Blinded Sample Size Re-estimation for Negative Binomial Counts using the R-package spass

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Example – Why present an R-Package too?

Adaptive designs in clinical trials: why use them, and how to run and report them


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Abstract

Adaptive designs can make clinical research designs more efficient. They require fewer participants. Adaptive designs can be applied across all phases of clinical research, from early-phase dose escalation to confirmatory trials. The pace of the uptake of adaptive designs in clinical research, however, has remained well behind that of the statistical literature introducing new methods and highlighting their potential advantages. We speculate that one factor contributing to this is that the full range of adaptations available to trial...
Example – Relapsing Remitting MS

New lesion counts from an RRMS trial, Tubridy 1998.

- 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, $t = 1, ..., T$
- Time dependent observations
- Count data for each patient at each time point (e.g. number of new lesions)
- Allow for incomplete observations at interim analysis
- Possible Model:
  - NB-INAR(1) model based on bionomial thinning \( (\text{McKenzie 1986, Al-Osh & Alzaid 1987}) \)
- Allow for underlying time trends
Study Design – Temporal Trends in Placebo ARR

(Steinvorth 2013)
Study Design – Temporal Trends in Placebo ARR

(Nicholas 2012)
Study Design

- Treatment group (E) and control group (C) with \( n_E \) and \( n_C \) patients
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- Allow for underlying time trends
- Possible Model:
  - Gamma Frailty (Henderson 2003, Fiocco 2009)
Incorporating Trends – Model Formulation (Fiocco 2009)

- Create observations $X_{ij}^{(t)}$ ($i = E, C; j = 1, ..., n_i; t = 1, ..., T$)
- Generate $Z_{ij} = (Z_{ij}^{(1)}, ..., Z_{ij}^{(T)}) \sim \Gamma(1, V)$ with $Cor\left(Z_{ij}^{(s)}, Z_{ij}^{(t)}\right) = \rho^{|s-t|}$ and $Var\left(Z_{ij}^{(s)}\right) = \eta^{-1}$
- Generate $X_{ij} = (X_{ij}^{(1)}, ..., X_{ij}^{(T)})$ s.t. $X_{ij}^{(t)}|Z_{ij}^{(t)} \sim Pois\left(\mu_i^{(t)}Z_{ij}^{(t)}\right)$
- Then $X_{ij}^{(t)} \sim NB\left(\mu_i^{(t)}, \eta\right)$ and $Cov\left(X_{ij}^{(s)}, X_{ij}^{(t)}\right) = \rho^{|s-t|}\mu_i^{(s)}\mu_i^{(t)}\eta^{-1}$

- Attain trends by adjusting values $\mu_i^{(t)}$ accordingly
- Careful! Correlation of observations $Cor\left(X_{ij}^{(s)}, X_{ij}^{(t)}\right)$ is not equal to $\rho^{|s-t|}$
Incorporating Trends – Possible Specifications

Functions of trend parameters which define the expected rates

▷ Constant:

\[ \mu_E^{(t)} = f_E^{(t)}(\lambda_1, \lambda_2) = \exp(\lambda_1 + \lambda_2) \]
\[ \mu_C^{(t)} = f_C^{(t)}(\lambda_1, \lambda_2) = \exp(\lambda_1) \]

▷ Exponential trend:

\[ \mu_E^{(t)} = f_E^{(t)}(\lambda_1, \lambda_2, \lambda_3) = \exp\left(\lambda_1 + \frac{t}{T} \cdot (\lambda_2 + \lambda_3)\right) \]
\[ \mu_C^{(t)} = f_C^{(t)}(\lambda_1, \lambda_2, \lambda_3) = \exp\left(\lambda_1 + \frac{t}{T} \cdot \lambda_2\right) \]

▷ Generally we will denote:

\[ \mu_i^{(t)} = f_i^{(t)}(\lambda) \]
Wald Type Statistic

- Null hypothesis \( H_0: h(\eta, \lambda) \geq h_0 \) vs. alternative hypothesis \( H_1: h(\eta, \lambda) < h_0 \)
- ML-estimators \( \hat{\lambda} \) for \( \lambda \) and \( \hat{\eta} \) for \( \eta \)
- Estimators \( \hat{H} \) and \( \hat{J} \) for sandwich estimator \( H^{-1}JH^{-1} \)
- Pivotal quantity for testing the null hypothesis:

\[
\sqrt{n_C + n_E} \cdot \frac{h(\hat{\eta}, \hat{\lambda}) - h_0}{\sqrt{(\nabla_{(\eta,\lambda)} h(\hat{\eta}, \hat{\lambda}))(\hat{H}^{-1} \hat{J} \hat{H}^{-1})\nabla_{(\eta,\lambda)} h(\hat{\eta}, \hat{\lambda})}} \approx N(0,1)
\]
Sample Size Formula

- Sample size formula (using normal approximation):

\[ n_C = \frac{(z_\beta + z_\alpha)^2 \cdot \sigma^2}{(1 + k) \cdot \theta^*} \]

