University of Zurich[UZH]

Master Thesis Biostatistics

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

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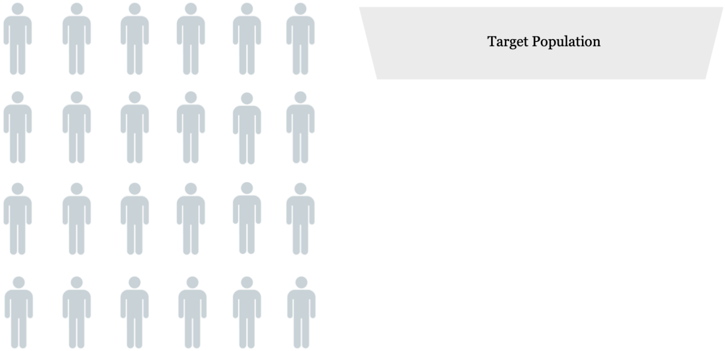
March 18, 2025

Why recruitment rates?

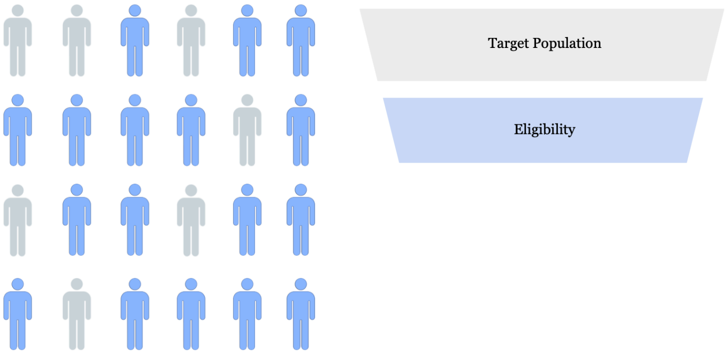
According to Carter (2004)

- 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
- Methods applicable to all the stages

