

**Frequentists and Bayesian methods to incorporate
recruitment rate stochasticity
at the design stage of a clinical trial**

Master Thesis in Biostatistics (STA495)

by

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Preface

Howdy!

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Chapter 1

Introduction

Why, what and how...

Chapter 2

Methodology

2.1 Definitions

The **Target Population** is a specific group within the broader population, defined by attributes relevant to the research question. This group is focused on criteria that match the study's goals (Willie, 2024). Defining the target population allows researchers to refine their objectives and recruitment methods to align with the study's aims.

The **Eligibility** criteria are the specific requirements that individuals must meet to participate in a study. Eligible patients will be selected from the target population. Inclusion criteria specify the conditions that allow individuals to participate in the trial, particularly focusing on the medical condition of interest. Any other factors that limit eligibility are classified as exclusion criteria (Van Spall *et al.*, 2007), conditions or circumstances that disqualify potential participants (Food *et al.*, 2018).

In clinical trials, **Enrollment** refers to the formal process of registering participants into a study after they have met all eligibility criteria and provided informed consent. This process includes verifying that each participant satisfies the inclusion and exclusion criteria outlined in the study protocol (National Institute of Allergy and Infectious Diseases, 2021). It is important to distinguish between recruitment and enrollment. Recruitment involves identifying and inviting potential participants to join the study, whereas enrollment occurs after these individuals have been screened, consented, and officially registered into the trial (Frank, 2004).

Once enrolled, participants are assigned to specific treatment groups or interventions as defined by the study design. The most common practice is **Randomization**. In clinical research, randomization is the process of assigning participants to different treatment groups using chance methods, such as random number generators or coin flips (Lim and In, 2019). Randomized controlled trials (RCTs) are considered the most effective method for preventing bias in the evaluation of new interventions, drugs, or devices. (Van Spall *et al.*, 2007).

In clinical research, **Statistical Analysis** involves applying statistical methods to collect, summarize, interpret, and present data derived from clinical studies. This process is essential for evaluating the safety, efficacy, and overall outcomes of medical interventions, ensuring that conclusions drawn are both reliable and valid (Panos and Boeckler, 2023). Not all participants who are randomized may be included in the final statistical analysis due to protocol deviations of patients not adhering to the protocol (Rehman *et al.*, 2020), missing data (Shih, 2002) or loss-to-follow-up, some participants may become unreachable or withdraw consent during the study, resulting in missing outcome data (Nüesch *et al.*, 2009).

The number of patients decreases at each stage of a clinical study, from defining the target population to final statistical analysis, see Figure 2.1. Eligibility criteria narrow down participants, and enrollment further reduces numbers as only those meeting strict criteria are registered. Randomization assigns individuals to treatment groups, but some may later be excluded due to protocol deviations, missing data, or loss to follow-up.

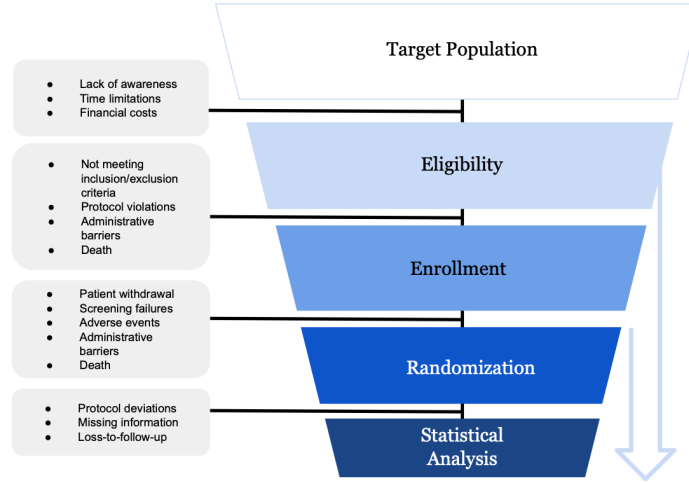


Figure 2.1: Patient Attrition at Each Stage of a Clinical Study. (Piantadosi and Meinert, 2022; Whelan *et al.*, 2018; Bogin, 2022)

The general notion of **Recruitment** in this Master Thesis refers to the number of patients (Counts) at the Eligibility, or Enrollment, or Randomization, or Statistical Analysis stage in Figure 2.1. We define **Accrual** as cumulative recruitment.

