



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

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Biostatistics Master Exam



Content

- Recruitment and Patient Leakage
- Methods for Recruited Counts
- Methods for Waiting Time
- Exact methods vs MC simulations
- Conclusions
- Reproducibility ([GitHub](#))



Recruitment and Patient Leakage



Why recruitment rates?

According to [Carter \(2004\)](#)

Timely recruitment vital to the success of a clinical trial

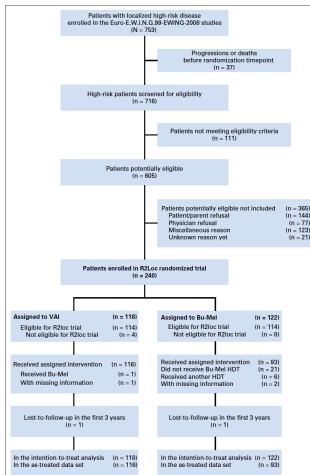
Inadequate number of patients → lack of power

Recruitment period too long → competing treatments

Recruitment of patients varies at each stage

Methods applicable to all the stages

CONSORT





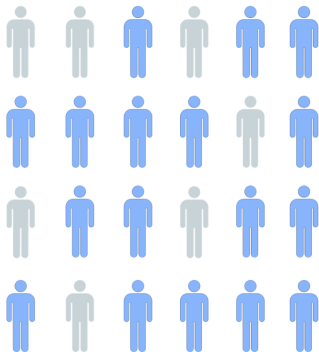
Target Population



Target Population

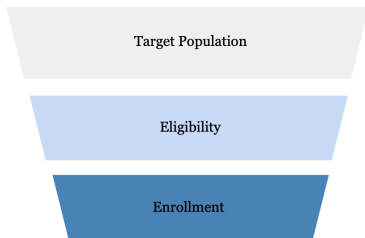
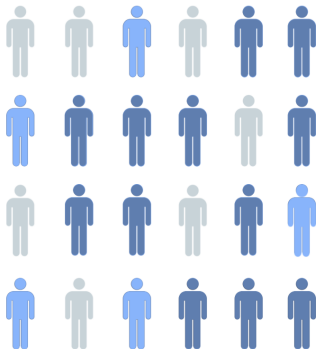


Eligibility



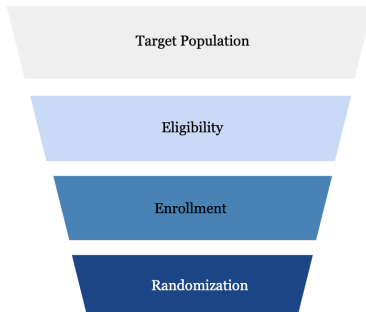
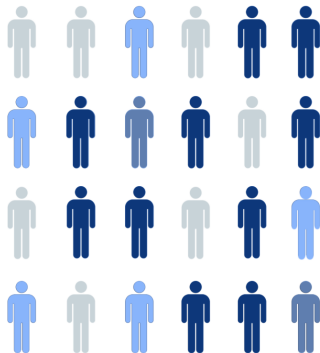


Enrollment



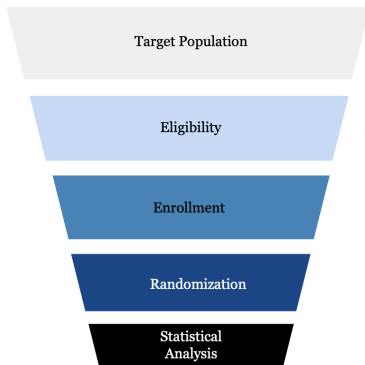
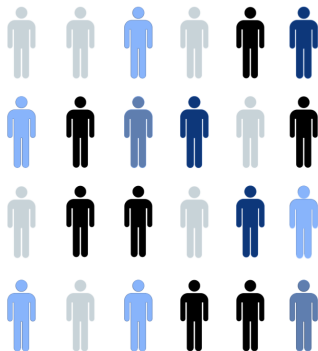


