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Blinded Sample Size Reestimation for Time Dependent Negative Binomial Counts with Incomplete Follow-up

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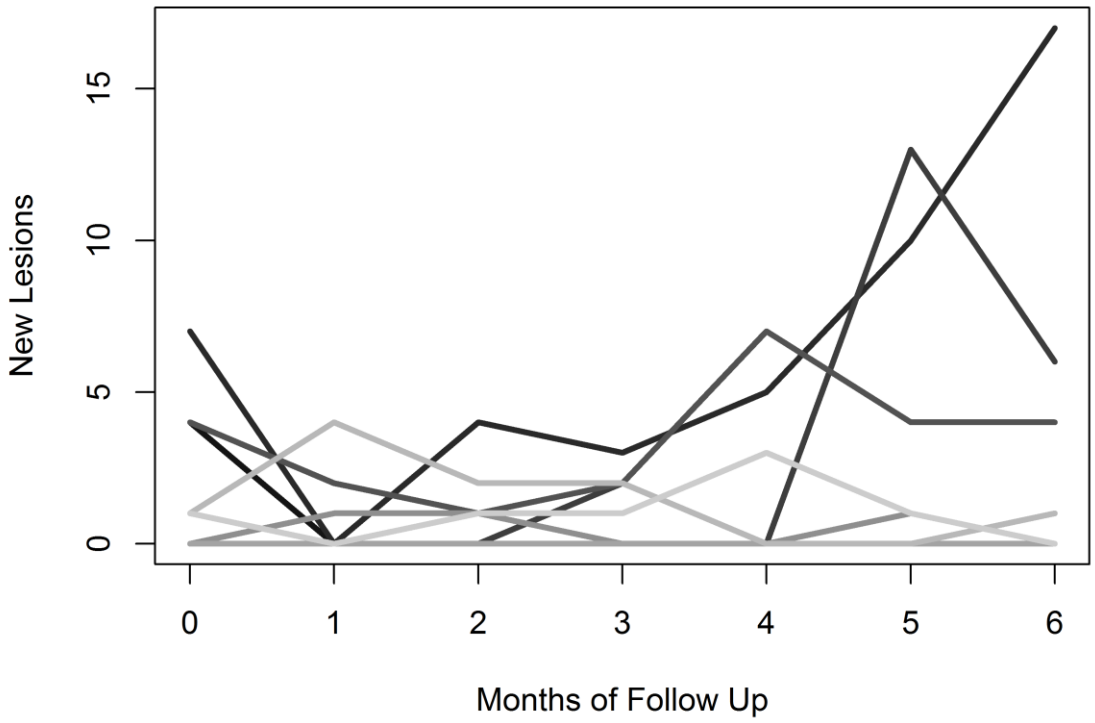
DFG Project: „Blinded sample size reestimation in clinical trials with recurrent event data and time-dependent event rates“

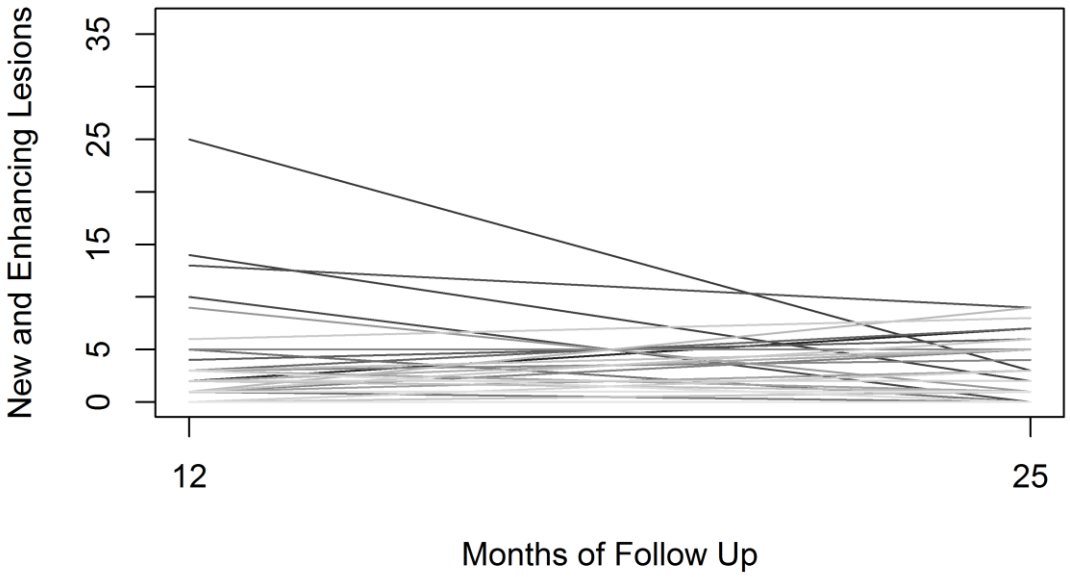
Example – Relapsing Remitting MS



New lesion counts from an RRMS trial, Tubridy 1998.

- Count data
- Time dependency
- Overdispersed observed counts

Example – Secondary Progressive MS



New lesion counts from an SPMS trial, Chataway 2014.