2.2 Uncertainty and models for counts

Let us define **Aleatory Uncertainty** as that which can be characterised by randomness. It is inherent, irreducible and unpredictable in nature. Whereas **Epistemic Uncertainty** arises primarily from limited or imperfect knowledge and can be reducible by obtaining more or better information.

Let us denote

- $T = \text{time}$
- $C = \text{counts}$
- $\lambda = \frac{C}{T}$

Methods	Counts	Expectation	Variance	Aleatory	Epistemic
Expectation	$C = \lambda t$	λt	0	No	No
Poisson	$C \sim \text{Po}(\lambda t)$	λt	λt	Yes	No
Negative Binomial	$C \sim \text{Po}(\Lambda t); \Lambda \sim G(\alpha, \beta)$	$\frac{\alpha}{\beta}$	$\frac{\alpha(\beta+1)}{\beta^2}$	Yes	Yes

Table 2.1: Aleatory and epistemic uncertainty in accrual shown by different models for counts.

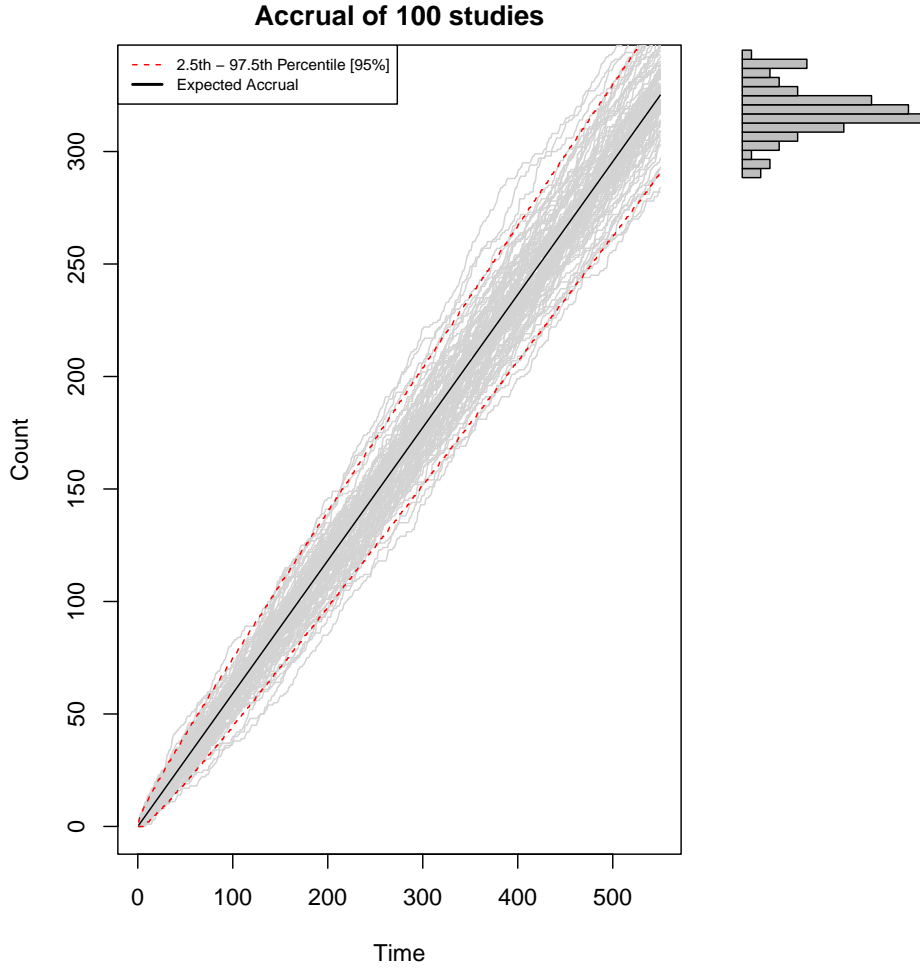


Figure 2.2: Poisson-distributed counts with $\lambda = 0.591$ over time and uncertainty range. The black line represents the point estimate of the expected accrual, while the red dashed lines indicate Poisson's 95% aleatory uncertainty. The histogram illustrates the distribution of observed counts at time $T = 550$ ([Spiegelhalter *et al.*, 2011](#)).

