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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# Why recruitment rates?

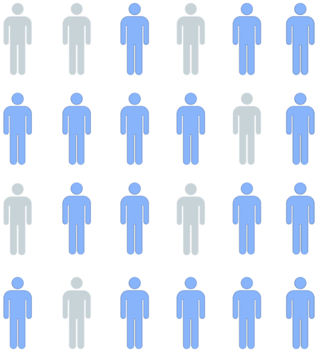
According to Carter (2004)

- 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

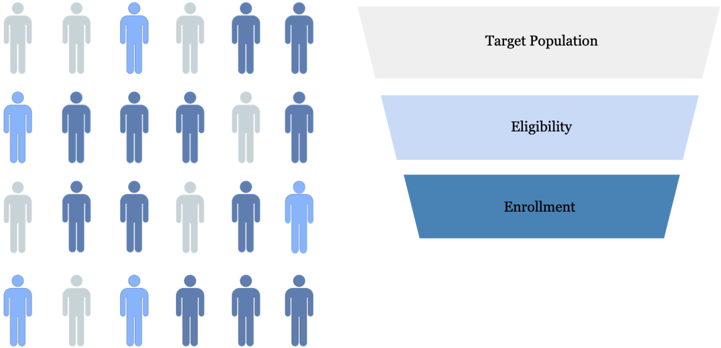
# Target Population



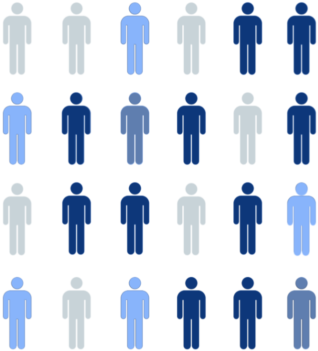
# Eligibility

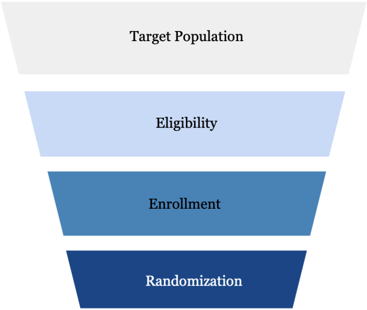


# Enrollment

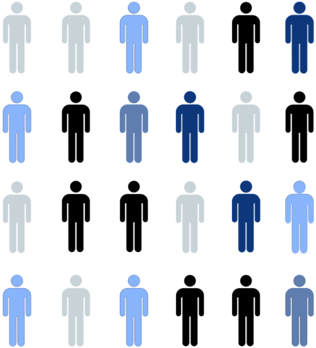


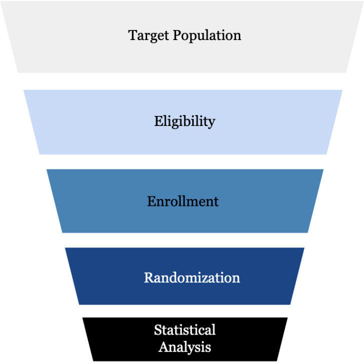
# Randomization



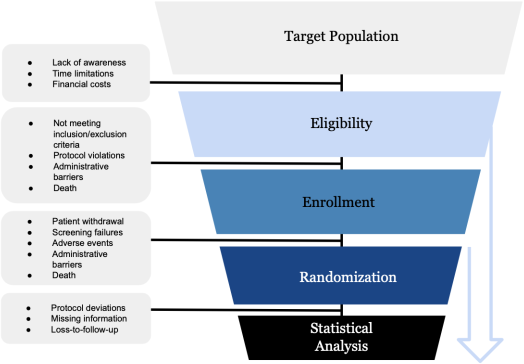


# Statistical Analysis





# 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 | $C = \lambda$ | $\lambda$ | 0 | No | No |
| Poisson | $C \sim \mathrm{Po}(\lambda)$ | $\lambda$ | $\lambda$ | 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 | $C(t) = \lambda t$ | $\lambda t$ | 0 | No | No |
| Poisson | $C(t) \sim \mathrm{Po}(\lambda t)$ | $\lambda t$ | $\lambda t$ | 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 $\lambda = \frac{\textit{Counts}}{\textit{Time}} = 0.591$ per day
- Time $t = 550$ days