- Count data
- Time dependency
- Overdispersed observed counts

Study Design

- Treatment group (E) and control group (C) with n_E and n_C patients
- Observations gathered over time, $t = 1, \ldots, T$
- Model should allow for time dependent observations
- Observe count data for each patient at each time point (e.g. number of new lesions)

- Possibilities for modeling:
  - Binomial Thinning (McKenzie 1986)
  - Gamma Frailty (Henderson 2003, Fiocco 2009)

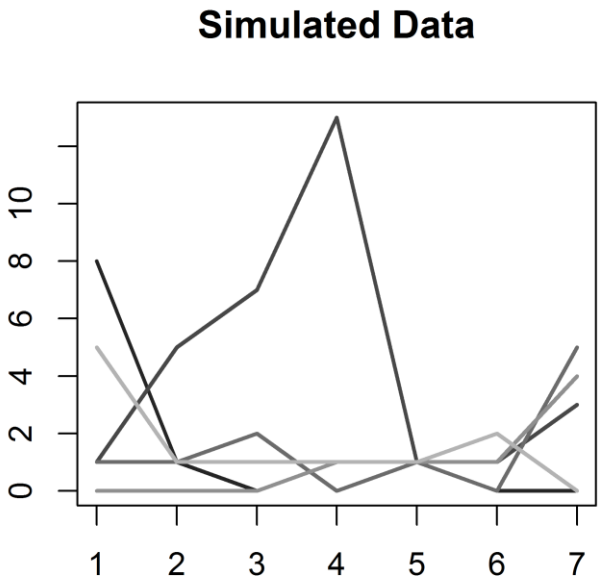
Statistical Model – Binomial Thinning (McKenzie 1986)

- Distribution of observations ($i = E, C; j = 1, \dots, n_i; t = 1, \dots, T$):

$$X_{ij}^{(t)} = \sum_{k=1}^{X_{ij}^{(t-1)}} B_{ik}^{(t)}\left(U_i^{(t)}\right) + W_{ij}^{(t)}$$

- $B_{ik}^{(t)}(p) \sim Bernoulli(p)$
- $U_i^{(t)} \sim Beta(a\eta, (1-a)\eta)$
- $W_{ij}^{(t)} \sim NB((1-a)\lambda_i, (1-a)\eta)$
- Marginal distribution: $X_{ij}^{(t)} \sim NB(\lambda_i, \eta)$, Covariance: $Cov\left(X_{ij}^{(t)}, X_{ij}^{(t+k)}\right) = a^k \lambda_i (1 + \frac{\lambda_i}{\eta})$
- Parameters: $a \in [0,1]$, $\eta \in (0, \infty)$, $\lambda_i \in (0, \infty)$

Binomial Thinning – Simulated Data



- Dependency larger for higher values of a
- Average new lesions given through λ_i
- Variance influenced through η

- Marginal NB distribution with equal means and equal shape parameter
- Autoregressive covariance structure with correlation parameter a

Wald Type Statistic – Definition

- Null hypothesis $H_0: \theta = \frac{\lambda_E}{\lambda_C} \geq 1$ vs. alternative hypothesis $H_1: \theta = \frac{\lambda_E}{\lambda_C} < 1$
- Moment estimators $\hat{\lambda}_i$ for $\lambda_i;\ i = E, C$ and $\hat{\eta}$ for η
- Moment estimator $\hat{\rho}$ for $\rho = \sum_{s=1}^{T} \sum_{t=1}^{T} a^{|t-s|}$
- Pivotal quantity for comparing rates:

$$T \cdot \frac{\log\left(\frac{\hat{\lambda}_E}{\hat{\lambda}_C}\right) - \log\left(\frac{\lambda_E}{\lambda_C}\right)}{\sqrt{\rho\left(\frac{1}{n_E}\left(\frac{1}{\lambda_E} + \frac{1}{\eta}\right) + \frac{1}{n_C}\left(\frac{1}{\lambda_C} + \frac{1}{\eta}\right)\right)}} \approx N(0,1)$$

Sample Size Formula – Derivation (Friede & Schmidli 2010)

- Sample size formula (using normal approximation):

$$n_C = \frac{\left(z_\beta + z_\alpha\right)^2 \rho}{T^2 \log(\theta^*)} \left(\frac{(1 + k\theta^*)^2}{(1+k)k\theta^* \bar{\lambda}} + \frac{1}{\eta}\left(1 + \frac{1}{k}\right)\right)$$

- Normal quantiles z_β and z_α
- Sample size allocation factor k s.t. $\mathrm{k} = n_E/n_C$
- Assumed effect size $\theta^* = \lambda_E^*/\lambda_C^*$
- Overall rate $\bar{\lambda} = \frac{1}{n_E+n_C}(n_E\lambda_E + n_C\lambda_\mathrm{C})$
- Shape parameter η, dependency parameter ρ

Blinded Sample Size Re-estimation (BSSR)

Three step procedure: Internal Pilot Study (IPS) Design (Wittes & Brittain, 1990)

