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

Pilar Pastor

Supervision by Malgorzata Roos

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Why recruitment rates?

According to Carter (2004)

- – Timely recruitment vital to the success of a clinical trial

- – Inadequate number of subjects $\rightarrow$ lack of power

- – Recruitment period too long $\rightarrow$ competing treatments
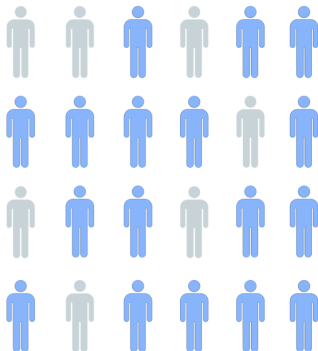
- – Recruitment of patients varies at each stage
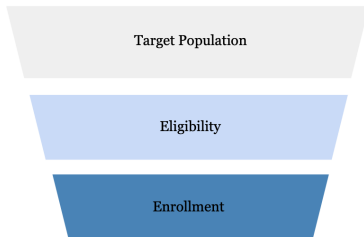
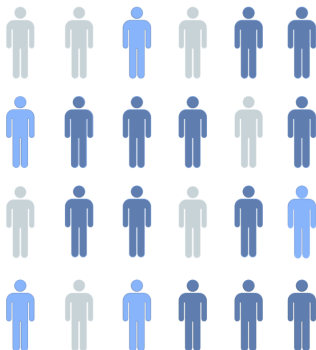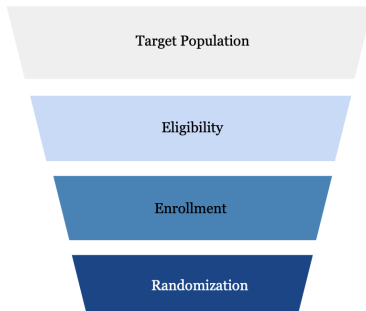# Target Population

Target Population
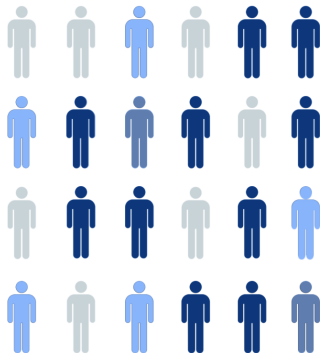
Eligibility
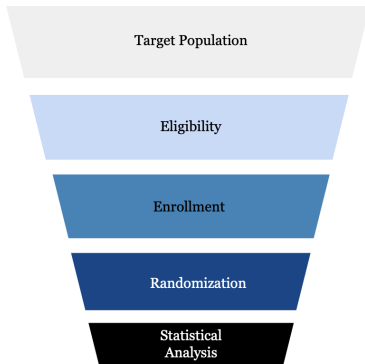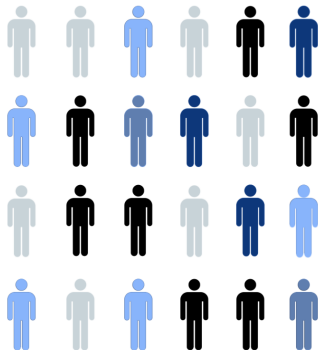

Target Population

Eligibility
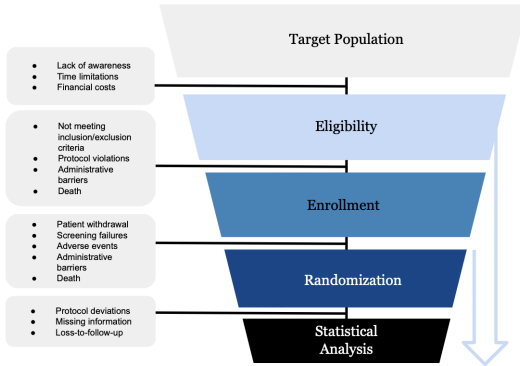
Enrollment

Randomization

Statistical Analysis

Patient Leakage

Definitions

– **Recruitment rate** = Per time-unit (Piantadosi, 2024)

– **Accrual** = Cumulative Recruitment

– **Aleatory uncertainty**: randomness inherent and unpredictable

– **Epistemic uncertainty**: arises from limited knowledge about parameters

Models for Counts

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

Table: Moments, aleatory and epistemic uncertainty in recruitment
shown by different models for counts.