2.3 Counts: Model based on Expectations

2.3.1 Expected recruitment in one unit of time

2.3.2 Expected accrual at time point t

2.4 Counts: Model based on Poisson Process

2.4.1 Recruitment in one unit of time

2.4.2 Accrual at time point t

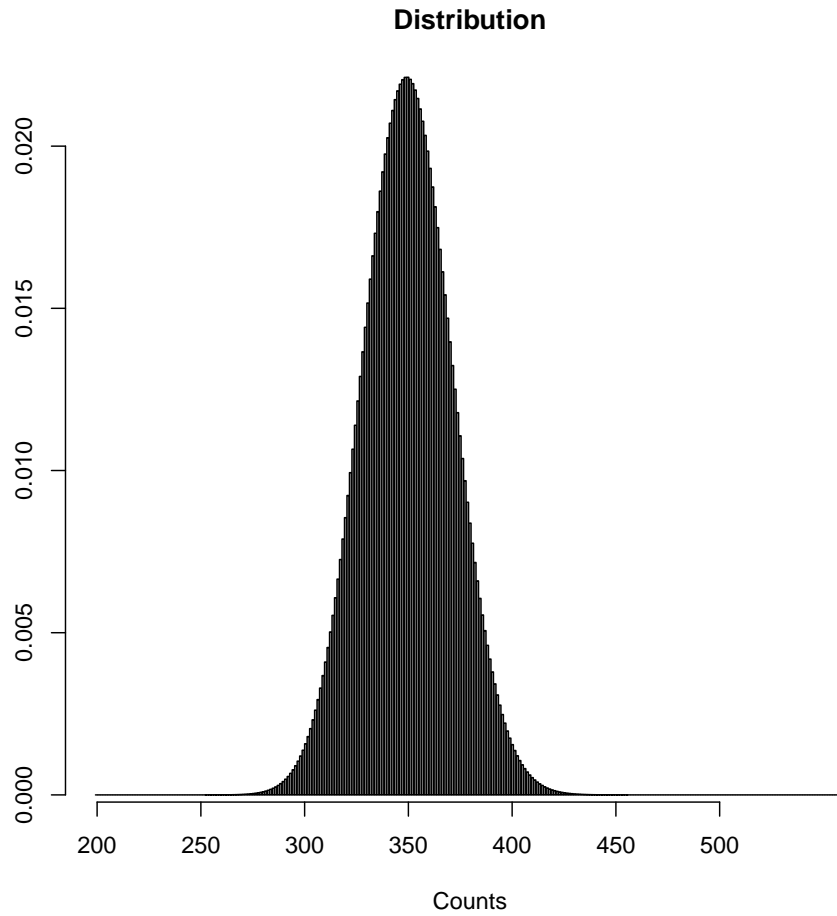


Figure 2.3: Poisson Distribution of Counts: This bar plot represents the probability mass function (PMF) of counts ranging from 200 to 500, using a Poisson distribution with a rate parameter $\lambda = 0.591$ based on 550 time periods.

2.5 Counts: Negative Binomial model derived from Poisson-Gamma model

The Negative Binomial $X \sim \text{NBin}(r, \pi)$ models the number of *trials* in a sequence of independent and identically distributed Bernoullis before r *successes* occur. Instead of representing the number of successes in n trials like a $Y \sim \text{Bin}(n, \pi)$, with the Negative Binomial we are looking at how many trials will it take to obtain r successes.

With respect to the parameters, $r > 0$ represents the number of successes until the experiment is stopped. The success probability in each experiment is represented by $\pi \in [0, 1]$. In R the functions `nbinom(..., size = r, prob = π)` relate to the random variable $X - r$, the number of successes (as opposed to the number of trials) until r successes have been achieved ([Held and Bové, 2014](#)).

