



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

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Why recruitment rates?

- Timely recruitment vital to the success of a clinical trial
- Inadequate number of subjects → lack of power
- Recruitment period too long → competing treatments
- Recruitment of patients varies at each stage
- Accrual = Cumulative Recruitment
- [Carter \(2004\)](#)



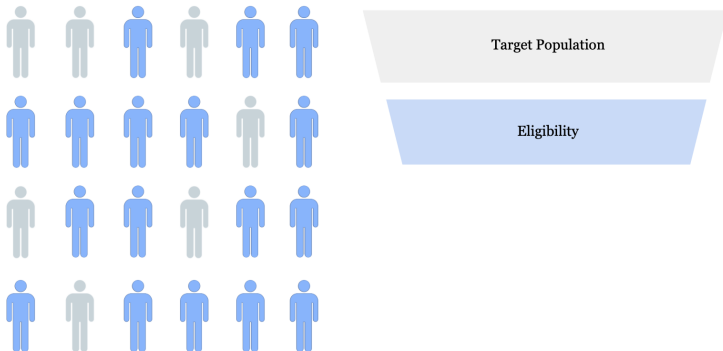
Target Population



Target Population

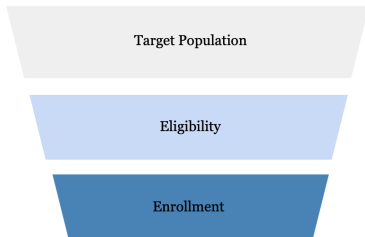
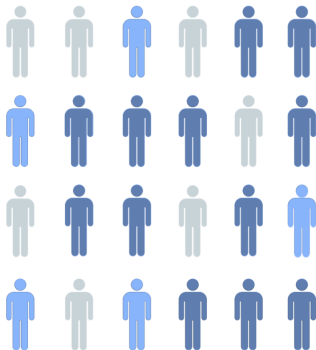


Eligibility

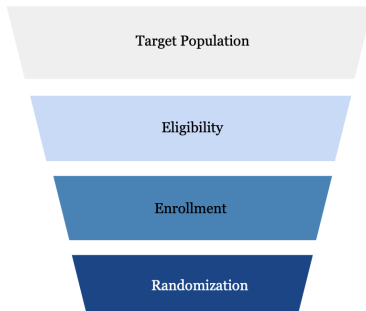
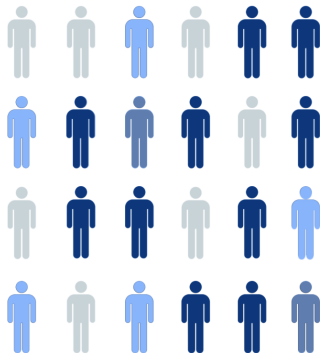




Enrollment

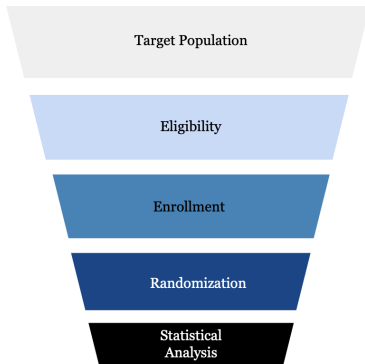
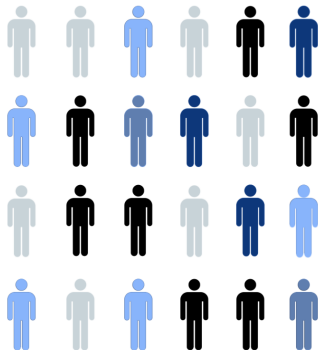


Randomization

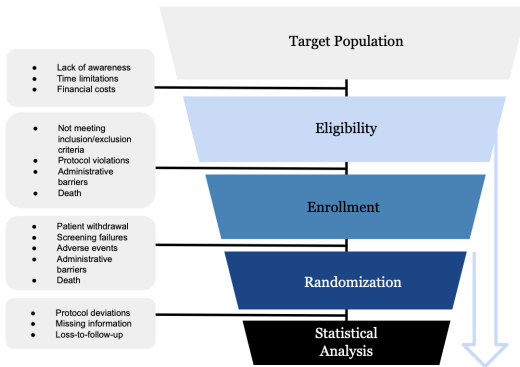




Statistical Analysis



Patient Leakage



Uncertainty

- **Aleatory**: randomness inherent and unpredictable
- **Epistemic**: arises from limited knowledge about parameters