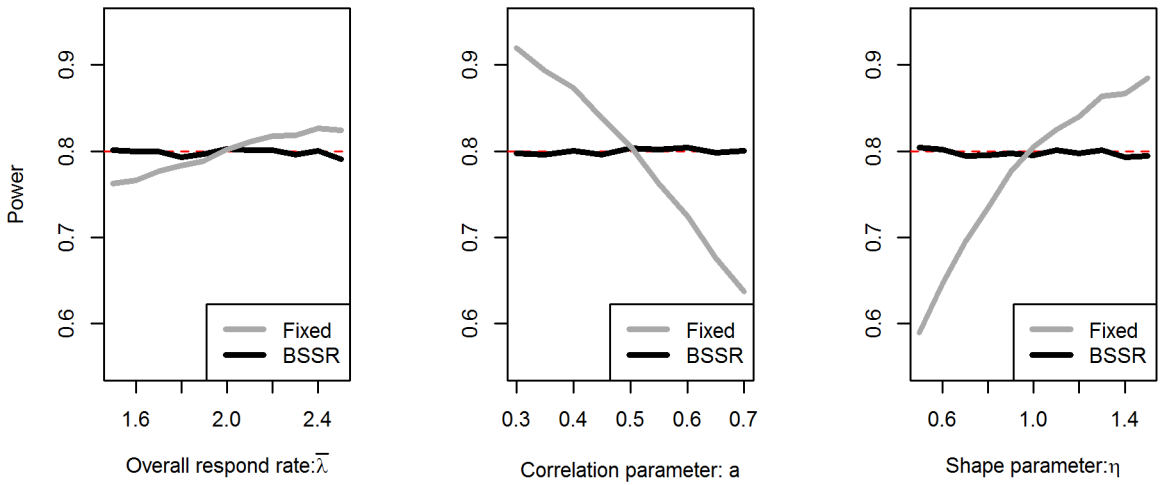
- **Initial sample size calculation** → N_0
  - Based on estimates of nuisance parameters from previous studies
- **Sample size review**
  - When $p \cdot N_0$ (e.g. $p = 1/2$) patients completed the study
  - Re-estimation of sample size based on **ML-estimates of nuisance parameters** → N_1
  - Recruit $N_1 - p \cdot N_0$ further patients and finish trial (Birkett & Day, 1994)
- **Final analysis** based on $\max(p \cdot N_0, N_1)$ patients

BSSR – Simulation Outline

- **Choose** clinically relevant effect size $\theta^* = 0.8$, wanted power $\beta = 0.8$, timepoints $T = 7$, sample size allocation $k = 1$ and **guess** nuisance parameters $\bar{\lambda} = 2$, $\eta = 1$ and $a = 0.5$
  - Calculate N_0 using sample size formula
- Generate data $(N_0/2)$ with $\theta^* = \theta$, but **different nuisance parameters** (i.e. wrong guess)
  - Blinded estimation of nuisance parameters $\bar{\lambda}$, η and a
  - Calculate N_1 using sample size formula with estimations of nuisance parameters
- Compare N_0 with N_1 as well as resulting test power

BSSR – Power Simulation

Simulated power for fixed design and sample size re-estimation.



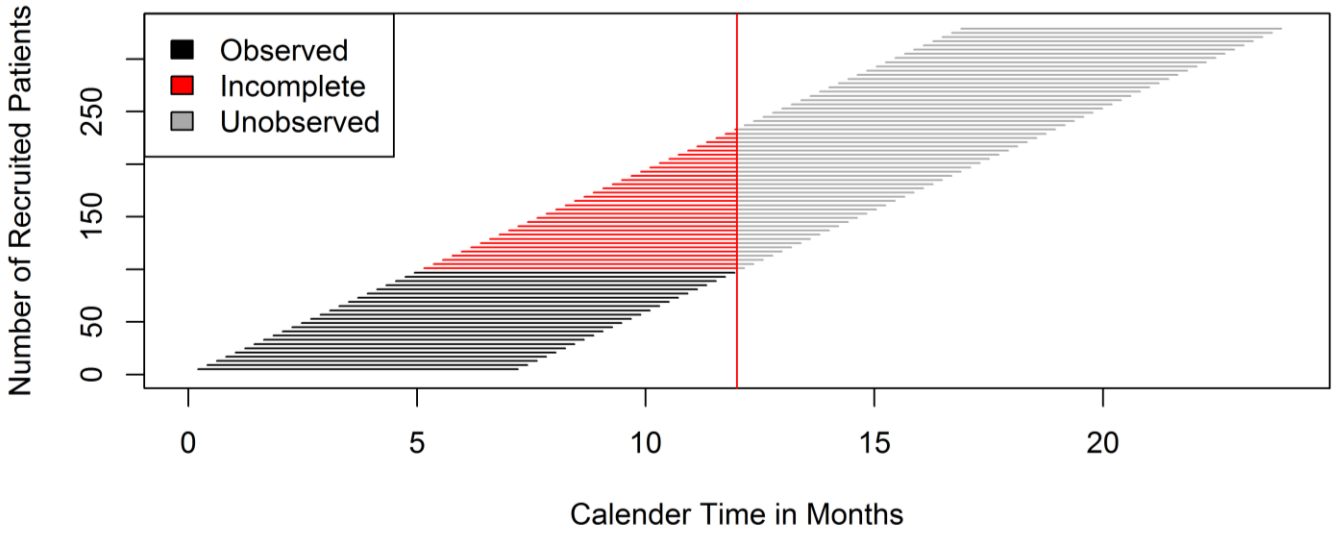
Effect size $\theta^* = \theta = 0.8$
Ass. Overall rate: $\bar{\lambda} = 2$
Ass. correlation: $a = 0.5$
Ass. shape: $\eta = 1$
IPS at $p = 0.5$
Fixed design leads to over-/under powered studies
Power attained through re-estimation is correct

Study Design – Incomplete Observations

- Treatment group (E) and control group (C) with n_E and n_C patients
- Observations gathered over time, $t = 1, \ldots, T$
- Model should allow for time dependent observations
- Observe count data for each patient at each time point (e.g. number of new lesions)
- Allow for incomplete observations at interim analysis

Incomplete Observations – Problem (Schneider 2013b)

- Patients are not examined simultaneously
- Different recruitment schemes lead to incomplete data on interim analysis



