the model for shared centres, the more realistic assumptions for unshared centres are U1(g) and U2. The average duration is closest to the true duration. Finally, exactly for the same reason as previously explained, one prefers Scenario U2. Notice that the overdispersion due to the gamma distribution is less important than for the shared parameters. That explains by the large proportion of shared centres. These results confirm the hypothesis we advocate for. Notice that U1(u) involving parameters of the unshared centres yields to the worse estimated duration and confirm the idea not to take these data into account specifically but only by means of the global parameters.

The results involving models with the restricted rates (U3(L), U3(M) and U3(H)) indicate that Assumption U3(H) yields to the smaller relative error. That can be explained by the fact that considering centres with high potential of recruitment balanced the bias due to the learning effect. The results obtained with these three assumptions highlight the link between the assumption on the rates and the expected recruitment duration.

To conclude, the results of Table III advocate for the use of model S2(s) for the shared centres and the relevancy of Assumption U2 and its restrictions (U3(L), U3(M) and U3(H)) for the unshared centres.

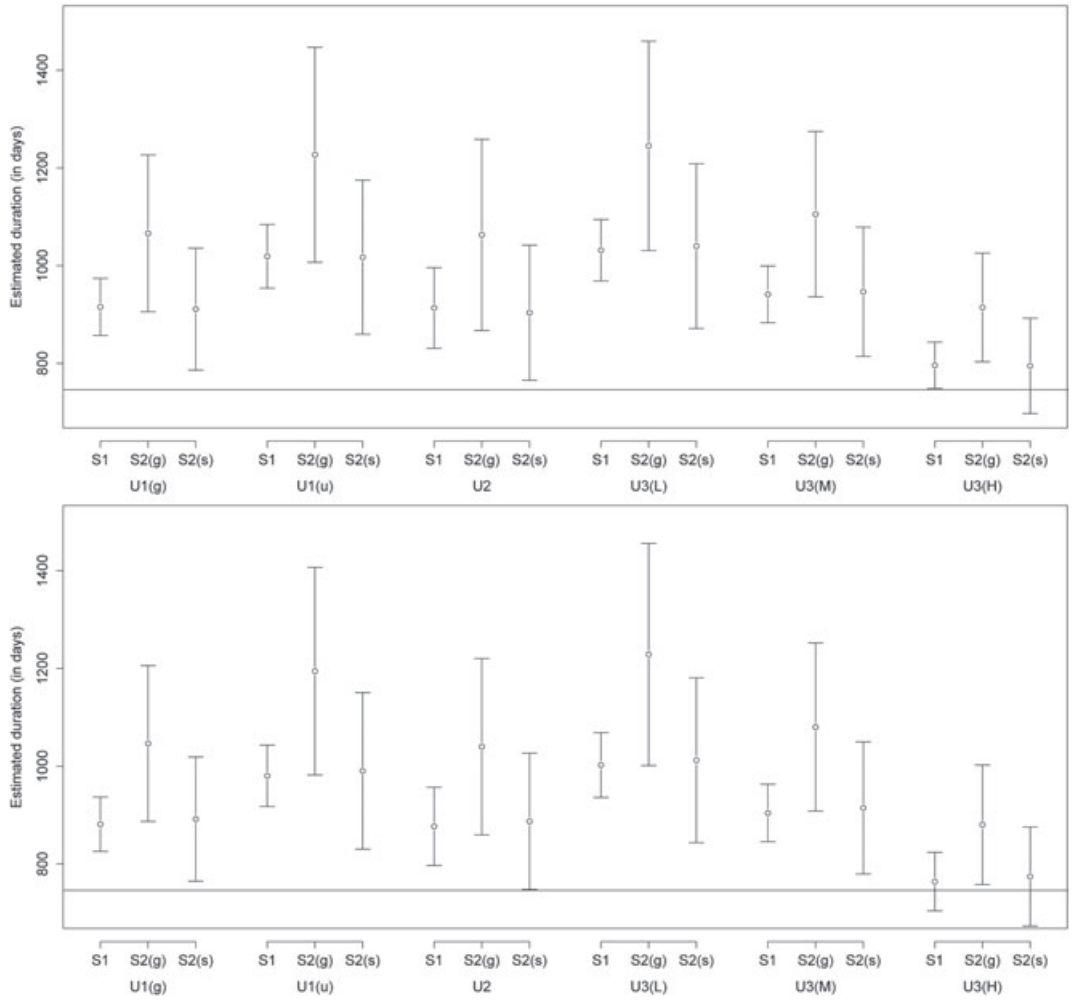

Figure 3. Plots of 95% confidence intervals of the estimation of IFM 2009 trial duration based on IFM 2005 trial data. Sub-plot on the top corresponds to Monte Carlo method, and sub-plot on the bottom corresponds to analytic method. Solid horizontal line is the real duration of IFM 2009 trial.