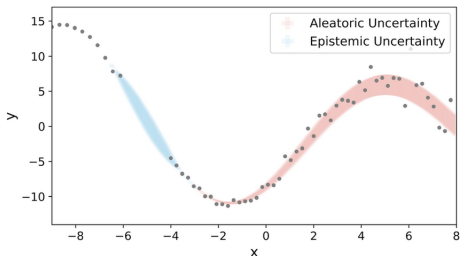


Figure: Visualization of two types of uncertainty (Yang and Li, 2023)

Models for Counts

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

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



A multicenter clinical trial evaluating the palliation benefits of radiation therapy and esophageal stents in subjects with terminal esophageal cancer

- Time $t = 550$ days
- Recruitment Rate $\lambda = \frac{\text{Counts}}{\text{Time}} = 0.591$ ([Piantadosi, 2024](#))



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- Models for Counts:
 - Expectation: $EC(t) = \lambda t = 0.591 \cdot 550 = 325$
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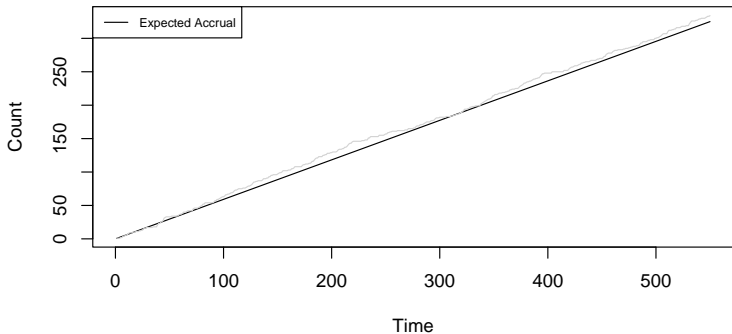
Accrual at time point t