Incomplete Observations - Model

- Leave sample size formula unchanged
- Use patient specific follow up ML–estimates of $\rho = \sum_{s=1}^{T} \sum_{t=1}^{T} a^{|t-s|}$, η and $\overline{\lambda}$

$$L\left(x_1^{(1)}, \dots, x_1^{(T_1)}, \dots, x_{n_E+n_C}^{\left(T_{n_E+n_C}\right)}\right) = \prod_{j=1}^{n_E+n_C} f_{X_j^{(1)}}\left(x_j^{(1)}\right) \cdot \prod_{t=1}^{T_j-1} f_{X_j^{(t+1)}|X_j^{(t)}}\left(x_j^{(t+1)}\right)$$

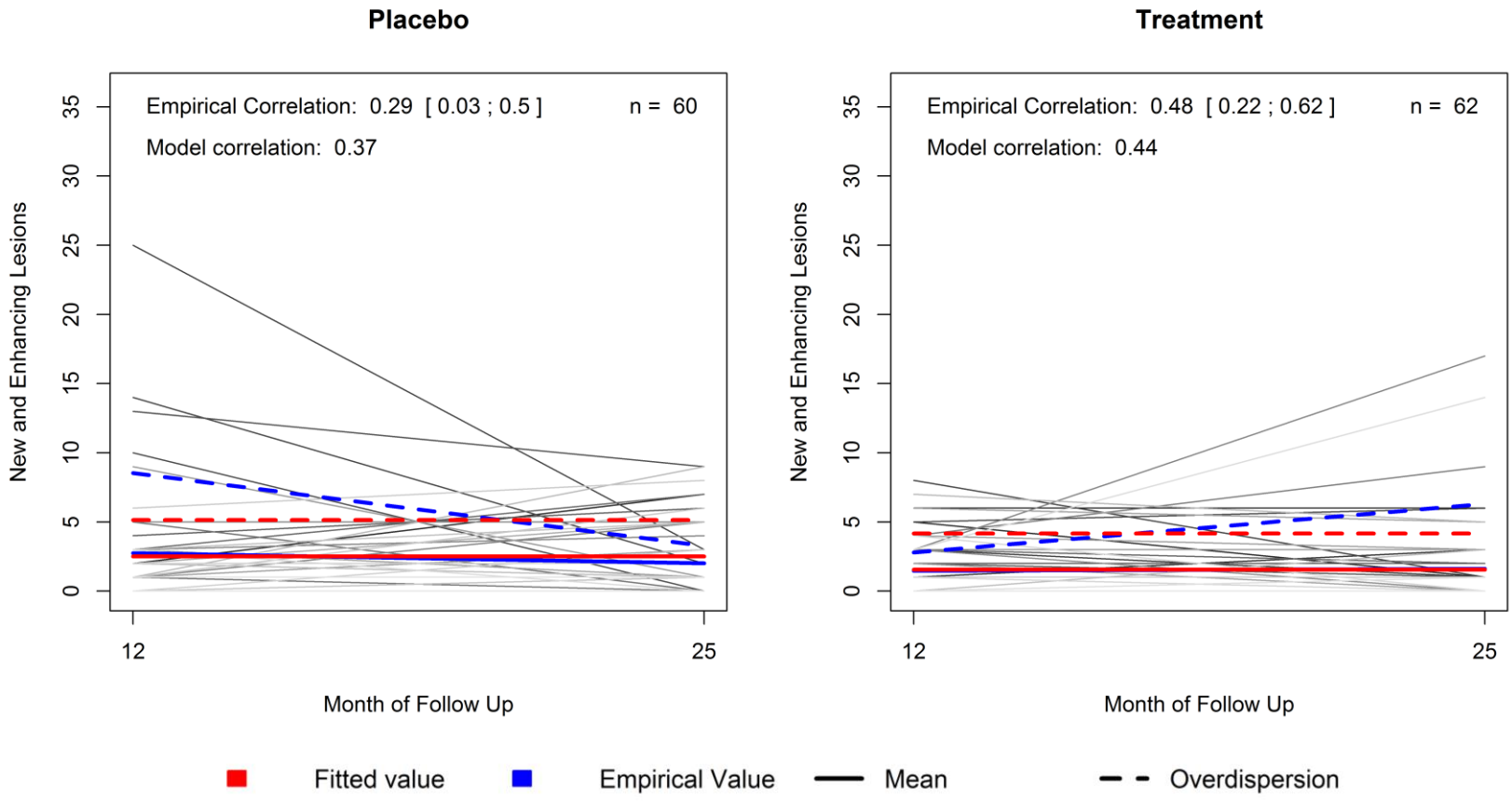
Incomplete Observations - Simulation

	Incomplete Observations		Complete Observations	
Month of Review	Mean	Sd	Mean	Sd
8	164.92	15.90	164.35	23.58
10	165.13	13.05	164.99	16.49
12	165.28	11.54	165.24	13.68
14	165.20	10.43	165.12	11.78
16	165.33	9.38	165.25	10.45