Randomization

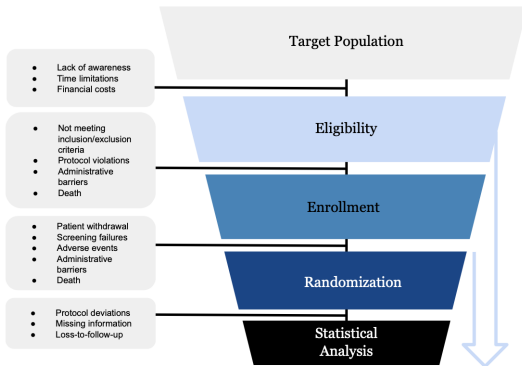




Statistical Analysis



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

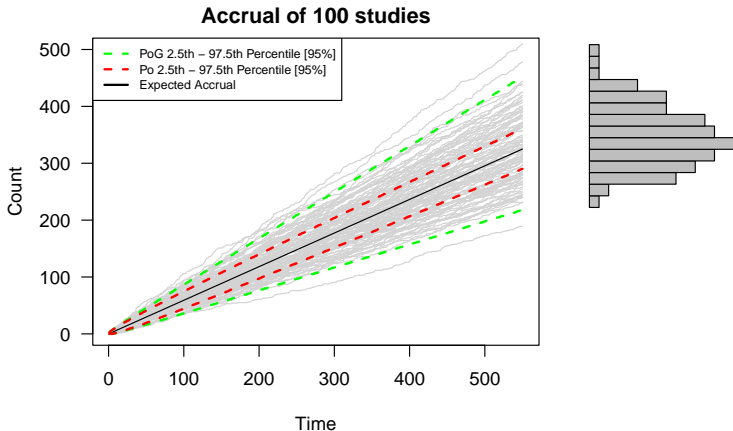
Epistemic uncertainty: arises from limited knowledge about recruitment rates



Methods for Recruited Counts



Motivation Models for Counts



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	$C \sim \text{Po}(\Lambda); \Lambda \sim G(\alpha, \beta)$	$\frac{\alpha}{\beta}$	$\frac{\alpha(\beta+1)}{\beta^2}$	Yes	Yes

Accrual for time t $[0, t]$:

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



Multicenter Trial on Palliation in Terminal Esophageal Cancer

Example from [Carter \(2004\)](#):

Recruitment Rate $\lambda = 0.591$ per day

Time $T_{\text{target}} = 550$ days



Multicenter Trial on Palliation in Terminal Esophageal Cancer

Example from [Carter \(2004\)](#):

Recruitment Rate $\lambda = 0.591$ per day

Time $T_{target} = 550$ days

Models for Counts at time point t :

Expectation: $EC(t) = \lambda t$

Poisson: $C(t) \sim Po(\lambda t)$

Poisson - Gamma: $C(t) \sim Po(\Lambda t); \Lambda \sim G(\alpha, \beta)$

$$\alpha = 32.4 \text{ and } \beta = 54.8$$

$$E\Lambda = \frac{\alpha}{\beta} = 0.591$$



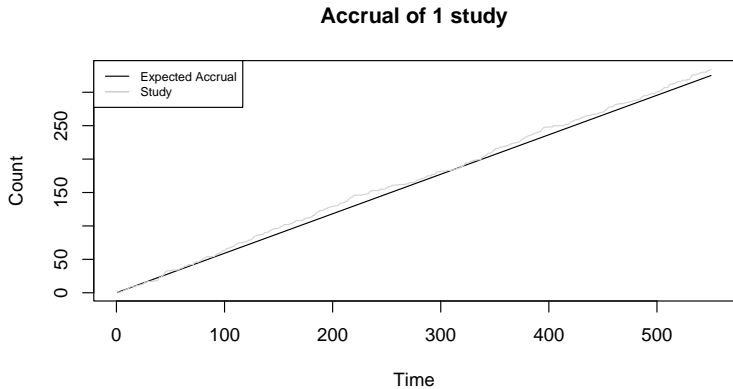
Accrual at time point t

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

$$\text{Poisson: } \underbrace{Po(\lambda) + \dots + Po(\lambda)}_{t \text{ times}} = Po(\lambda t)$$