5. Recommendations and illustrative example: Feasibility of IFM 2014 trial

5.1. Recommendations

Here, we provide some recommendations using the results of the previous sections. First of all, the methodology presented here is only available when the completed trial is similar to the designed trials by therapeutic area, inclusion/exclusion criteria, similar patient's cohorts and regions for recruitment. The results highlight the use of Poisson–gamma modelling to evaluate the feasibility of a new trial. The modelling is different considering the shared centres and the unshared centres. An important point is that the relevancy of the method increases with the proportion of shared centres.

- For the shared centres, one suggests to model the rates using i.i.d. random variables having a gamma distribution where the parameters are those estimated from the historical recruitment data of the shared centres.
- For the unshared centres, one suggests to model the rates using i.i.d. random variables having a gamma distribution where the parameters are those estimated from the historical recruitment data of all centres. Different scenarios can be considered accounting for the recruitment rates given by investigators.

Finally, modelling of the dates of centres initiation has to be taken into account. Results of [7] and [12] encourages us to use the 'uniform' strategy.

5.2. *Illustrative example: Feasibility of IFM 2014 trial*

The proposed methodology is applied to estimate the duration of recruitment in IFM 2014 trial. The expected duration of recruitment is $T^n = 730$ days. The context of this clinical trial is summarized in Section 2, and information about the centres is presented in Table I. The estimation of the trial duration is made using IFM 2009 data. Using IFM 2005 data is not relevant because of the training's effect of the clinical teams and because targeted population for IFM 2014 is closer to the one of IFM 2009 rather than IFM 2005. Table IV presents the estimated values of the rates from the historical database.

IFM 2014 is still recruiting patients. The opening dates are not used for the prediction of the duration of recruitment. This issue has been discussed in Section 3.4, and the 'uniform' strategy has been introduced. The results are illustrated in Figure 4, which is the plot of these predictions together with 95% confidence intervals. Figure 4 is enriched with the plot of the 95% confidence interval [526–1145] (E-G) given by the online program [13] based on an Poisson-exponential model [14]. This is a particular case of the Poisson–gamma model when only one centre is involved. Because of the assumptions involved for this model (one centre, no delays in centre initiation and no use of historical data), these results can be seen as a reference to emphasize the improvement of our method.

As usual, Assumptions U1(g) and U2 exhibit close expected duration as well as the standard deviation. That last point is due to small proportion of unshared centres. Finally, it is of interest to notice that results for Assumptions U2, U3(L) and U3(M) are not so different, whereas result for Assumption U3(H) is really smaller; this indicates the importance of centres with large recruitment rate.

A discussion with the clinical team encourages us consider Assumption U3(M) for the unshared centres (centres with a medium potential of recruitment). The Monte Carlo simulation allows us to claim that the expected duration of the trials is 577 days and the 95% confidence interval of prediction of the expected duration of [505;650] days.

Table IV. Recruitment parameters for each category of centres.

Parameters	Historical dataset: New dataset:	IFM 2009 IFM 2014
Global	Number of centres (new)	47
	Number of centres (hist.)	67
	Recruited (hist.)	693
	$\frac{1}{C^h}\sum_{i=1}^{C^h}\widehat{\lambda}_i^h$	0.016
	Bounds	[0.003 ; 0.033]
	α_G	1.99 ± 0.84
	μ_G	0.017 ± 0.035
Shared	Number of centres (hist.)	41
	Recruited (hist.)	534
	$\frac{1}{C^{h,s}}\sum_{i=1}^{C^{h,s}}\widehat{\lambda}_i^h$	0.021
	Bounds	[0.002 ; 0.038]
	α_S	2.31 ± 1.25
	μ_S	0.022 ± 0.050
Unshared	Number of centres (hist.)	6
	Recruited (hist.)	159
	$\frac{1}{C^{h,u}}\sum_{i=1}^{C^{h,u}}\widehat{\lambda}_i^h$	0.011
	Bounds	[0.003 ; 0.020]
	α_U	3.45 ± 1.96
	μ_U	0.014 ± 0.047
1/3-fractiles	q_1	0.0103
	q_2	0.0198

Bounds denote the 84% empirical quantiles (which corresponds more or less to a standard deviation) of the historical rates. Parameters of the gamma distribution for the new trial estimated from the historical data are explicited on the format (mean ± standard deviation).
IFM, Intergroupe Francophone du Myélome.