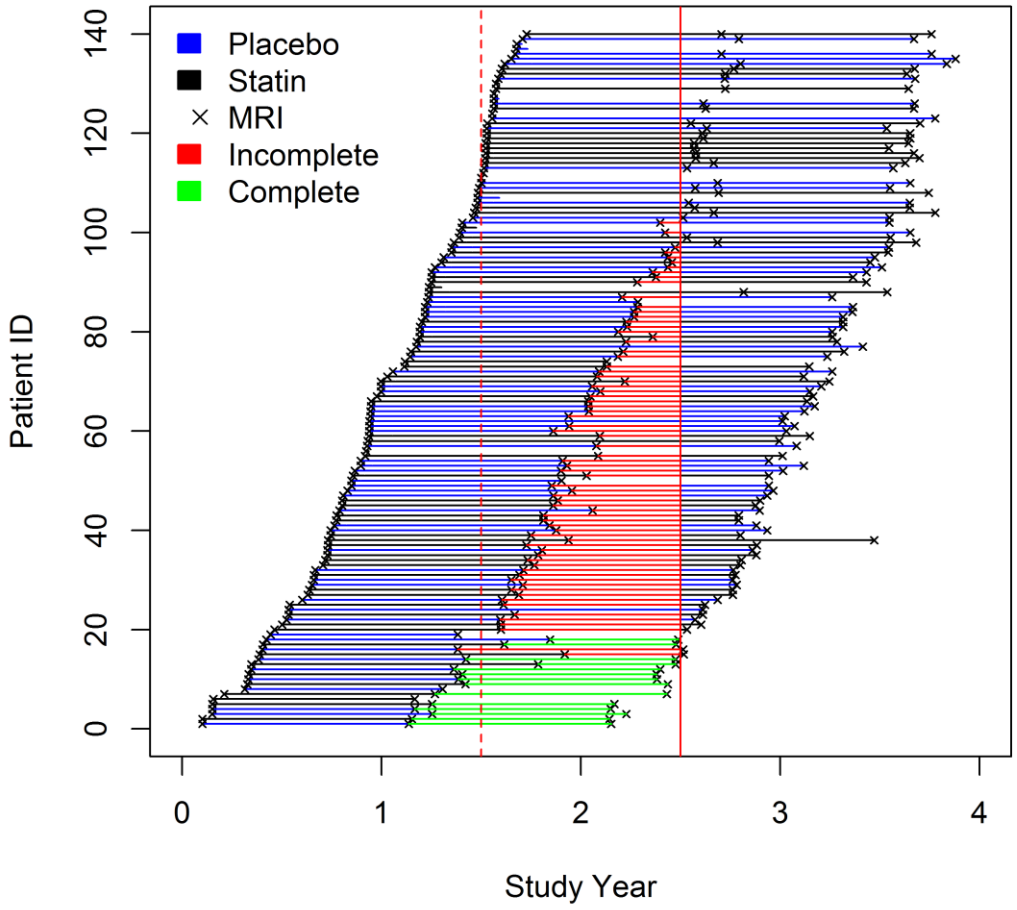
Simulate BSSR with use of complete observations vs. including incomplete observations

- Effect size $\theta^* = \theta = 0.8$
- Ass. Overall rate: $\bar{\lambda} = 2$
- Ass. dependency: $a = 0.5$
- Ass. shape: $\eta = 1$
- Required sample size: $n_C = 165$
- IPS at 8,…,16 months
- Using incomplete data leads to lower standard deviation of sample size estimate

Example – Fitting Data



Example – Recruitment Scheme



Example – Initial Sample Size

- Initial sample size calculation using parameters observed in other studies:

```
> n.estimate<-n.nb.inar1(alpha=0.05, beta=0.8,
                         delta=0.6, muC=2.5, size=0.6, rho=0.4, tp=2, k=1)
> summary(n.estimate)

     Initial Sample Size Calculation
     -------------------------------
     alpha level: 0.05
     testing power: 0.8
     rate ratio: 0.6
     rate control group: 2.5
     dispersion parameter: 0.6
     correlation parameter: 0.4
     time points: 2
     allocation factor: 1

     Sample Size
     -------------------------------
     control group: 72.97
     treatment group: 72.97
```

Example – Blinded Sample Size Reestimation

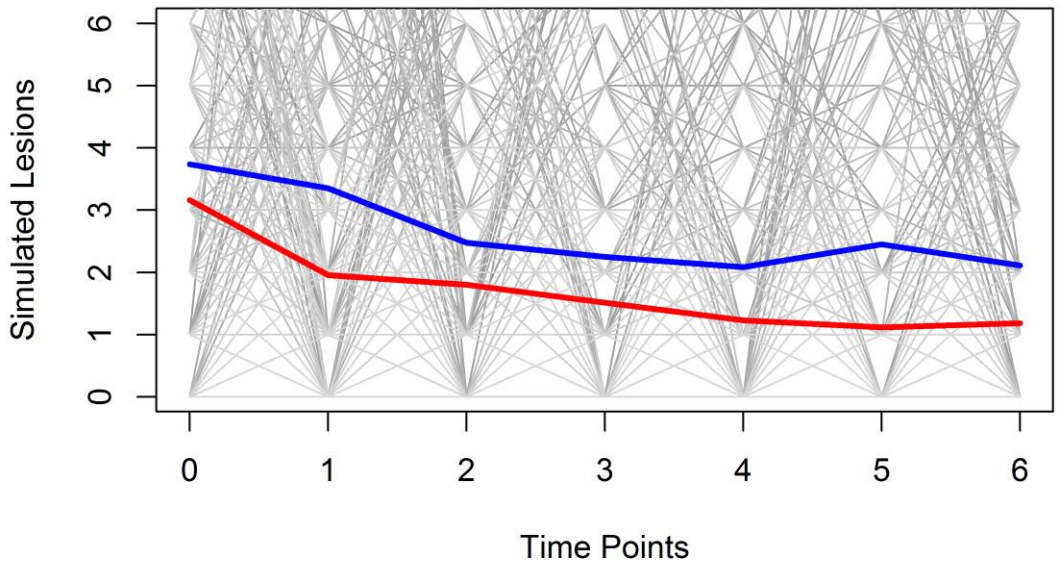
- Blinded sample size reestimation after 2.5 years into the study:

```
> n.reestimate<-bssr.nb.inar1(alpha=0.05, beta=0.8, delta=0.6,
                      x=data.bssr, n=c(46, 46), k=1)
> summary(n.reestimate)

     Blinded Sample Size Reestimation
     --------------------------------
     alpha level: 0.05
     testing power: 0.8
     rate ratio: 0.6
     est. overall rate: 2.16
     est. dispersion parameter: 0.56
     est. correlation parameter: 0.42
     time points: 2
     desired allocation factor: 1

     Reestimated Sample Size
     --------------------------------
     control group: 76.45
     treatment group: 76.45
```