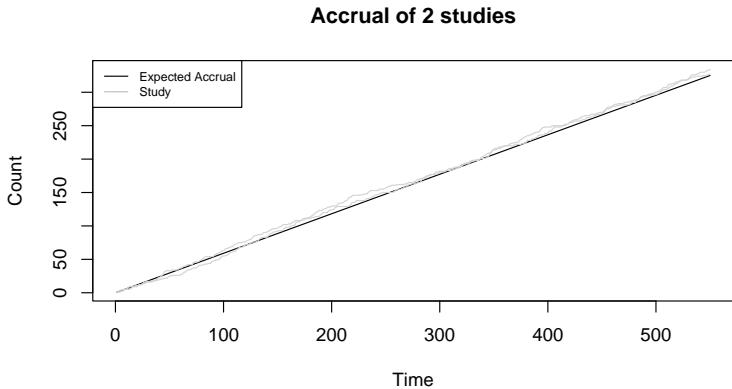


Accrual of 1 study



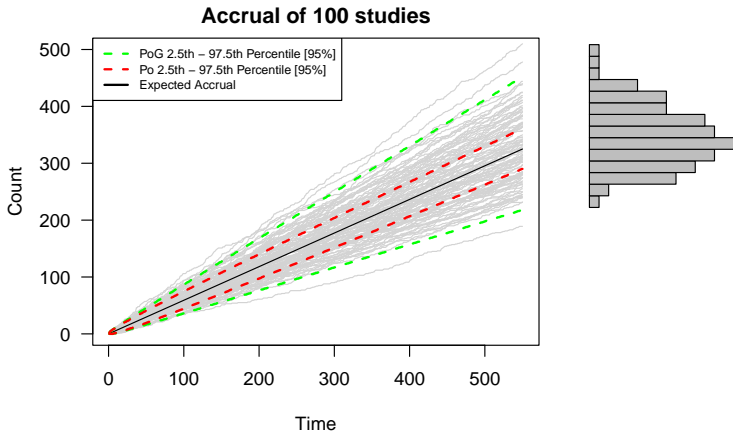


Accrual of 2 studies

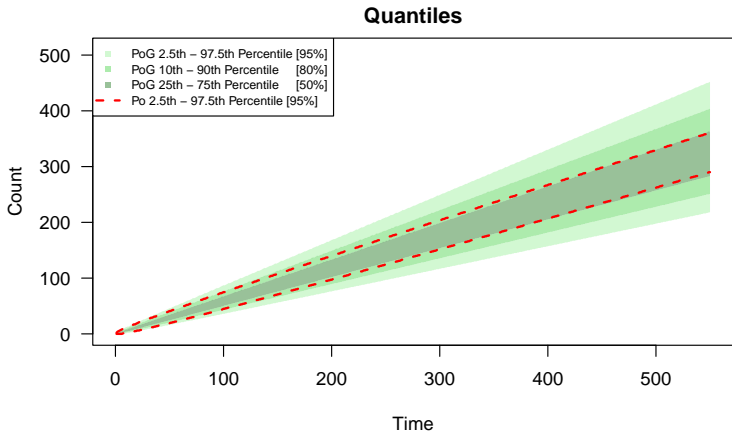




Accrual of 100 studies



Exact uncertainty bands





Two versions of randomness of λ

Version 1 (random-constant): Random recruitment rate realization λ varies across studies and remains **fixed** within study **over time**

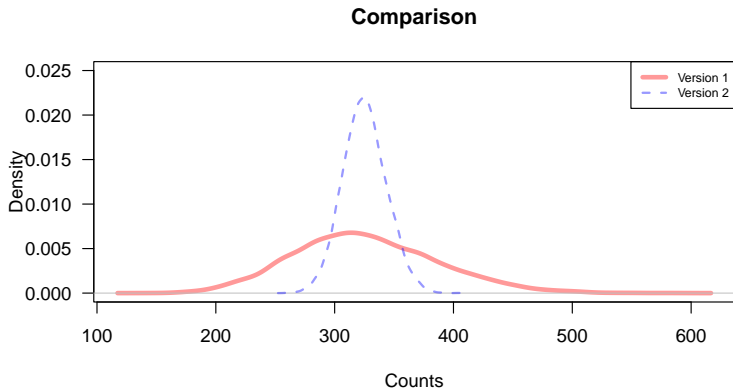
→ PoG distribution

Version 2 (random-random): Random recruitment rate realization λ varies across studies and **varies** within study **over time**

→ Distribution with surprising properties



Version 1 different from Version 2



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

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

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

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

Expectation and Variance for Counts

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

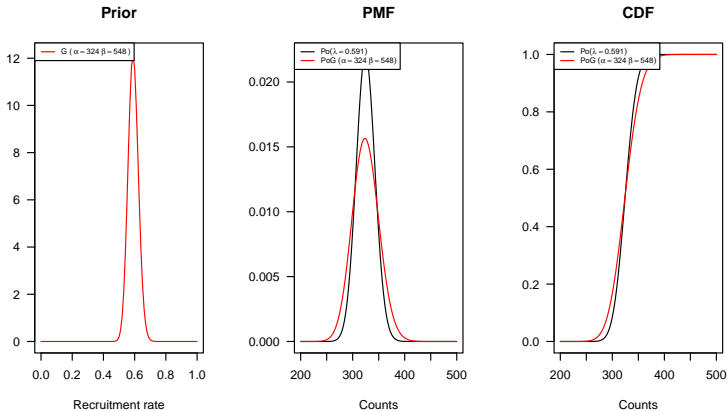
$$E(C(t)) = E_{\Lambda}[E_{C(t)}(C(t)|\Lambda)] = E_{\Lambda}[\Lambda t] = t\alpha/\beta$$