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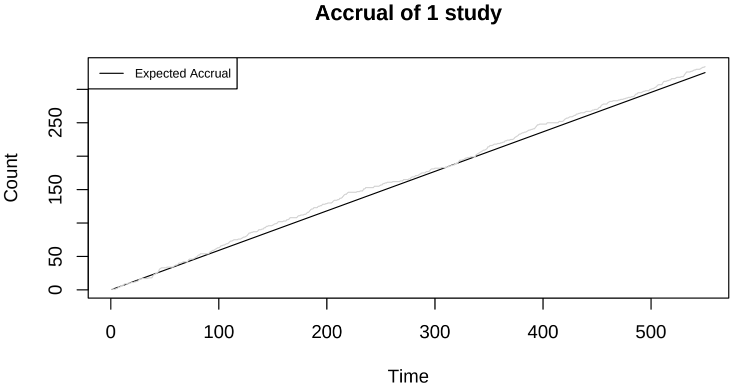
- Models for Counts:
  - Expectation: $\mathrm{E}C(t) = \lambda t = 0.591 \cdot 550 = 325$
  - Poisson: $C(t) \sim \mathrm{Po}(\lambda t)$

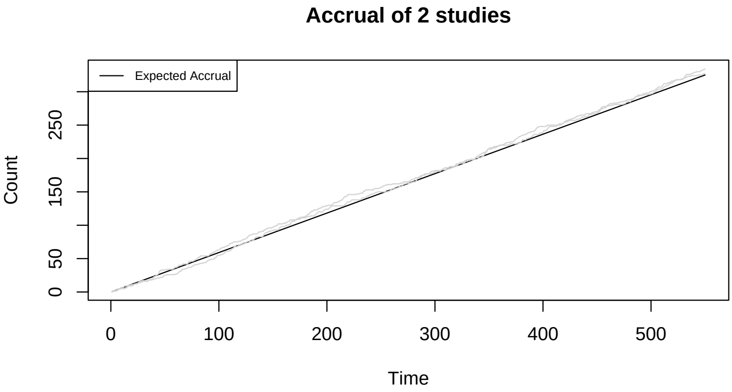
# Accrual at time point $t$

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

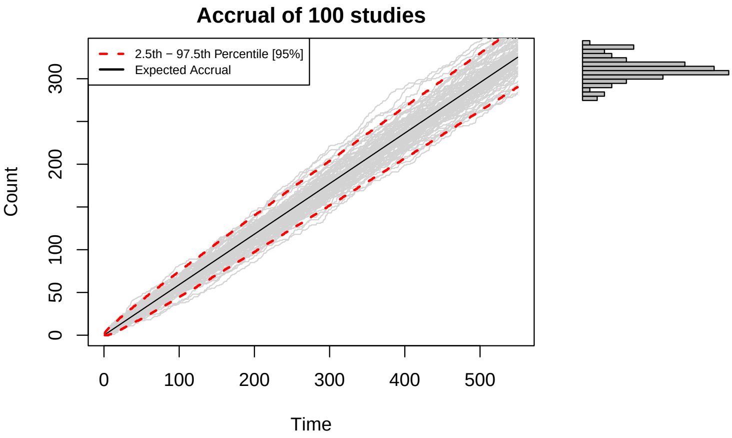
# Accrual of 1 study



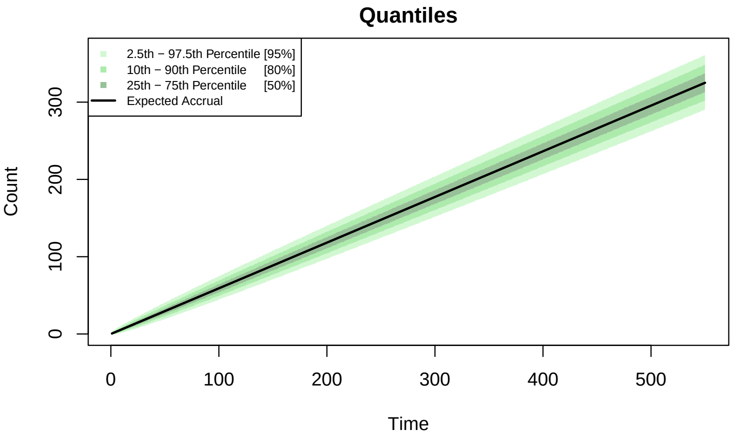
# Accrual of 2 studies



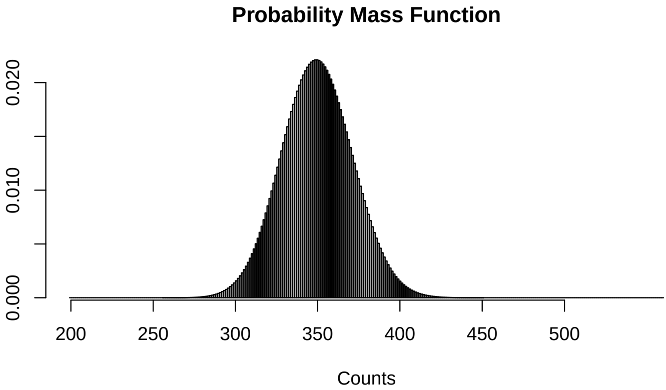
# Accrual of 100 studies



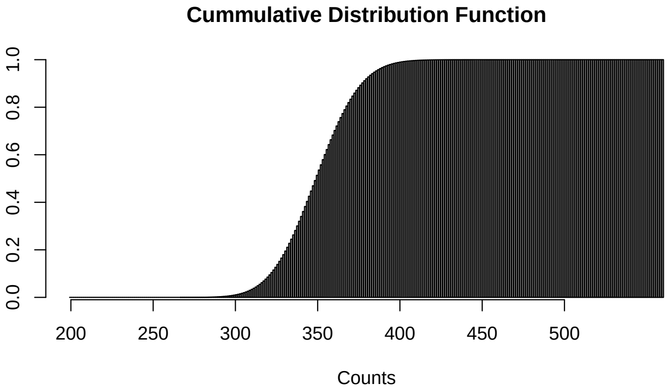