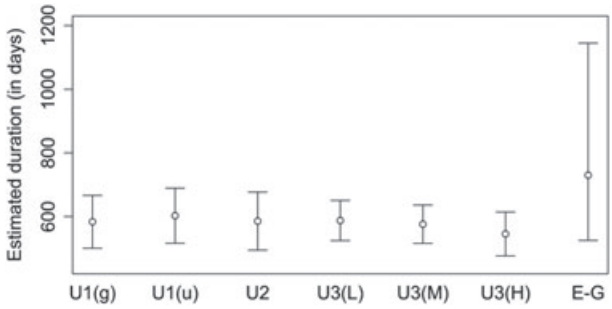

Figure 4. Plots of the 95% confidence intervals of the estimation of IFM 2014 trial duration based on IFM 2009 trial data.

At the time of the writing of this manuscript, 20 patients are still to be included in the IFM 2014 study. The elapsed duration of recruitment for 280 patients is 560 days. Our strategy for modelling duration of recruitment process using historical trials seems appropriate.

6. Conclusions

In the framework of a feasibility study of a clinical trial, this paper advocates in favour of the use of a Poisson–gamma model for estimating the duration of the recruitment basing on parameters estimated from recruitment data of a historical completed trial. Indeed, this approach provides more relevant results compared with plugging historical rates in the recruitment model of the new trial. The estimation of the expected duration using a Poisson–gamma model is at least as good as the one using historical rates, and the randomness generated by considering random rates yields to larger confidence intervals and thus to more realistic conclusions on the estimated duration of the trial.

Section 5.2 illustrates how to deal with this tool to estimate the duration of a clinical trial at the designing stage. Two strategies of computation (analytic and Monte Carlo) are introduced and both yield to relevant and similar results. The benefit is –of course– the computation of confidence intervals of this duration, which is of a major practical interest for trials.

It is also important to notice that the performance of the Poisson–gamma model increases with the proportion of patients recruited by the shared centres. Indeed, the quality of the estimation of the rate of the shared and all centres increases with that proportion of shared parameters. This is a point of paramount interest because in practice, the centres that are reappointed for a new trial are the ones that exhibits good recruitment rates.

The recommendations stated in Section 5.1 propose a relevant methodology to make use of data of a completed trial, similar to the trial one aims to design by therapeutic area, inclusion/exclusion criteria, similar patient's cohorts and regions for recruitment, in order to estimate the trial duration.

Appendix A: Fisher information matrix

The Fisher information matrix $\mathrm{J}_i^h(\alpha^h, \mu^h)$ for a centre i comes from the second derivatives of the log-likelihood function given by (2) and takes the form:

$$\begin{pmatrix} \left(\mathrm{J}_i^h\right)_{11} & \left(\mathrm{J}_i^h\right)_{12} \\ \left(\mathrm{J}_i^h\right)_{21} & \left(\mathrm{J}_i^h\right)_{22} \end{pmatrix},$$

with

$$\left(\mathrm{J}_i^h\right)_{11} = \psi^{(1)}(\alpha^h) - \mathbb{E}_{(\alpha^h,\mu^h)}[\psi^{(1)}(\alpha^h + n_i^h)] - \frac{\mu^h \tau_i^h}{\alpha^h(\alpha^h + \mu^h \tau_i^h)},$$

$$\left(\mathrm{J}_i^h\right)_{21} = \left(\mathrm{J}_i^h\right)_{12} = \mathbb{E}_{(\alpha^h,\mu^h)}\left[\frac{\mu^h(\tau_i^h)^2 - n_i^h \tau_i^h}{(\alpha^h + \mu^h \tau_i^h)^2}\right],$$

$$\left(\mathrm{J}_i^h\right)_{22} = \frac{\alpha^h \tau_i^h}{\mu^h(\alpha^h + \mu^h \tau_i^h)},$$

where $\psi^{(1)}$ is the trigamma function defined for any $x > 0$ by

$$\psi^{(1)}(x) = \frac{d^2}{dx^2}\ln(\Gamma(x)).$$

Now, as $\mathbb{E}_{(\alpha^h,\mu^h)}\left[n_i^h\right] = \mu^h \tau_i^h$, we have

$$\left(\mathrm{J}_i^h\right)_{21} = \left(\mathrm{J}_i^h\right)_{12} = \mathbb{E}_{(\alpha^h,\mu^h)}\left[\frac{\mu^h(\tau_i^h)^2 - n_i^h \tau_i^h}{(\alpha^h + \mu^h \tau_i^h)^2}\right] = \frac{\mu^h(\tau_i^h)^2 - \mathbb{E}_{(\alpha^h,\mu^h)}\left[n_i^h\right]\tau_i^h}{(\alpha^h + \mu^h \tau_i^h)^2} = 0.$$

See [7, 12] for a rigourous proof of existence.