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

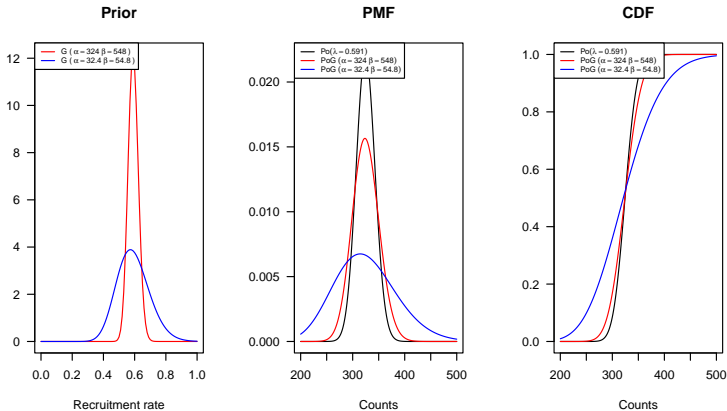


Sensitivity Analysis

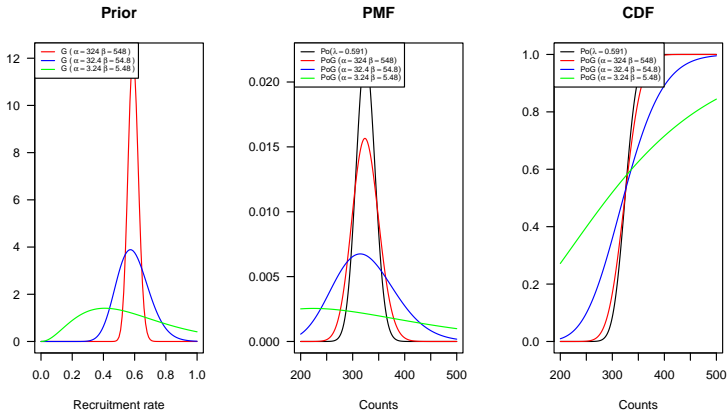
Sensitivity Analysis



Sensitivity Analysis



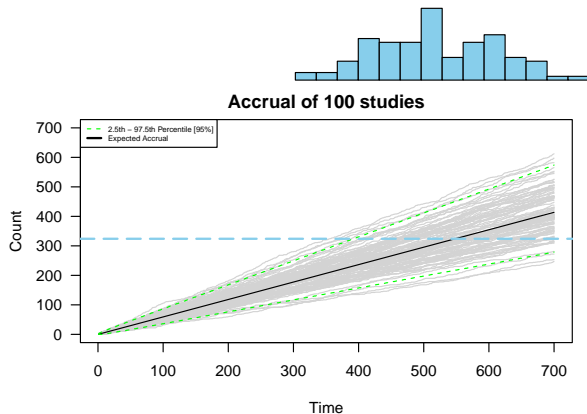
Sensitivity Analysis





Methods for Waiting Time

Motivation Models for Waiting Time





Models for Waiting Time until Target Sample Size c

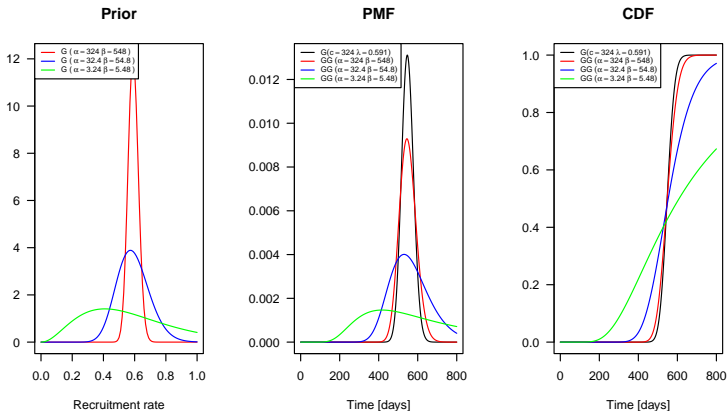
Methods	Time	Expectation	Variance	Aleatory	Epistemic
Expectation	$T(c) = c/\lambda$	c/λ	0	No	No
Erlang	$T(c) \sim G(c, \lambda)$	c/λ	c/λ^2	Yes	No
Gamma-Gamma	$T(c) \sim G(c, \Lambda); \Lambda \sim G(\alpha, \beta)$	$c \frac{\beta}{\alpha-1}$	$\frac{c\beta^2(c+\alpha-1)}{(\alpha-1)^2(\alpha-2)}$	Yes	Yes