Study Design – Incorporating Trends

- Treatment group (E) and control group (C) with n_E and n_C patients
- Observations gathered over time, $t = 1, \ldots, T$
- Model should allow for time dependent observations
- Observe count data for each patient at each time point (e.g. number of new lesions)
- Allow for incomplete observations at interim analysis
- Allow for an underlying time trend which influences the rates

Incorporating Trends



Rates of new lesion counts may gradually decline/increase over time (Stellmann 2015)

Possible modeling: serially correlated gamma-frailty process (Henderson 2003, Fiocco 2009)

Outlook

- Find sample size estimates and reestimation methods for trend model
- Test for robustness of models / compare binomial thinning and gamma frailty
- Incorporate intermittent missing values
- Adjust time points T opposed to sample size

Acknowledgments: Research Supported by DFG Project: „Blinded sample size reestimation in clinical trials with recurrent event data and time-dependent event rates“, Chataway et. al. for real data example

References 1

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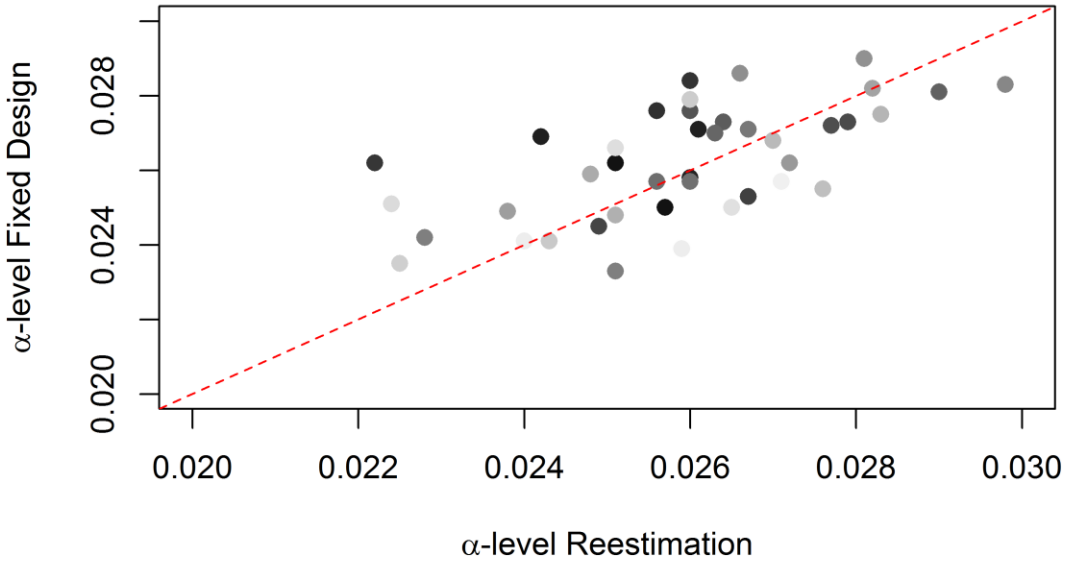
Incorporating Trends – Model Formulation

- Medication might take some time to fully develop → Trend (Stellmann 2015)
- Distribution of observations $(i = E, C; j = 1, \dots, n_i; t = 0, \dots, T)$:

$$X_{ij}^{(t)} = \sum_{k=1}^{X_{ij}^{(t-1)}} B_{ik}^{(t)}\left(U_i^{(t)}\right) + W_{ij}^{(t)}$$

- Before: $X_{ij}^{(1)} \sim NB(\lambda_i, \eta)$, $W_{ij}^{(t)} \sim NB\big((1-a)\lambda_i, (1-a)\eta\big)$ and $U_i^{(t)} \sim Beta(a\eta, (1-a)\eta)$
- Trend Model: $X_{ij}^{(0)} \sim NB(\lambda_0, \eta_0)$, $U_i^{(t)} \sim Beta(a\eta, (1-a)\eta)$ for $t = 1, \dots, T$
- Innovation Distribution: $W_{ij}^{(t)} \sim NB\big((1-a)\lambda_i, \eta\big)$ for $t = 1, \dots, T$