Methods	Counts	Expectation	Variance	Aleatory	Epistemic
Expectation	$C(t) = \lambda t$	λt	0	No	No
Poisson	$C(t) \sim \mathrm{Po}(\lambda t)$	λt	λt	Yes	No
Negative Binomial	$C(t) \sim \mathrm{Po}(\Lambda t); \Lambda \sim \mathrm{G}(\alpha, \beta)$	??	??	Yes	Yes

Table: Moments, aleatory and epistemic uncertainty in accrual shown
by different models for counts.

Multicenter Trial on Palliation in Terminal Esophageal Cancer

Example from Carter (2004):

- Recruitment Rate $\lambda = \frac{Counts}{Time} = 0.591$ per day
- Time $t = 550$ days

Multicenter Trial on Palliation in Terminal Esophageal Cancer

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– Models for Counts:

– **Expectation**: $\mathrm{E}C(t) = \lambda t = 0.591 \cdot 550 = 325$
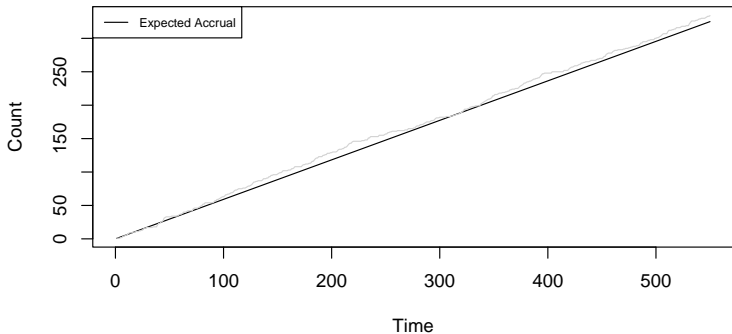
– **Poisson**: $C(t) \sim \mathrm{Po}(\lambda t)$

Accrual at time point t

– **Expectation**: $\mathrm{E}C(t) = \underbrace{\mathrm{E}C + \ldots + C}_{t \text{ times}} = t\mathrm{E}C = \lambda t$

– **Poisson**: $\underbrace{\mathrm{Po}(\lambda) + \ldots + \mathrm{Po}(\lambda)}_{t \text{ times}} = \mathrm{Po}(\lambda t)$
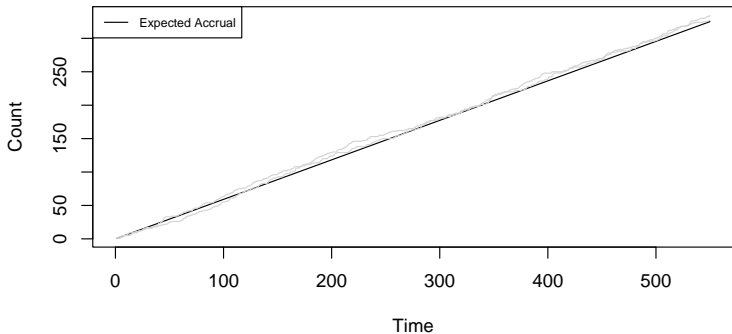
Accrual of 1 study