- Normal quantiles \( z_\beta \) and \( z_\alpha \) (power = 1 − \( \beta \))

- Sample size allocation factor \( k \) such that \( k = n_E/n_C \)

- Assumed effect size \( \theta^* = h(\eta^*, \lambda^*) - h_0 \)

- Variance \( \sigma^2 = V_{(\eta, \lambda)}h(\eta, \lambda)'(H^{-1}JH^{-1})V_{(\eta, \lambda)}h(\eta, \lambda) \)

- Rates, shape parameter and correlation are components of \( \sigma^2 \)
Blinded Sample Size Re-estimation – Procedure

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 *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 $\lambda_3^* = -0.05$, wanted power $1 - \beta = 0.8$, significance level $\alpha = 2.5\%$ timepoints $T = 7$, sample size allocation $k = 1$ and **guess** nuisance parameters $\lambda_1 = 0$, $\lambda_2 = 0$, $\eta = 1$ and $\rho = 0.5$.
  - Calculate $N_0$ using sample size formula

- Generate data ($N_0/2$) with $\lambda_3^* = \lambda_3$, but **different nuisance parameters** (i.e. wrong guess)
  - Blinded estimation of nuisance parameters $\lambda_1$, $\lambda_2$, $\eta$ and $\rho$
  - 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

[Graphs showing power and sample size in relation to different parameters such as intercept, slope, correlation, and shape.]
BSSR – Example  (R package: spass)

- n.nb.gf(...): calculate initial sample size estimate
- get.groups(...): simulate observations from the gamma frailty model
- bssr.nb.gf(...): blinded sample size re-estimate
Outlook & Conclusion

- Blinded sample size reestimation for arbitrary trends in longitudinal negative binomial data
- User friendly implementation of custom trends in R
- Handle intermittent missingness
- Extension to other arbitrary dependency structures
References 1


References 2

References 3


Blinded Estimation

\[
l_{\text{blind}}(\eta, \lambda | x) = \frac{1}{n_C + n_E} \sum_{j=1}^{n_E+n_C} \sum_{t=1}^{T} \ln \left( \frac{k}{1+k} \cdot P_{NB} \left( x_j^{(t)}, f_E^{(t)}(g(\lambda_C)), \eta \right) + \frac{1}{1+k} \cdot P_{NB} \left( x_j^{(t)}, f_C^{(t)}(\lambda_C), \eta \right) \right)
\]

\[
c_{\text{blind}}(\rho | \eta, \hat{\lambda}, x) = \frac{1}{n_C + n_E} \sum_{j=1}^{n_E+n_C} \sum_{t=1}^{T-1} \sum_{s=t+1}^{T} \ln \left( \frac{k}{1+k} \cdot P_{NB}^{\text{pair}} \left( x_j^{(t)}, x_j^{(s)}, \rho, f_E^{(t)}(g(\hat{\lambda}_C)), f_E^{(s)}(g(\hat{\lambda}_C)), \hat{\eta} \right) \right)
\]

\[
P_{NB}^{\text{pair}} \left( x_{ij}^{(t)}, x_{ij}^{(s)}; \rho, \mu_i^{(t)}, \mu_i^{(s)}, \eta \right) = \sum_{k=0}^{x_{ij}^{(s)}} \sum_{l=0}^{x_{ij}^{(t)}} P_{NB} \left( k, \mu_i^{(s)}(1 - \rho^{s-t}), \eta(1 - \rho^{s-t}) \right)
\]

\[
\cdot P_{NB} \left( k, \mu_i^{(t)}(1 - \rho^{s-t}), \eta(1 - \rho^{s-t}) \right)
\]

\[
\cdot P_{NB} \left( x_{ij}^{(t)} + x_{ij}^{(s)} - k - l, (\mu_i^{(s)} + \mu_i^{(t)})(1 - \rho^{s-t}), \eta \rho^{s-t} \right)
\]

\[
\cdot P_{BIN} \left( x_{ij}^{(s)} - k, x_{ij}^{(s)} + x_{ij}^{(t)} - k - l, \frac{\mu_i^{(s)}}{\mu_i^{(s)} + \mu_i^{(t)}} \right)
\]
Type I Error Simulation
Study Design – Incomplete Observations

- Patients are not examined simultaneously
- Different recruitment schemes lead to incomplete data on interim analysis
BSSR – Type I Error Simulation

Type I error simulation for two settings with 102 and 27 samples per group, respectively

- No influence of BSSR on Type I Error
- Testing procedure showed Type I Error inflation
- Solution: restrict estimation of sandwich estimator to \( \{(\eta, \lambda) \in \mathbb{R}^{D+1} \mid h(\eta, \lambda) \geq h_0\} \)
BSSR – Example (Fernandez et al. 2018)

Example from phase II clinical trial in MS

- Treatment: Adipose-derived mesenchymal stem cells
- Placebo group \((n = 11)\)
- Low-Dose group \((n = 10)\)
- Overdispersed observed counts \((\eta = 0.5)\)