University of Zurich[UZH]

Master Thesis Biostatistics

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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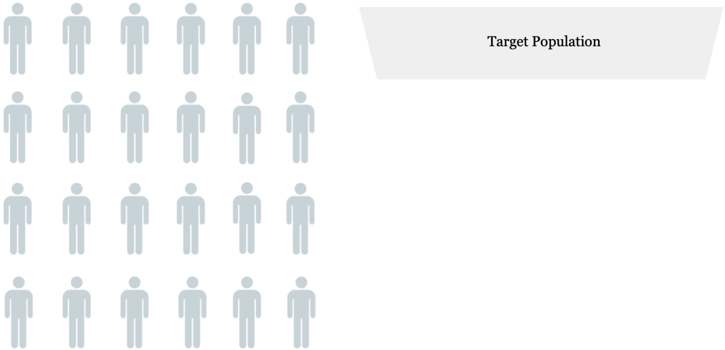
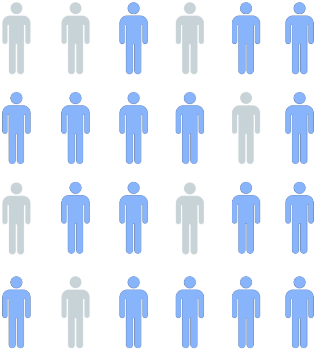
Why recruitment rates?

- 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
- Accrual = Cumulative Recruitment
- Carter (2004)

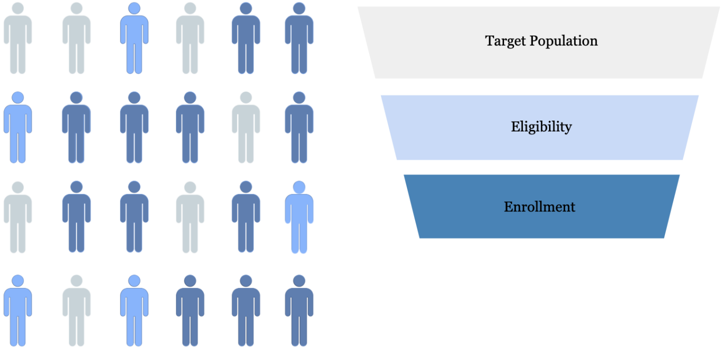
Target Population



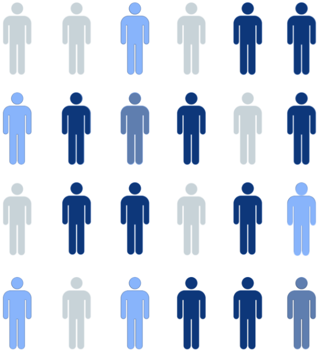
Eligibility

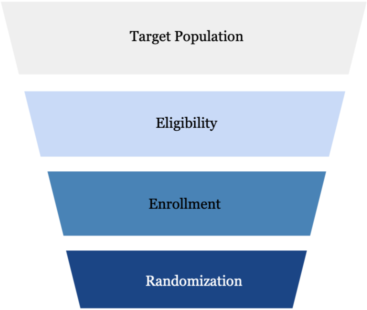


Enrollment

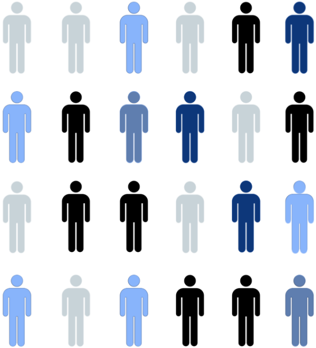


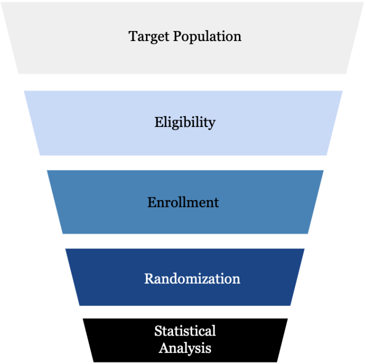
Randomization



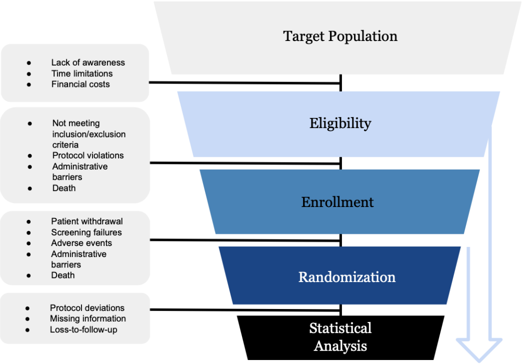


Statistical Analysis





Patient Leakage



Uncertainty

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

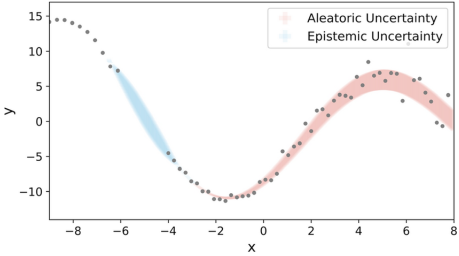


Figure: Visualization of two types of uncertainty (Yang and Li, 2023)