# Poisson’s uncertainty bands



# 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:
  - **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 $\Lambda \sim \mathrm{G}(\alpha, \beta)$

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

# Expectation and Variance

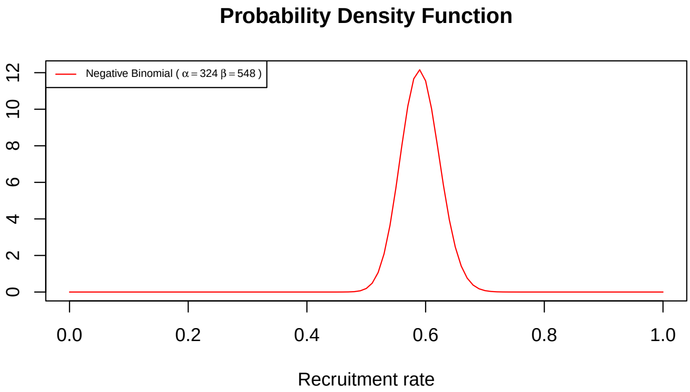
Using the expressions of iterated expectation and variance (Held and Bové, 2014)

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

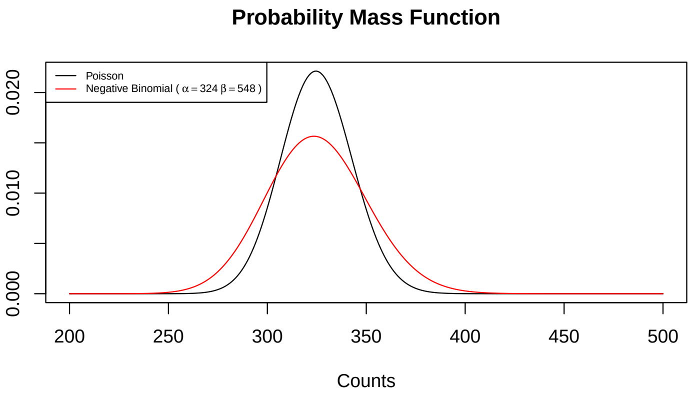
$$\begin{aligned}\mathrm{Var}(C) &= \mathrm{Var}_{\Lambda}[\mathrm{E}_{C}(C|\Lambda)] + \mathrm{E}_{\Lambda}[\mathrm{Var}_{C}(C|\Lambda)] \\ &= \mathrm{Var}_{\Lambda}[\Lambda] + \mathrm{E}_{\Lambda}[\Lambda] \\ &= \alpha/\beta^{2} + \alpha/\beta = \frac{\alpha(\beta+1)}{\beta^{2}}\end{aligned}$$