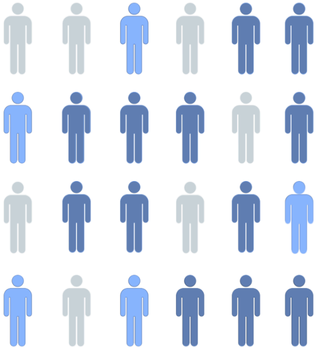
Target Population

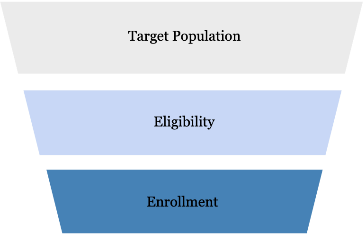


Eligibility

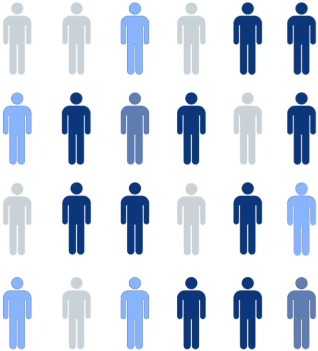


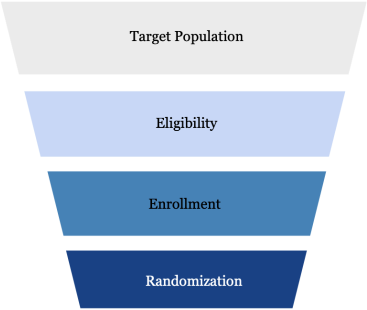
Enrollment



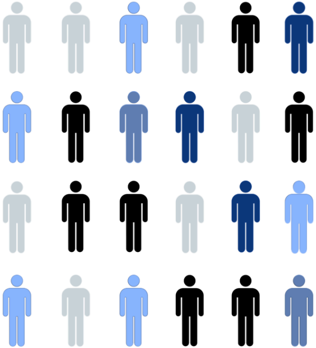


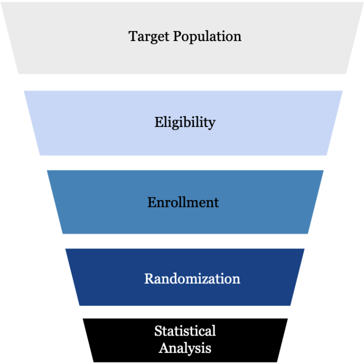
Randomization



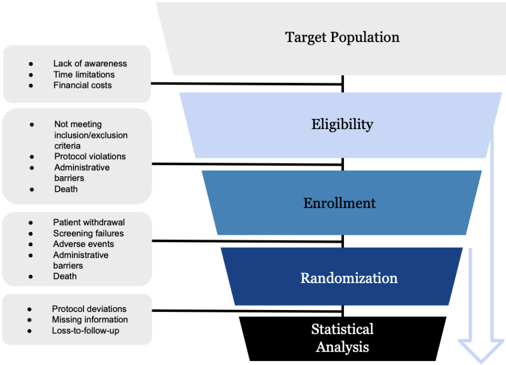


Statistical Analysis





Patient Leakage



Definitions

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

$$\lambda = \frac{\Delta C}{\Delta T} = \frac{C_1 - C_0}{T_1 - T_0} = \frac{C_1}{T_1}$$

- **Accrual**: Cumulative Recruitment
- **Aleatory uncertainty**: randomness inherent and unpredictable
- **Epistemic uncertainty**: arises from limited knowledge about parameters

Models for Counts

Recruitment in unit of time (t=1):

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

Accrual for time t [0,t]:

Methods	Counts	Expectation	Variance	Aleatory	Epistemic
Expectation	$C(t) = \lambda t$	λt	0	No	No
Poisson	$C(t) \sim Po(\lambda t)$	λt	λt	Yes	No
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Multicenter Trial on Palliation in Terminal Esophageal Cancer

Example from Carter (2004):

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

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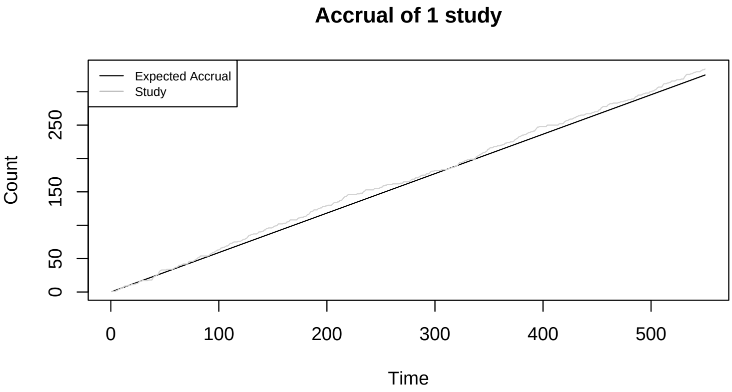
- Recruitment Rate $\lambda = \frac{Counts}{Time} = 0.591$ per day
- Time $t = 550$ days
- Models for Counts at time point t:
  - **Expectation**: $EC(t) = \lambda t = 0.591 \cdot 550 = 325$
  - **Poisson**: $C(t) \sim Po(\lambda t)$

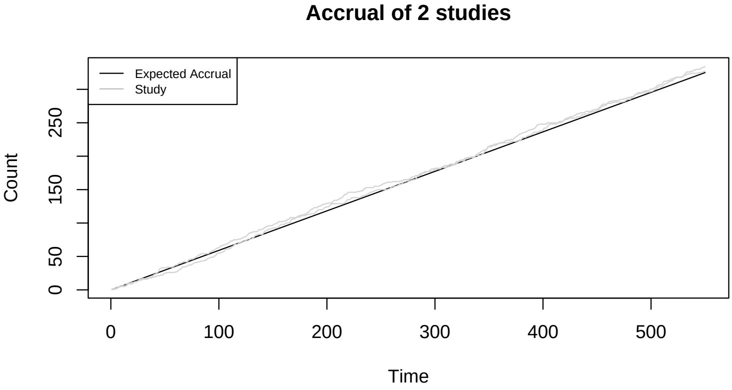
Accrual at time point t

- **Expectation**: $EC(t) = E\underbrace{(C + \ldots + C)}_{t \text{ times}} = tEC = \lambda t$
- **Poisson**: $\underbrace{Po(\lambda) + \ldots + Po(\lambda)}_{t \text{ times}} = Po(\lambda t)$

