# Recruitment to Phase III Clinical Trials

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## 1. Background

Clinical trials aim to evaluate the effectiveness of one, or more, forms of treatment. Failure to achieve the recruitment target in the given time period results in increased running costs, and failure to recruit enough patients results in the test having insufficient power.

Kasenda et al. (2014) found that out of 1017 trials that they studied, 24.9% of trials were discontinued and 39.9% of these were discontinued due to poor recruitment.

## 2. The Model

- $C$ - number of centres,
- $\tau_c$ - the number of days centre $c$ is open for,
- $N_c^{(t)}$ - number of arrivals in centre $c$ on day $t$,
- $N_c$ - number of arrivals in centre $c$ over the whole time period,
- $\lambda_c^0$ - rate of arrivals in centre $c$,
- $g_c(s;\theta)$ - curve shape.

Arrival to centre $c$ on given day $t$ is modelled using as a Poisson Process.

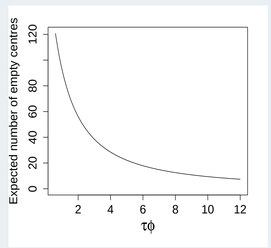
$$N_c^{(t)}|\lambda_c^0 \sim \text{Pois}\left(\lambda_c^0 \int_{t-1}^{t} g_c(s;\theta)\, \text{d}s\right), \quad \text{where} \quad \lambda_c^0 \sim \text{Gamma}\left(\alpha, \alpha/\phi\right).$$

## 3. Constant Rate of Arrivals

If the rate of arrivals remains constant with time, we have a homogeneous Poisson process with $g_c(s) = 1$. The model becomes

$$N_c|\lambda_c^0 \sim \text{Pois}\left(\lambda_c^0 \tau_c\right).$$

For $\tau\phi \in (0, 12]$, the expected number of empty centres gets close to, but does not reach zero. Therefore, it is reasonable to assume that a substantial number of centres will be empty.




## 4. Parameter Estimation

The probability of a centre having $n_c$ recruits is

$$\mathbb{P}\left(N_c = n_c|\alpha,\phi\right) = \frac{\Gamma\left(\alpha + n_c\right)}{\Gamma(\alpha) n_c!}\left(\frac{\alpha}{\tau\phi+\alpha}\right)^{\alpha}\left(\frac{\tau\phi}{\tau\phi+\alpha}\right)^{n_c}.$$

By taking the product over all centres we can find the log-likelihood. We can then use this to find the profile log-likelihood for $\alpha$ in order to find a maximum likelihood estimate for $\alpha$, $\hat{\alpha}$ where

$$\hat{\phi} = \frac{n_\Sigma}{\tau C} \quad \text{and} \quad n_\Sigma = \sum_{c=1}^{C} n_c.$$

## 5. Bias of the Estimators

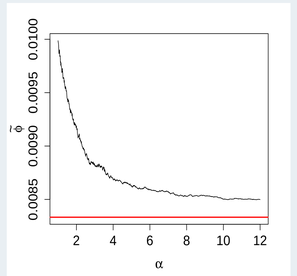
Anisimov and Federov (2007) assumes that the empty centres do not have an effect on the parameter estimation.

Define:

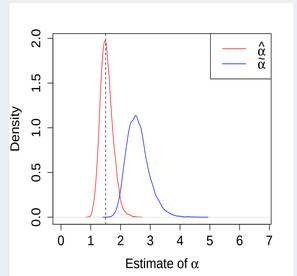
- $N_c^+$ - total number of recruits in the non-empty centres,
- $C^+$ - number of non-empty centres,
- $N_\Sigma^+$ - total number of recruits across all centres.

The truncated estimate of $\phi$, $\tilde{\phi}$, and its bias are

$$\tilde{\phi} = \frac{n_\Sigma^+}{\tau C^+} \qquad \mathbb{E}[\tilde{\phi}] - \phi = \frac{\phi\alpha^\alpha}{(\tau\phi+\alpha)^\alpha - \alpha^\alpha}.$$




(a) How $\tilde{\phi}$ varies with $\alpha$.




(b) Estimates of $\hat{\alpha}$ and $\tilde{\alpha}$.