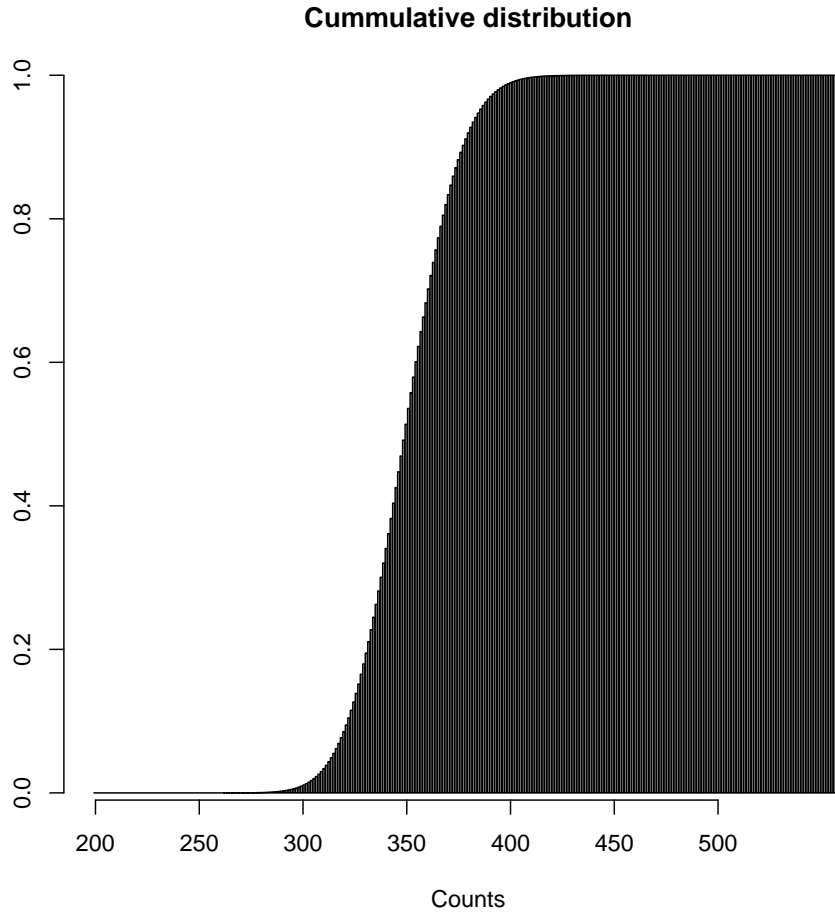


Figure 2.4: Cumulative Distribution of Poisson-Distributed Counts: The plot illustrates the cumulative probability distribution for counts within the range of 200 to 500, using a Poisson distribution with a rate parameter $\lambda = 0.591$ adjusted for 550 time periods.

2.5.1 Recruitment in one unit of time

Let $Y|\Lambda \sim \text{Po}(\Lambda)$ and $\Lambda \sim G(\alpha, \beta)$

$$\begin{aligned}
 p(y) &= \int_0^\infty p(y|\Lambda)p(\Lambda)d\Lambda \\
 &= \int_0^\infty \frac{\Lambda^y \exp(-\Lambda)}{y!} \left[\Lambda^{\alpha-1} \exp(-\beta\Lambda) \frac{\beta^\alpha}{\Gamma(\alpha)} \right] d\Lambda \\
 &= \frac{\beta^\alpha}{y!\Gamma(\alpha)} \int_0^\infty \Lambda^{\alpha+y-1} \exp(-\Lambda) \exp(-\Lambda\beta) d\Lambda \\
 &= \frac{\Gamma(\alpha+y)}{y!\Gamma(\alpha)} \int_0^\infty \beta^\alpha \exp(-\Lambda\beta) d\Lambda \\
 &= \frac{\Gamma(\alpha+y)}{y!\Gamma(\alpha)} \left(1 - \frac{\beta}{\beta+1}\right)^\alpha \left(\frac{\beta}{\beta+1}\right)^y \sim \text{NBin}\left(\alpha, \frac{\beta}{\beta+1}\right)
 \end{aligned}$$