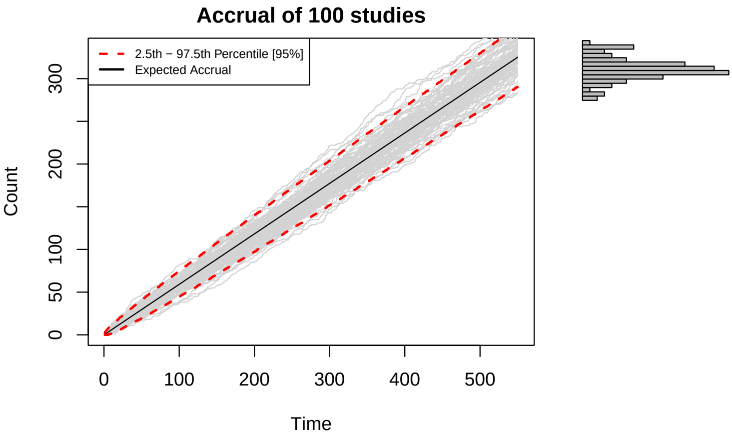
Accrual of 1 study



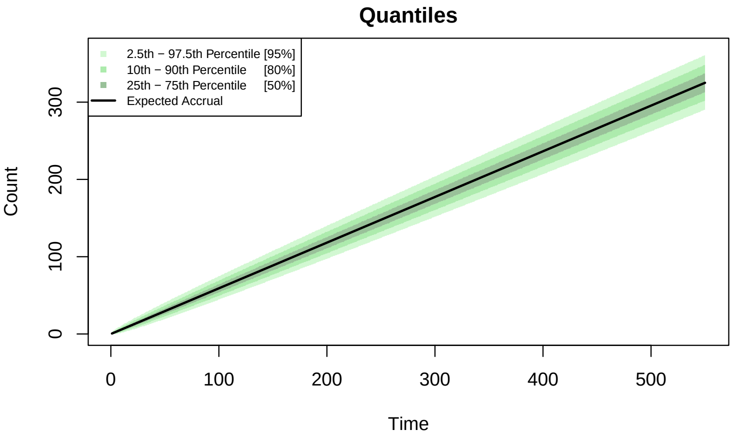
Accrual of 2 studies



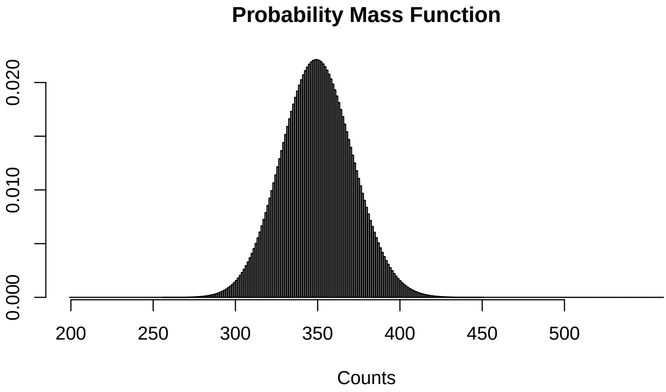
Accrual of 100 studies



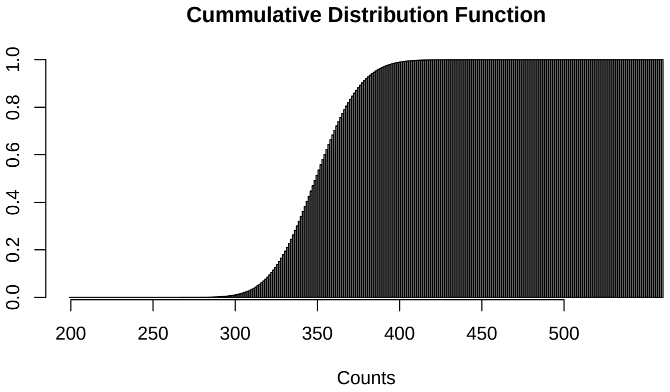
Poisson's uncertainty bands



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



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



Multicenter Trial on Palliation in Terminal Esophageal Cancer

Example from Carter (2004):