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



Accrual of 1 study

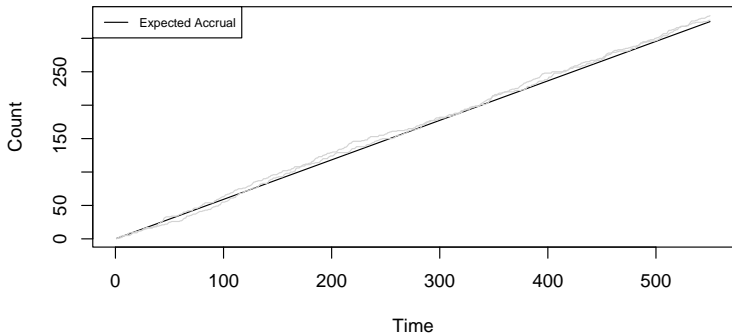
Accrual of 1 study



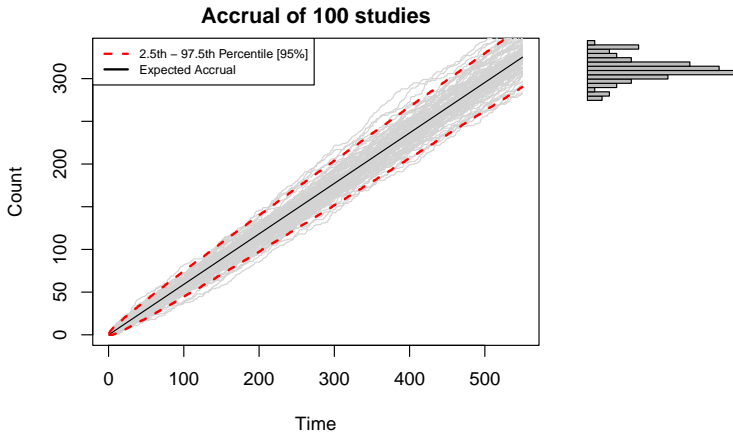


Accrual of 2 studies

Accrual of 2 studies

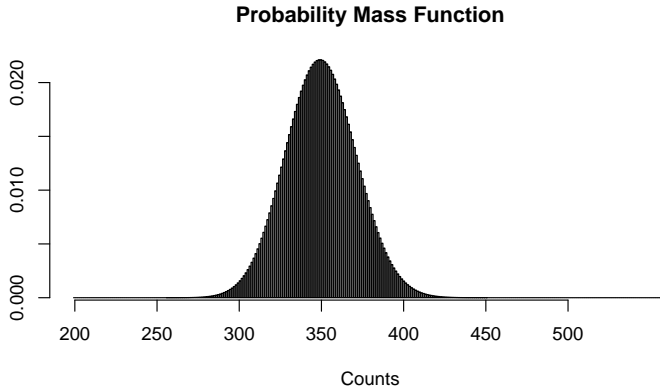


Accrual of 100 studies



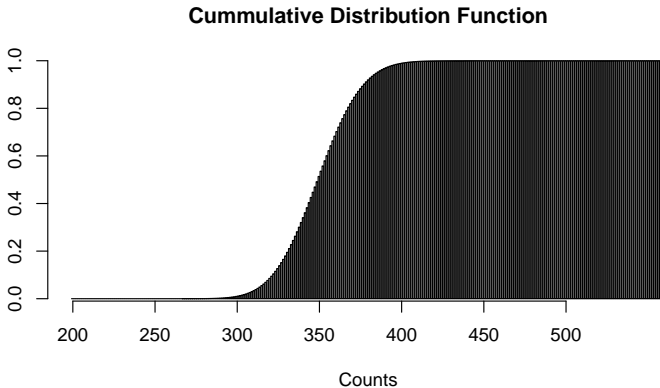


Poisson's theoretical PMF



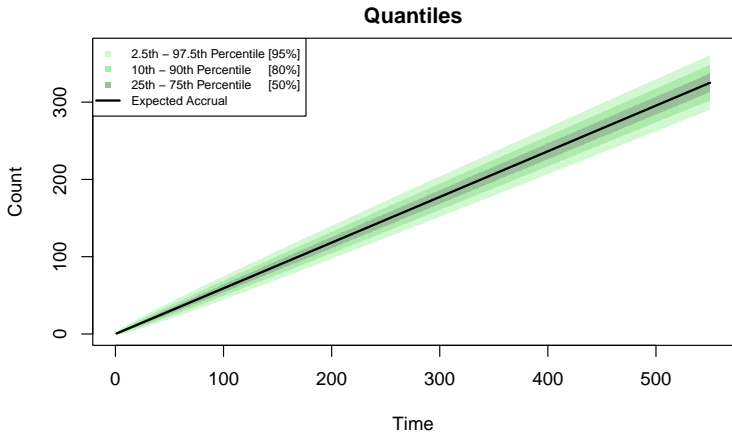


Poisson's theoretical CDF





Poisson's uncertainty bands





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 - **Poisson:** $C(t) \sim \text{Po}(\lambda t)$
 - **Negative Binomial:** $C(t) \sim \text{Po}(\Lambda t); \Lambda \sim G(\alpha, \beta)$
 - $\alpha = 325$
 - $\beta = 1.5 \cdot 365$
 - $E\Lambda = \frac{\alpha}{\beta} = 0.591 = \lambda$

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

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

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

Expectation and Variance

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

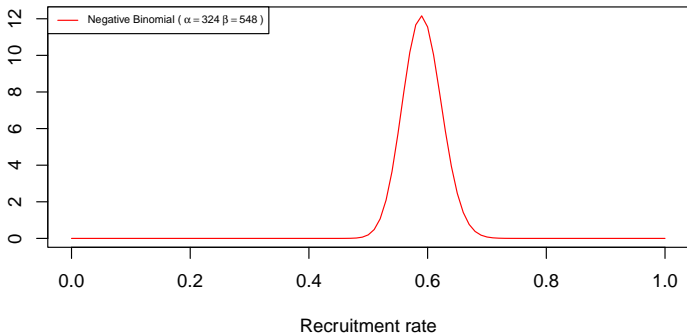
$$E\mathbf{C} = E_{\Lambda}[E_{\mathbf{C}}(\mathbf{C}|\Lambda)] = E_{\Lambda}[\Lambda] = \alpha/\beta$$