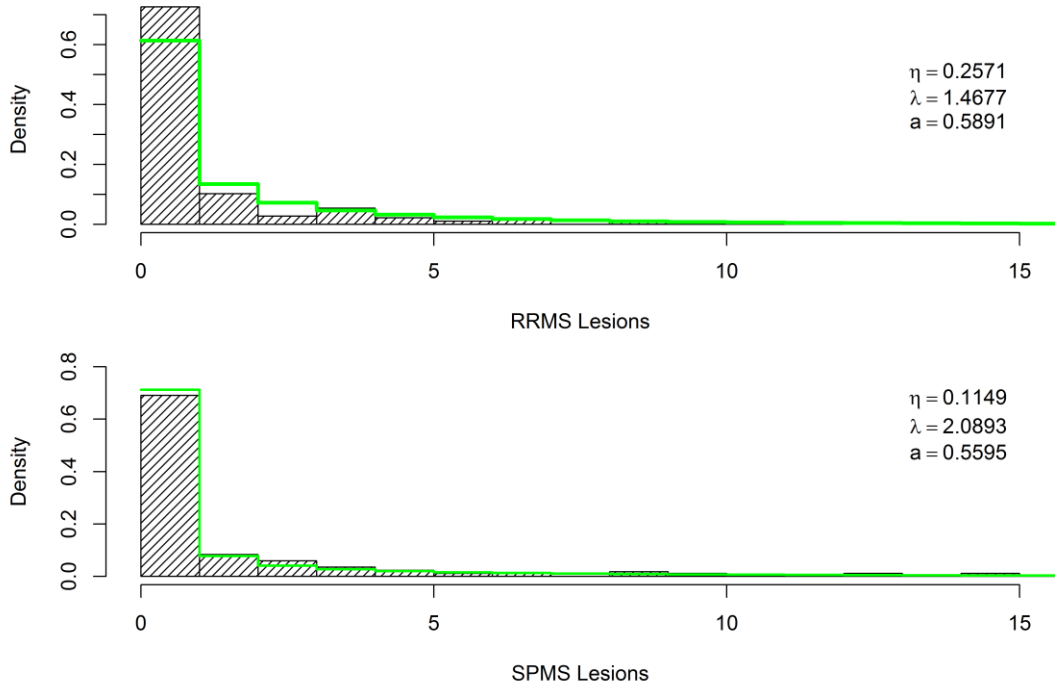
BSSR – Type I Error



Simulated type I error ($\alpha = 0.025$)

- Effect size $\theta^* = 1$
- IPS at $p = 0.5$
- Overall rate $\bar{\lambda} \in [0.5, 4]$
- Shape $\eta \in [0.15, 2.40]$
- Dep. parameter $a \in [0.30, 0.95]$
- No type I error inflation through BSSR observed