Models for Counts

Methods	Counts	Expectation	Variance	Aleatory	Epistemic
Expectation	$C(t) = \lambda t$	λt	0	No	No
Poisson	$C(t) \sim \mathrm{Po}(\lambda t)$	λt	λt	Yes	No
Negative Binomial	$C(t) \sim \mathrm{Po}(\Lambda t); \Lambda \sim \mathrm{G}(\alpha, \beta)$	$\frac{\alpha}{\beta}$	$\frac{\alpha(\beta+1)}{\beta^2}$	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 $\lambda = \frac{\textit{Counts}}{\textit{Time}} = 0.591$ (Piantadosi, 2024)

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

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- Models for Counts:
  - Expectation: $\mathrm{E}C(t) = \lambda t = 0.591 \cdot 550 = 325$
  - Poisson: $C(t) \sim \mathrm{Po}(\lambda t)$
  - Negative Binomial: $C(t) \sim \mathrm{Po}(\Lambda t)$; $\Lambda \sim \mathrm{G}(\alpha, \beta)$

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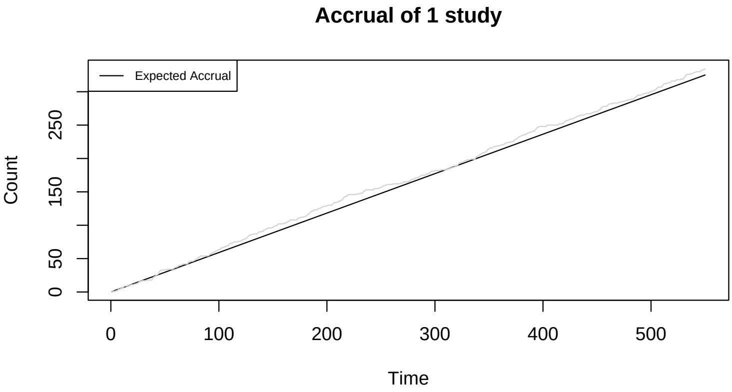
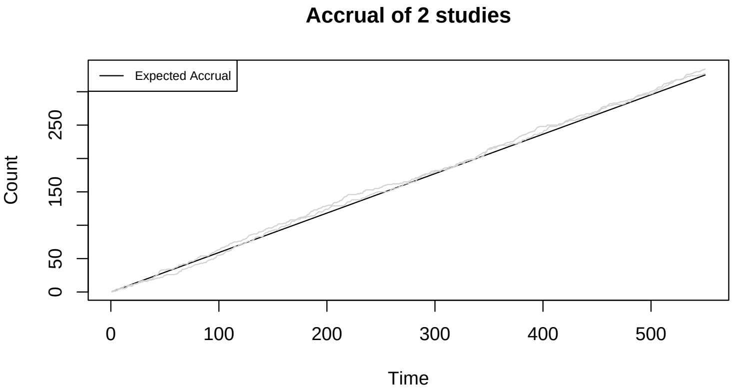
Accrual at time point t