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

Gamma Prior

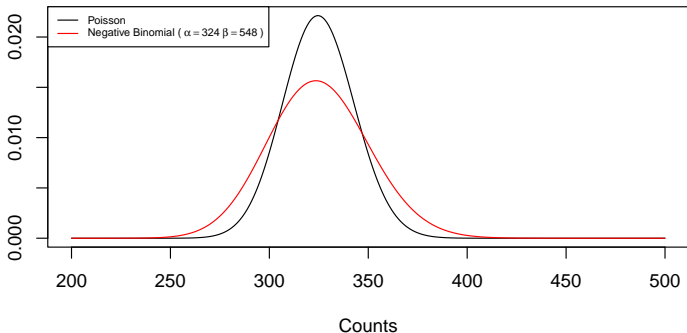
$$\Lambda \sim G(\alpha, \beta)$$

Probability Density Function



Comparison between Poisson and Negative Binomial

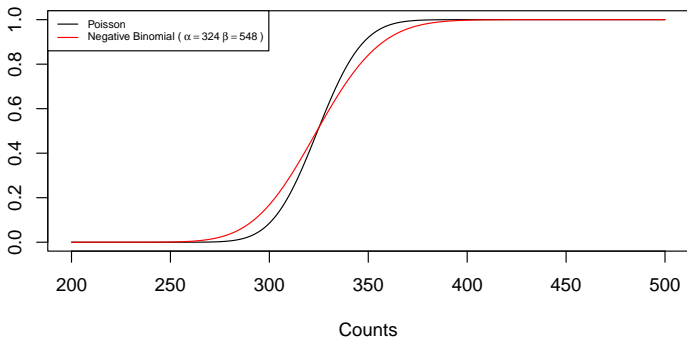
Probability Mass Function





Comparison between Poisson and Negative Binomial

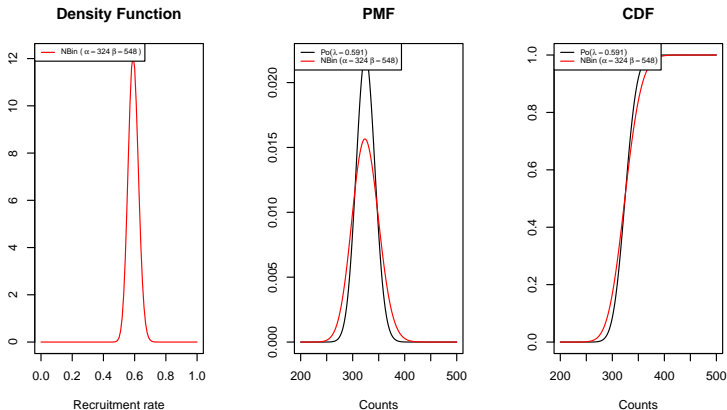
Cummulative Distribution Function



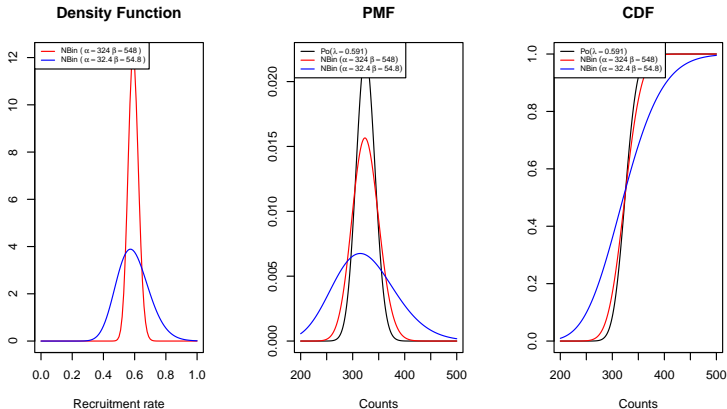


Sensitivity Analysis

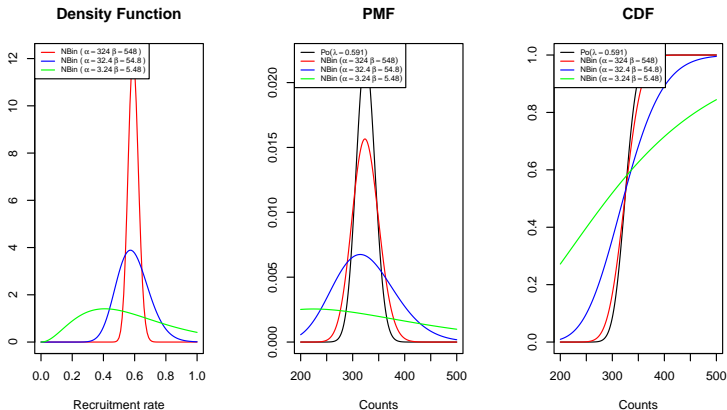
Sensitivity Analysis



Sensitivity Analysis



Sensitivity Analysis





Summary

- Theoretical models for **counts**
- Extended Carter's simulation to exact distributions
- Unified notation
- Visualization of study accrual and uncertainty bands



Next steps

- Application to simulation on [Carter \(2004\)](#)
- Models for **time**
 - Theoretical
 - Application on [Carter \(2004\)](#)
- Shiny App
- Predictions using theoretical models developed on Daniore Nittas dataset of rates (cite?)



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.
- Yang, C.-I. and Li, Y.-P. (2023). Explainable uncertainty quantifications for deep learning-based molecular property prediction. *Journal of Cheminformatics*, 15(1):13.