- Recruitment Rate $\lambda = \frac{\mathit{Counts}}{\mathit{Time}} = 0.591$ per day
- Time $t = 550$ days
- Models for Counts at time point t:
  - **Poisson - Gamma**: $C(t) \sim Po(\Lambda t)$; $\Lambda \sim G(\alpha, \beta)$
    - $\alpha = 325$
    - $\beta = 548$
    - $E\Lambda = \frac{\alpha}{\beta} = 0.591 = \lambda$

Negative binomial derived from Poisson-Gamma model at time point t

Let $C(t)|\Lambda \sim Po(\Lambda t)$ and $\Lambda \sim G(\alpha, \beta)$

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

$$C(t) \sim NBin\left(\alpha, \frac{\beta}{\beta+t}\right)$$

Expectation and Variance

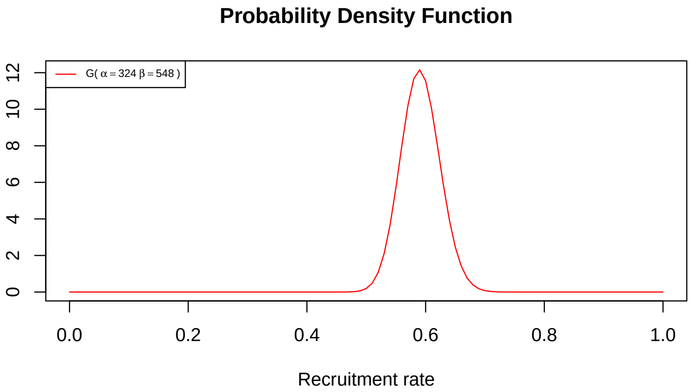
Using the expressions of iterated expectation and variance (Held and Bové, 2014)

$$E(C(t)) = E_{\Lambda}[E_{C(t)}(C(t)|\Lambda)] = E_{\Lambda}[\Lambda t] = t\alpha/\beta$$

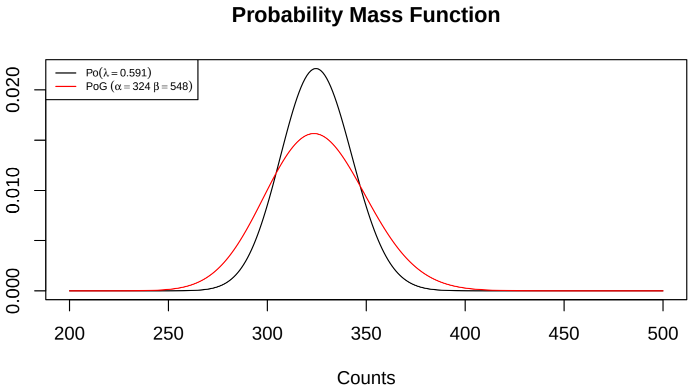
$$\begin{aligned} Var(C(t)) &= Var_{\Lambda}[E_{C(t)}(C(t)|\Lambda)] + E_{\Lambda}[Var_{C(t)}(C(t)|\Lambda)] \\ &= Var_{\Lambda}[\Lambda t] + E_{\Lambda}[\Lambda t] \\ &= t^2\alpha/\beta^2 + t\alpha/\beta = \frac{t\alpha(\beta + t)}{\beta^2} \end{aligned}$$