Proof of the analytic estimation (4) of the average recruitment duration

Assume that $\mathbb{E}\left[\Sigma(L^n)\right] \ll N^n$. It is a well-known fact that for a doubly stochastic Poisson process with rate $\Sigma^n(t)$, for any $t > 0$,

$$\mathbb{E}\left[X^n(t)\right] = \mathbb{E}\left[\Sigma^n(t)\right] \quad \text{and} \quad \mathbb{V}\left[X^n(t)\right] = \mathbb{E}\left[\Sigma^n(t)\right] + \mathbb{V}\left[\Sigma^n(t)\right].$$

Moreover, for $t > L$, the cumulative rate is

$$\Sigma^n(t) = \Sigma^n(L^n) + (t - L^n)\sum_{i \in \mathcal{C}_g^n} \lambda_i^n.$$

Thus,

$$\mathbb{E}\left[X(t)\right] = \mathbb{E}\left[\Sigma^n(L^n)\right] + (t - L^n)\sum_{i \in \mathcal{C}_g^n} \mathbb{E}\left[\lambda_i^n\right].$$

The average recruitment duration is approximately the time such that $\mathbb{E}\left[X(T^n)\right] = N^n$, and thus, it is approximated by (4). The $(1-\delta)$-predictive interval for recruitment time is calculated following lemma 2.1 of [6], noticing that there is no interim time of analysis ($t_0 = 0$) in our setting.

Expressions of $\mathbb{E}\left[\Sigma^n(L^n)\right]$ *and* $\mathbb{V}\left[\Sigma^n(t)\right]$ *for each scenario*

To compute the expected duration and its $(1-\delta)$-predictive interval, we can use a normal approximation and compute $\mathbb{E}\left[\lambda_i^n\right]$, $[\mathbb{E}\Sigma^n(t)]$ and $[\mathbb{V}\Sigma^n(t)]$. Independence of the rates' distributions allows us to split the expressions of the mean and of the variance in two terms corresponding to the rates of shared and unshared centres and to write

$$\mathbb{E}\left[\Sigma^n(t)\right] := M_s(t) + M_u(t) \qquad \text{and} \qquad \mathbb{V}\left[\Sigma^n(t)\right] := V_s(t) + V_u(t).$$

These values depend on a particular choice as the distribution of the (λ_i^n)s depends on the assumption. In calculations, we use the fact that for a $\mathrm{Ga}(\alpha, \mu)$-distributed random variable G, $\mathbb{E}G = \mu$ and $\mathbb{V}G = \mu^2/\alpha$. Given $q_1 > 0$ and $q_2 > 0$, denote $p_{1,2} = \int_{q_1}^{q_2} f(x; \{\alpha, \mu\})\, dx$, where f is defined by (1), the mean and variance of the distribution of G restricted to the values between q_1 and q_2 express as

$$\mu_r = \frac{1}{p_{1,2}}\int_{q_1}^{q_2} x f(x; \{\alpha, \mu\})\, dx \qquad \text{and} \qquad \sigma_r^2 = \frac{1}{p_{1,2}}\int_{q_1}^{q_2} (x - \mu_r)^2 f(x; \{\alpha, \mu\})\, dx.$$

Considering these notations related to the gamma distribution of interest estimated from the historical trial, the results for the different choices of distribution are, for any $t > L$, as follows:

- For the shared centres, under Assumption S1,

$$M_s(t) = \sum_{i \in \mathcal{C}_s^n} \widehat{\lambda}_i^h (t - \gamma_i^n) \qquad \text{and} \qquad V_s(t) = 0$$

and under Assumptions S2,

$$M_s(t) = \mu^h \sum_{i \in \mathcal{C}_s^n} (t - \gamma_i^n) \qquad \text{and} \qquad V_s(t) = \frac{(\mu^h)^2}{\alpha^h} \sum_{i \in \mathcal{C}_s^n} (t - \gamma_i^n)^2.$$

- For the unshared centres, under Assumptions U1,

$$M_u(t) = \frac{1}{C_u^h} \sum_{k \in \mathcal{C}_u^h} \widehat{\lambda}_k^h \sum_{i \in \mathcal{C}_u^n} (t - \gamma_i^n) \qquad \text{and} \qquad V_u(t) = 0,$$

under Assumption U2,

$$M_u(t) = \mu^h \sum_{i \in \mathcal{C}_u^n} (t - \gamma_i^n) \qquad \text{and} \qquad V_u(t) = \frac{(\mu^h)^2}{\alpha^h} \sum_{i \in \mathcal{C}_u^n} (t - \gamma_i^n)^2,$$

and under Assumptions U3,

$$M_u(t) = \mu_r^h \sum_{i \in \mathcal{C}_u^n} (t - \gamma_i^n) \qquad \text{and} \qquad V_u(t) = (\sigma_r^h)^2 \sum_{i \in \mathcal{C}_u^n} (t - \gamma_i^n)^2.$$

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