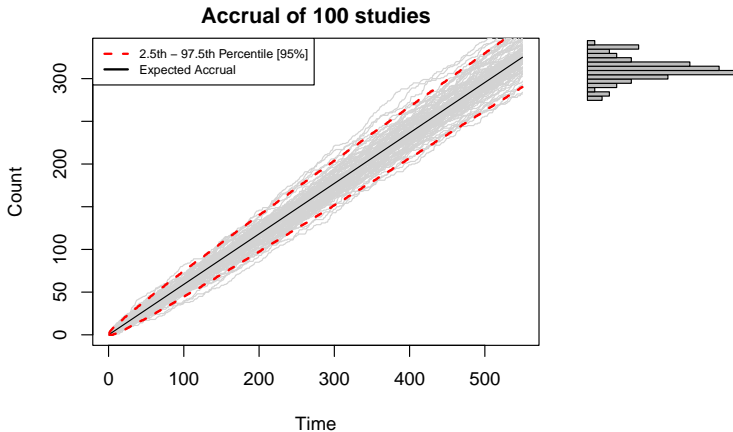**Accrual of 1 study**
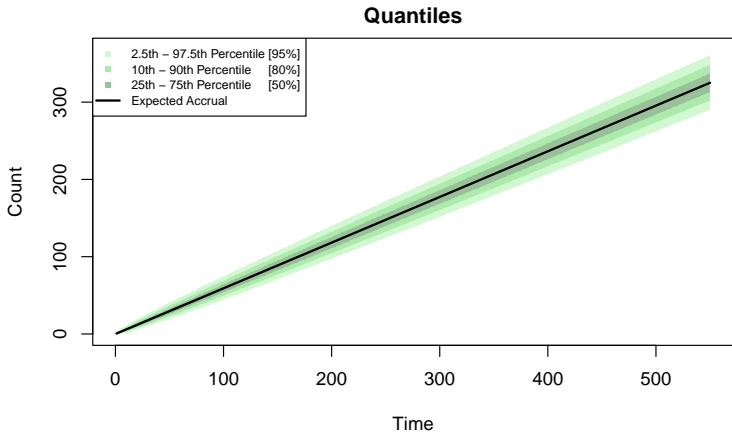
Accrual of 2 studies
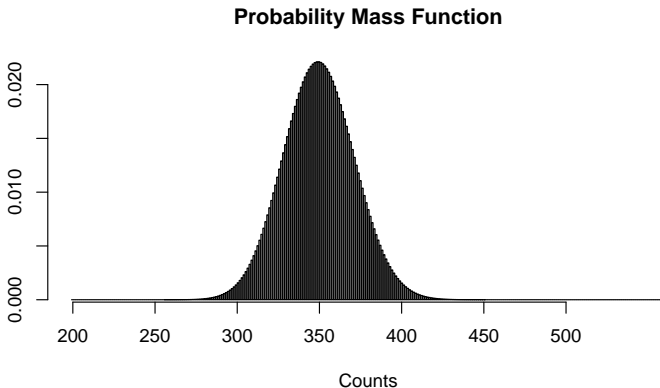
Accrual of 2 studies

Accrual of 100 studies

Accrual of 100 studies

Poisson's uncertainty bands

Poisson's exact PMF at time point $t = 550$ with $\lambda = 0.591$

Probability Mass Function

Poisson's exact CDF at time point $t = 550$ with $\lambda = 0.591$
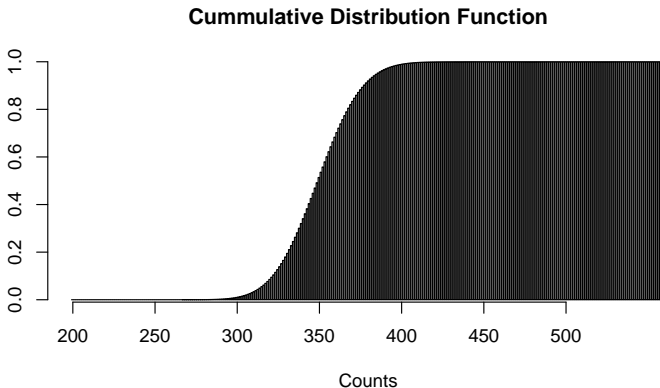
Cummulative Distribution Function

Counts

Multicenter Trial on Palliation in Terminal Esophageal Cancer

Example from Carter (2004):

– Recruitment Rate $\lambda = \frac{Counts}{Time} = 0.591$ per day

– Time $t = 550$ days

– Models for Counts:

    – **Negative Binomial**: $C \sim \mathrm{Po}(\Lambda); \Lambda \sim \mathrm{G}(\alpha, \beta)$

        – $\alpha = 325$

        – $\beta = 548$

        – $\mathrm{E}\Lambda = \frac{\alpha}{\beta} = 0.591 = \lambda$

Negative binomial derived from Poisson-Gamma model (t=1)