Gamma Prior

$$\Lambda \sim G(\alpha, \beta)$$



Comparison between Poisson and Poisson - Gamma



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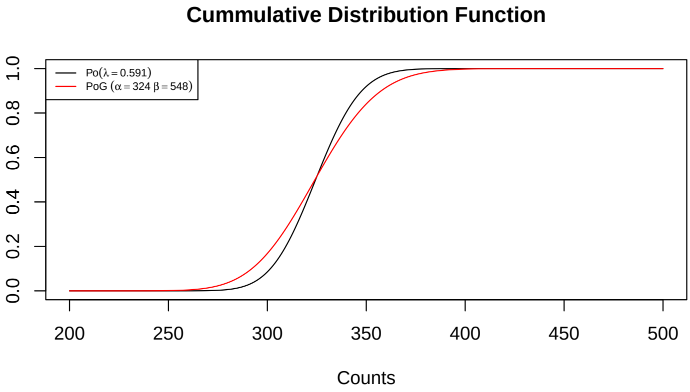

Sensitivity Analysis

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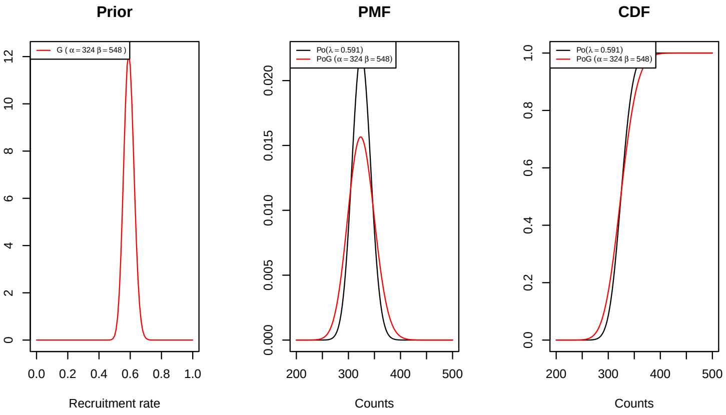

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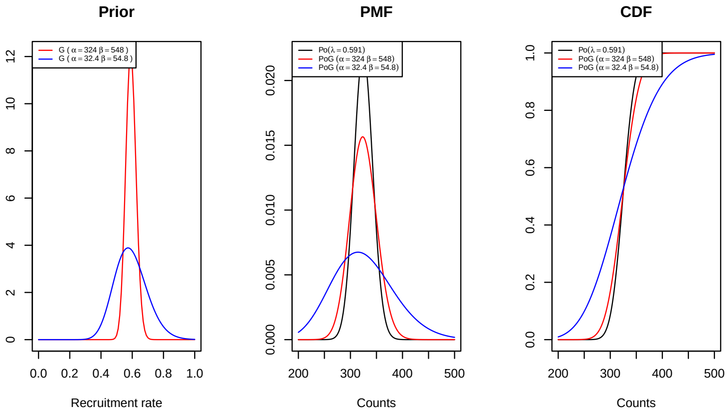

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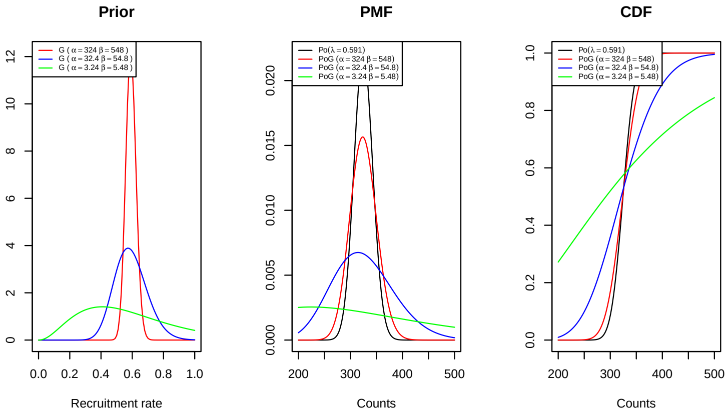

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Summary

- Exact distributions which extend Carter's approach
- Exact models for **counts** and their properties
- Unified notation
- Visualization of study accrual and uncertainty bands
- Sensitivity analysis

Next steps

- Compare exact models for counts to those provided by Carter (2004) based on MC simulations
- Models for **time**
  - Exact models
  - Compare them to those provided by Carter
- Apply theoretical results to dataset
- Shiny App

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.

Piantadosi, S. (2024). *Clinical Trials: A Methodologic Perspective*. John Wiley & Sons.

Thank you for your attention