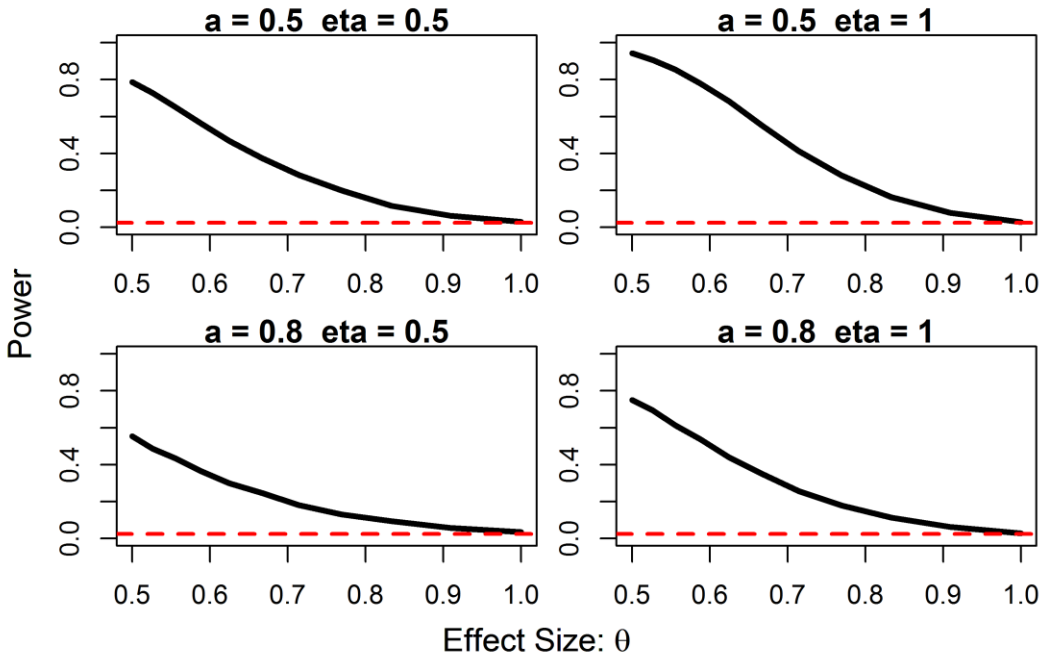
Statistical Model – NB vs Real Data



Comparison of real data and negative binomial distribution

- Resemblance with NB distribution
- Fit for SPMS slightly better than RRMS

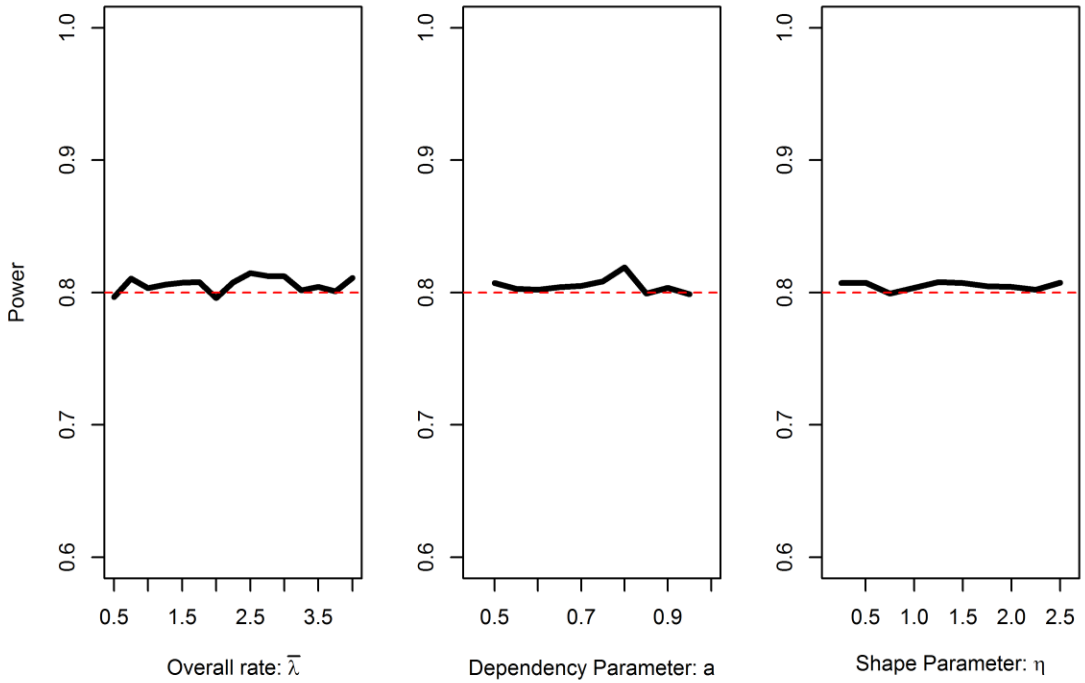
Wald Type Statistic – Power Simulation



Power simulation for the Wald type statistic.

- $n_E = 25, n_C = 25$
- $T = 7$
- Alpha level is controlled
- Power increases under alternative

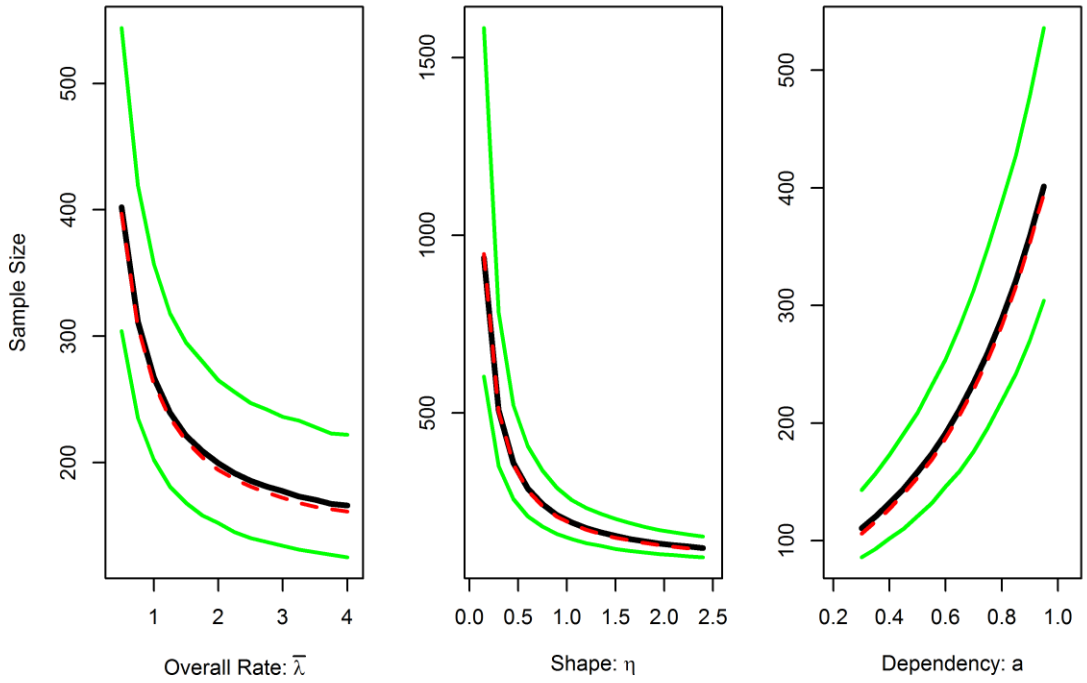
Sample Size Formula – Simulation



Simulated sample size estimation.

- Effect size $\theta^* = \theta = 0.6$
- Desired power $\beta = 0.8$
- Dep. parameter $a = 0.6$
- Overall Rate $\bar{\lambda} = 2$
- Shape parameter $\eta = 0.5$

BSSR – Sample Size Simulation



Simulated sample size re-estimation.

- Effect size $\theta^* = \theta = 0.8$
- IPS at $p = 0.5$
- Re-estimated sample size coincides with sample size formula
- Deviation of up to 25% of total sample size

Incorporating Trends – Model Formulation (Fiocco 2009)

- Generate $\boldsymbol{Z} = (Z_1, \dots, Z_T) \sim \Gamma(\mathbf{1}, \boldsymbol{V})$ with $Cor\big(Z(s), Z(t)\big) = \rho^{|s-t|}$ and $Var\big(Z(s)\big) = \eta^{-1}$
- Generate $\boldsymbol{Y} = (Y_1, \dots, Y_T)$ s.t. $Y_t | Z_t \sim Poi(\mu_t Z_t)$
- Then $Y_t \sim NB(\mu_t, \eta)$ and $Cov(Y_s, Y_t) = \rho^{|s-t|}\mu_s\mu_t\eta^{-1}$

- Attain trend through: $\mu_t = \lambda_0 \cdot a^t + \lambda_i \cdot (1-a)^t$ for $i = E, C$

Gamma frailty model vs. Binomial thinning

- Marginal NB distribution while allowing **unequal means**

- Full likelihood not attainable → But composite likelihood approach possible (Varin 2011)
- Correlation ist defined within gamma frailty. Correlation between observed values is not arbitrary
- Correlation structure between gamma frailty terms is autoregressive. For unequal means, the correlation between observed values differs