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

$$
\begin{aligned}
p(c) &= \int_0^\infty p(c|\lambda)p(\lambda)d\lambda \\
&= \int_0^\infty \frac{\lambda^c \exp(-\lambda)}{c!} \left[\lambda^{\alpha-1}\exp(-\beta\lambda)\frac{\beta^\alpha}{\Gamma(\alpha)}\right] d\lambda \\
&= \frac{\beta^\alpha}{c!\Gamma(\alpha)} \int_0^\infty \lambda^{\alpha+c-1}\exp(-\lambda)\exp(-\lambda\beta)d\lambda \\
&= \frac{\beta^\alpha\Gamma(\alpha+c)}{c!\Gamma(\alpha)(\beta+1)^{\alpha+c}} \underbrace{\int_0^\infty \frac{(\beta+1)^{\alpha+c}}{\Gamma(\alpha+c)}\lambda^{\alpha+c-1}\exp(-(\beta+1)\lambda)d\lambda}_{=1} \\
&= \beta^\alpha \binom{\alpha+c-1}{\alpha-1}\left(\frac{1}{\beta+1}\right)^{\alpha+c} \\
&= \binom{\alpha+c-1}{\alpha-1}\left(\frac{1}{\beta+1}\right)^c\left(\frac{\beta}{\beta+1}\right)^\alpha, \quad C|\Lambda \sim \mathrm{NBin}\left(\alpha, \frac{\beta}{\beta+1}\right)
\end{aligned}
$$

Expectation and Variance

Using the expressions of iterated expectation and variance
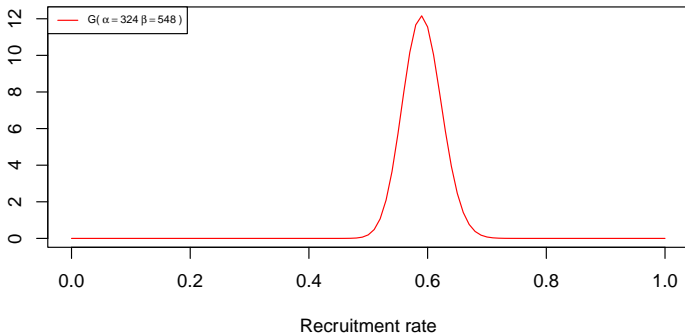(Held and Bové, 2014)

$$\mathrm{E}C = \mathrm{E}_\Lambda[\mathrm{E}_C(C|\Lambda)] = \mathrm{E}_\Lambda[\Lambda] = \alpha/\beta$$

$$\begin{aligned}
\mathrm{Var}(C) &= \mathrm{Var}_\Lambda[\mathrm{E}_C(C|\Lambda)] + \mathrm{E}_\Lambda[\mathrm{Var}_C(C|\Lambda)] \\
&= \mathrm{Var}_\Lambda[\Lambda] + \mathrm{E}_\Lambda[\Lambda] \\
&= \alpha/\beta^2 + \alpha/\beta = \frac{\alpha(\beta + 1)}{\beta^2}
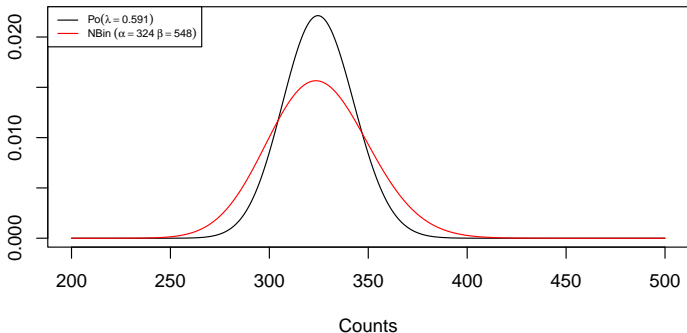\end{aligned}$$

Gamma Prior

$$\Lambda \sim \mathrm{G}(\alpha, \beta)$$

Probability Density Function

G($\alpha = 324$ $\beta = 548$)

Recruitment rate

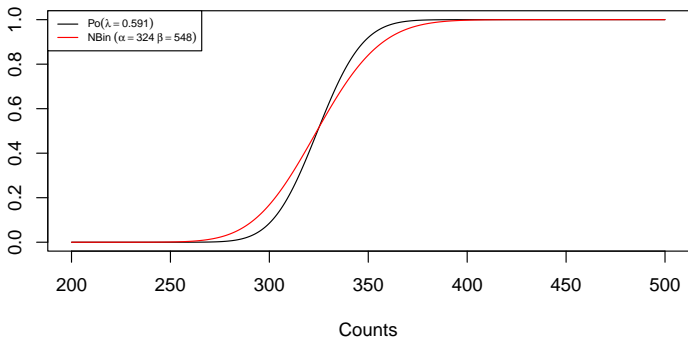# Comparison between Poisson and Negative Binomial