The bias of $\tilde{\phi}$ decreases as $\alpha$ increases, but in practice, $\alpha$ usually lies between 1 and 3. This is demonstrated in the plot above which shows that $\tilde{\phi}$ gets closer to the true $\phi$ value (indicated by the red line) as $\alpha$ increases.

The bias of $\tilde{\phi}$ affects the estimate of $\alpha$ when the profile log-likelihood is maximised numerically. The plot above illustrates this when $C = 200$, $\alpha = 1.5$, $\tau = 600$ and $\phi = 1/120$. The MLE estimate for $\alpha$ when we use $\hat{\phi}$ is $\hat{\alpha}$ and the MLE for $\alpha$ when we use the truncated estimate $\tilde{\phi}$ is $\tilde{\alpha}$.

## 6. The Adapted Model

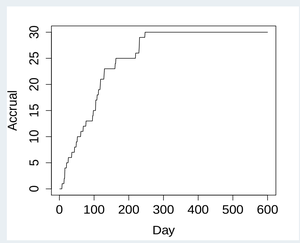
In reality, some centres will have a decaying rate of arrivals. We can model these with intensity function

$$g_\infty(s;\theta) = \frac{\tau\theta\exp(-\theta s)}{1-\exp(-\theta\tau)}.$$

When we have a combination of constant recruitment intensity and decaying recruitment intensity, we set

$$g = \begin{cases} 1 & \text{with probability } \eta_0 \\ g_\infty & \text{with probability } \eta_\infty. \end{cases}$$

To extend this model further, we could look at a combination of multiple different decaying intensities.




## 7. Identifying Decaying Centres

When there are two rates of recruitment, the probability of one centre having $\mathbf{n}_c$ recruits is

$$\frac{\Gamma\left(\alpha+n_c\right)}{\Gamma(\alpha)\prod_{t=1}^{\tau_c} n_c^{(t)}!}\left(\frac{\alpha/\phi}{\tau_c+\alpha/\phi}\right)^{\alpha}\left(\frac{1}{\tau_c\phi+\alpha/\phi}\right)^{n_c}\left[\sum_i \eta_i \prod_{t=1}^{\tau_c}\int_{t-1}^{t} g_i(s;\theta)\, \text{d}s\right].$$

We can categorise the centres into the two types as follows:

- Calculate the log-likelihood by taking the product over the number of days and number of centres and marginalising with respect to $g_i$.
- Optimise the log-likelihood to find MLE estimates for $\alpha$, $\phi$, $\theta$, and $\eta_0$.
- Use Bayes Rule to calculate $\mathbb{P}(g_c = g_i|\mathbf{n}_c)$.

$$\mathbb{P}(g_c = g_i|\mathbf{n}_c) = \frac{\mathbb{P}(\mathbf{N}_c = \mathbf{n}_c|g_i)\mathbb{P}(g_i)}{\sum_k \mathbb{P}(\mathbf{N}_c = \mathbf{n}_c|g_k)\mathbb{P}(g_k)}.$$

- Assign the centre to the recruitment type with the highest probability.

The plot below shows how many correct classifications are being made as $\tau$ varies for two different $\phi$ values where $\alpha = 1.5$, $\theta = 0.01$, $\eta_0 = 0.5$ and $C = 200$.

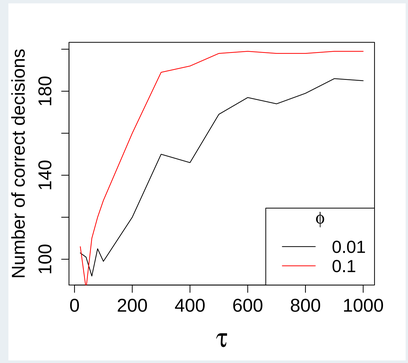



Figure 1: Number of correct classifications against study length.

For shorter recruitment periods, the plot above shows that this method of classification does not work well. Also, a lower $\phi$ value means that the number of correct classifications is lower.

To continue this work further, it would be interesting to consider what occurs when we have $\eta_0$ close to 0 or 1.

## 8. References

- Anisimov, V. V. and Fedorov, V. V. (2007).
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  *Statistics in Medicine, 26(27):4958-4975.*
- Kasenda, B. et al. (2014).
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  *JAMA, 311(10):1045-1052.*



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