# Gamma Prior

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



# Comparison between Poisson and Negative Binomial



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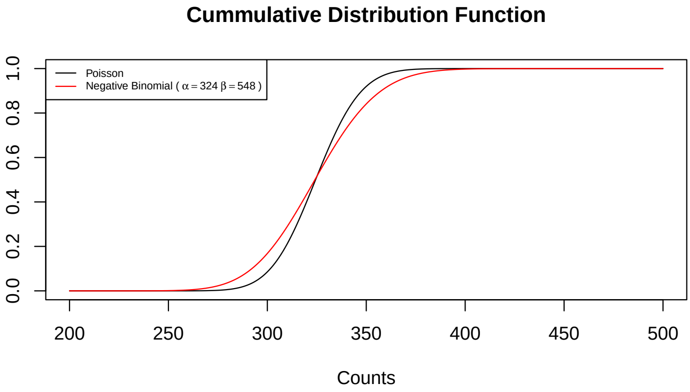

# Sensitivity Analysis

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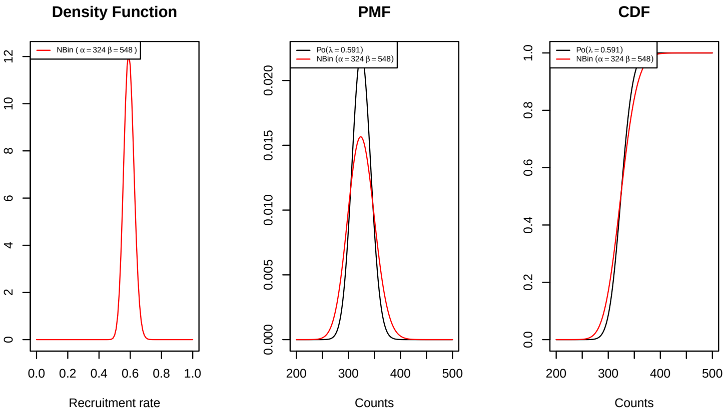

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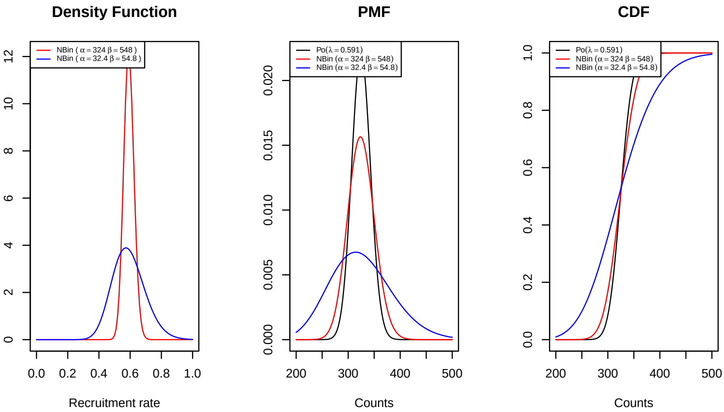

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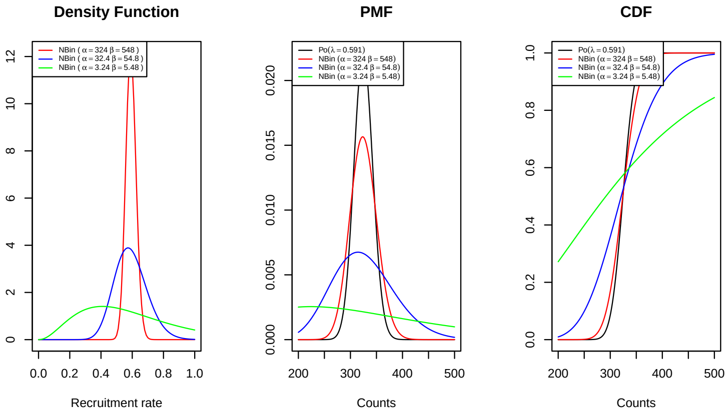

# Summary

- Extension of Carter's approach based on MC simulations
- Exact models for **counts**
- Unified notation
- Visualization of study accrual and uncertainty bands

# Next steps

- Extend Negative Binomial proof for accrual
- Compare exact models 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