Probability Mass Function
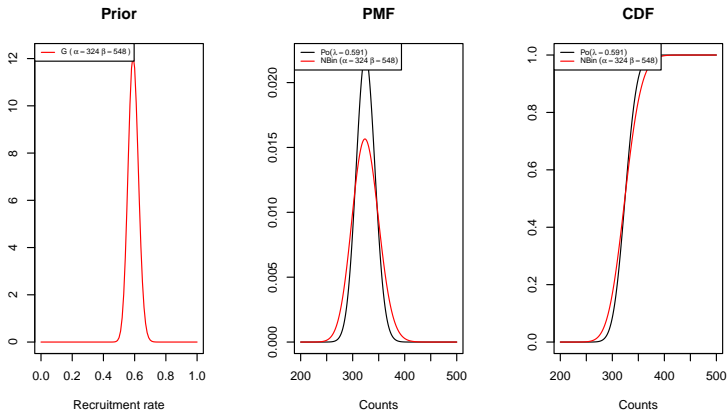
Comparison between Poisson and Negative Binomial
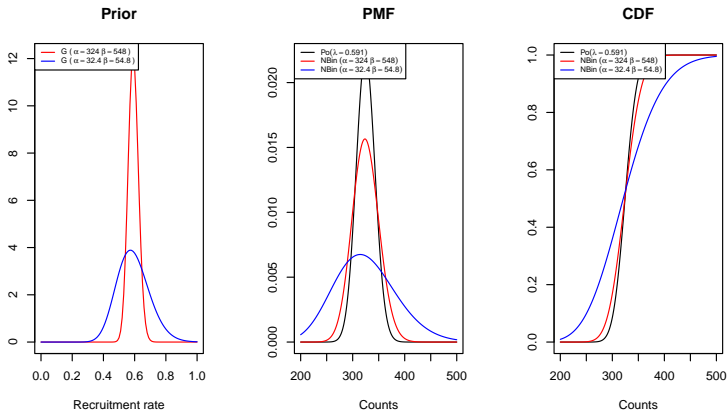

Cummulative Distribution Function
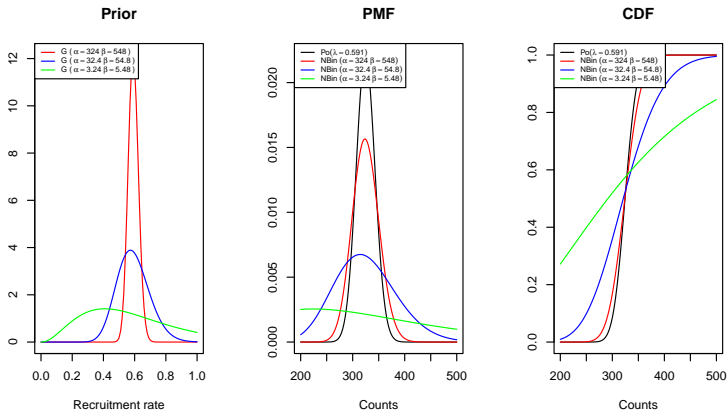
Sensitivity Analysis

Sensitivity Analysis

Sensitivity Analysis

Sensitivity Analysis

Summary

– Extension of Carter's approach based on MC
  simulations

– Exact models for **counts**

– Unified notation

– Visualization of study accrual and uncertainty bands

– Sensitivity analysis

Next steps

- Extend Negative Binomial proof for accrual
- Compare exact models for counts to those provided by Carter (2004)
- Models for **time**
  - Exact models
  - Compare them to those provided by Carter
- Shiny App
- Apply theoretical results to dataset

References

Carter, R. E. (2004). Application of stochastic processes to
participant recruitment in clinical trials. *Controlled clinical trials*,
25(5):429–436.

Held, L. and Bové, D. S. (2014). Applied statistical inference.
Springer, Berlin Heidelberg, doi, 10(978-3):16.

Piantadosi, S. (2024). *Clinical trials: a methodologic perspective*.
John Wiley & Sons.

Thank you for your attention