Two versions of randomness of Λ

Version 1 \rightarrow GG distribution

Similar derivations as shown for counts

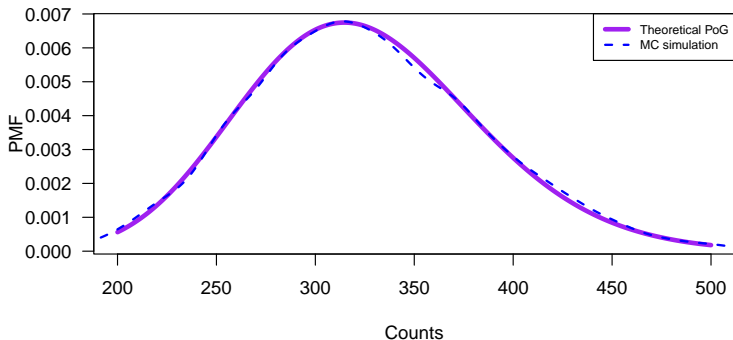
Sensitivity Analysis for Waiting Time





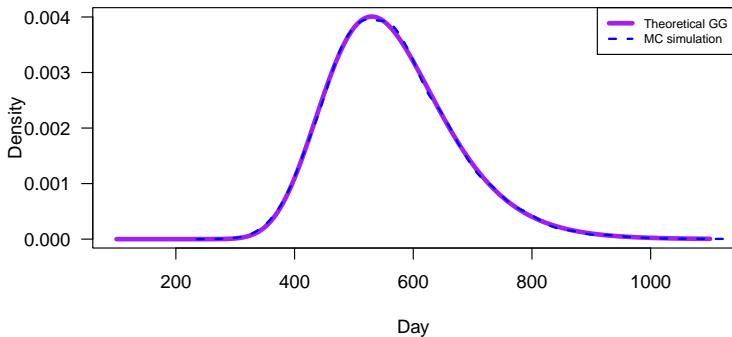
Exact Methods vs MC simulations

Exact Methods vs MC simulations – Poisson-Gamma Counts





Exact Methods vs MC simulations – Gamma-Gamma Time





Exact Methods vs MC simulations

Model	Estimated Probability	MCse	Exact Probability
$C(T) \sim \text{Po}(\lambda T)$	$P(C(T) \geq 324) = 0.5044$	0.005	0.5085
$C(T) \sim \text{PoG}(T, \alpha, \beta)$	$P(C(T) \geq 324) = 0.4799$	0.005	0.5008

Model	Estimated Probability	MCse	Exact Probability
$T(C) \sim G(C, \lambda)$	$P(T(C) \geq 548) = 0.4978$	0.005	0.4955
$T(C) \sim \text{GG}(C, \alpha, \beta)$	$P(T(C) \geq 548) = 0.5196$	0.005	0.5201

Number of simulations: $M = 10^4$



Aleatory VS Aleatory & Epistemic

90% chance of accruing $C_{target} = 324$ patients:

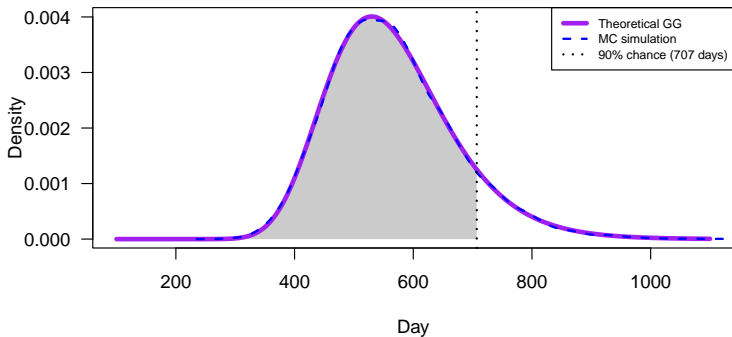
$M = 10^3$ from Carter's \rightarrow 580 days (innacurate)

Erlang exact distribution \rightarrow 588 days

Gamma-Gamma exact distribution \rightarrow 707 days



Aleatory & Epistemic





Conclusions

- Visual tools
- Unified Notation
- Exact Methods
- Flexible Recruitment
- Practical Impact



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