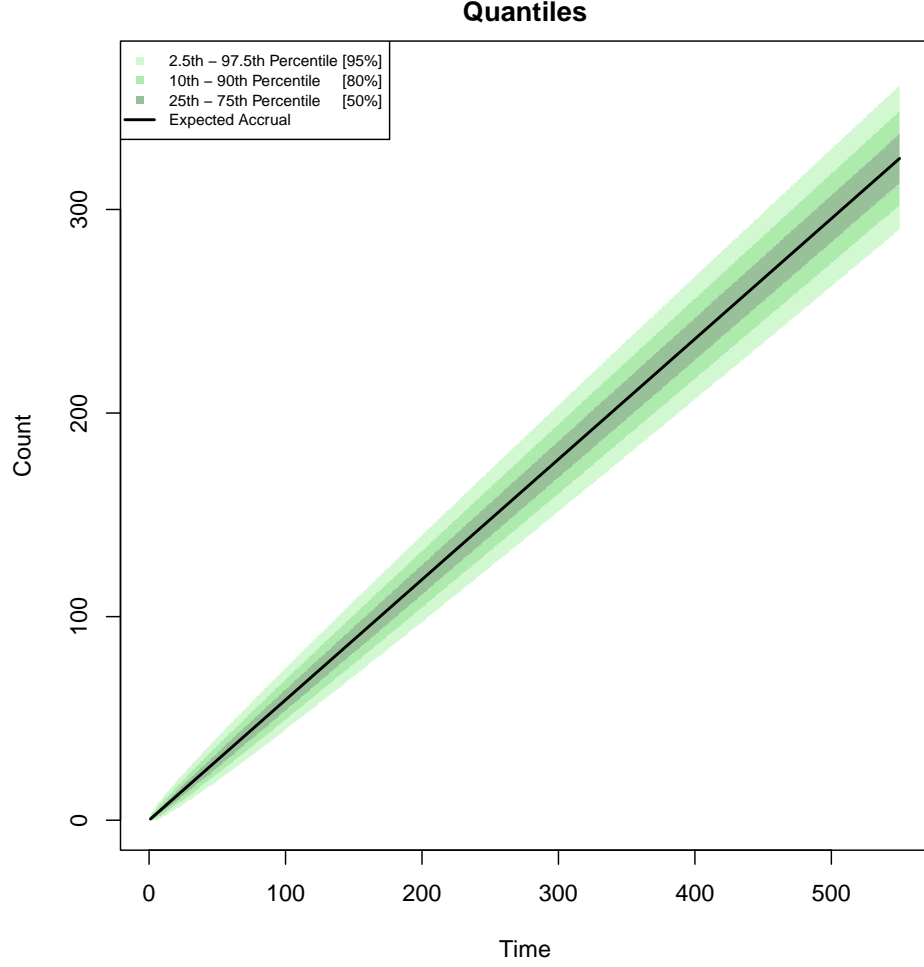


Figure 2.5: Predicted uncertainty bands for Poisson process with $\lambda = 0.591$ over time. The black line represents the expected accrual, while the green shaded regions indicate aleatory uncertainty: the dark green band spans the interquantile range (25th - 75th percentiles), the lighter green band cover the 10th - 90th percentile range and the light green the 2.5th - 97.5th percentile range (Spiegelhalter *et al.*, 2011).

Using the expressions of iterated expectation and variance (Held and Bové, 2014) and the expectation and variance from the respective random variables $Y|\Lambda \sim \text{Po}(\Lambda)$ and $\Lambda \sim \text{G}(\alpha, \beta)$, we have that:

$$\begin{aligned}
 EY &= E_{\Lambda}[E_Y(Y|\Lambda)] = E_{\Lambda}[\Lambda] = \Lambda \\
 \text{Var}(Y) &= \text{Var}_{\Lambda}[E_Y(Y|\Lambda)] + E_{\Lambda}[\text{Var}_Y(Y|\Lambda)] \\
 &= \text{Var}_{\Lambda}[\Lambda] + E_{\Lambda}[\Lambda] \\
 &= \alpha/\beta^2 + \alpha/\beta = \frac{\alpha(\beta + 1)}{\beta^2}
 \end{aligned}$$

2.5.2 Accrual at time point t

Let $Y|\Lambda \sim \text{Po}(\Lambda t)$ and $\Lambda \sim \text{G}(\alpha, \beta)$

Chapter 3

Results

Chapter 4

Discussion and Outlook

Chapter 5

Conclusions

5.0.1 Personal Statement

NOT AI: This thesis was not written by any generative AI. It was written independently and without assistance from third parties. All sources utilized in this thesis are appropriately cited in the references

AI: During the preparation of this Master Thesis, I used [NAME OF TOOLS AND SERVICES] in order to [REASON]. After using this tool/service, I reviewed and edited the content as needed and I take full responsibility for the content of the Master Thesis.

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