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

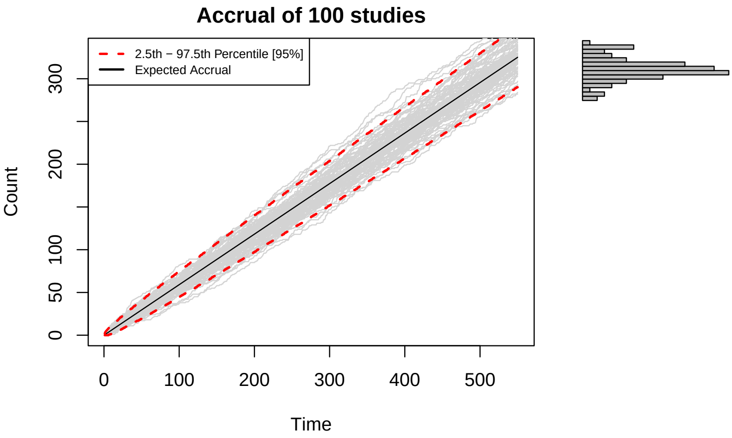
Accrual of 1 study



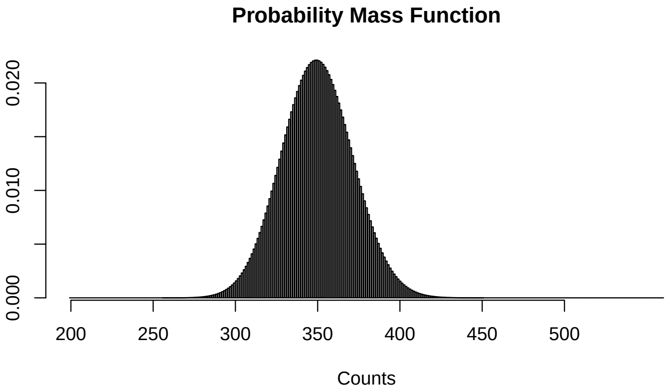
Accrual of 2 studies



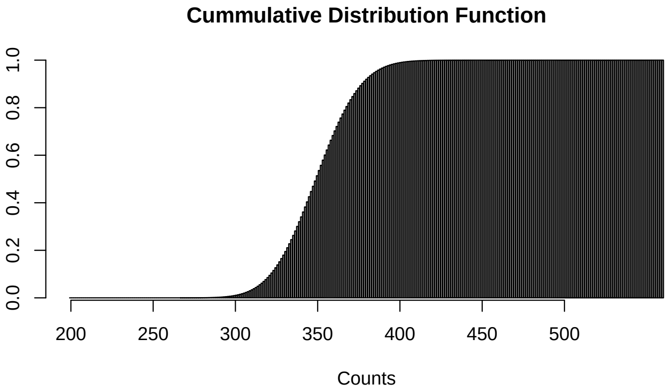
Accrual of 100 studies



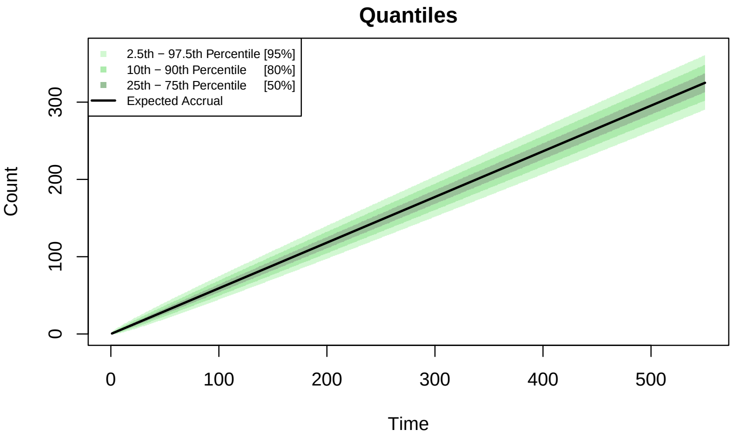
Poisson's theoretical PMF



Poisson’s theoretical CDF



Poisson's uncertainty bands



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

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

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

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

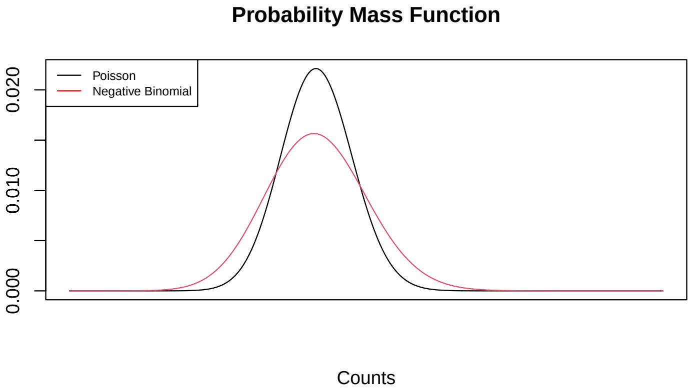
Expectation and Variance

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

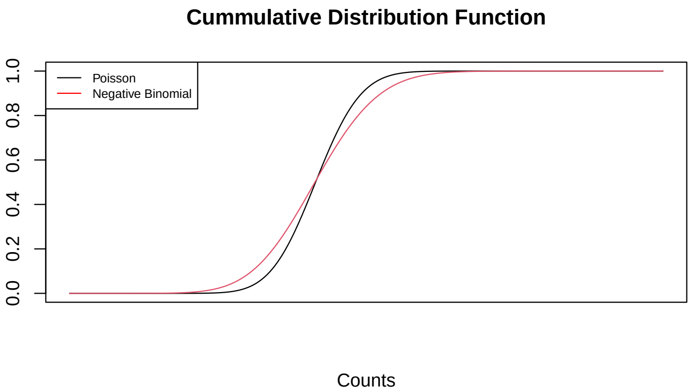
$$\mathrm{E}C = \mathrm{E}_\Lambda[\mathrm{E}_C(C|\Lambda)] = \mathrm{E}_\Lambda[\Lambda] = \alpha/\beta$$

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

Comparison between Poisson and Negative Binomial



Comparison between Poisson and Negative Binomial



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.