Sample Size Calculations for Population Pharmacodynamic Experiments Involving Repeated Dichotomous Observations

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Introduction

✓ During clinical trials, pharmacodynamic (PD) measurements are obtained at baseline and at intervals across a period of fixed duration from subjects randomized into treatment and placebo groups

✓Such longitudinal measurements can be dichotomous i.e. data from an individual consists of multiple yes/no or success/failure responses

✓Correlations between repeated measurements from an individual presents an additional challenge for the modelling of this data

✓There are two main approaches for the analysis of repeated binary data: population-averaged (marginal) and subject specific modelling[1]

✓Population-averaged (PA) modelling involves modelling the PA response without accounting explicitly for individual subjects hence suitable for making inference only for the population

✓Correlations are modelled using a damped exponential correlation structure such as the compound symmetry (exchangeable), autoregressive and moving average models. Generalised estimating equations (GEE) analysis is an example of PA approach

✓Subject specific (SS) modelling involves modelling explicitly the individual heterogeneity of the data and suitable for making population and individual inferences

✓Mixed-effects modelling[2] represents an example of SS modelling

✓Sample size calculation is an important part of clinical trial design and it is often based on the method of analysis of the resulting data

✓While sample size calculations for analysis of repeated binary data based on PA modelling approach have been well defined[3,4,5], sample size calculations for analysis by mixed effects modelling have not been defined

Objective

✓ To describe an analytical method for calculating sample size for population PD experiments involving dichotomous measurements based on analysis by mixed effects modelling for detecting difference between two groups i.e. treatment and placebo

Methodology

Response y_{ijs} (1 or 0) *jth* measurement *ith* individual *sth* subpopulation $(i=1,...,N \quad j=1,...,n \quad s=1,...,S)$

p_{ijs} = the probability of y_{ijs} being 1, using the logit link transformation

$$logit(p_{ijs}) = \log\left(\frac{p_{ijs}}{1-p_{ijs}}\right) = X_{js}\theta_{is} \qquad p_{ijs} = logit^{-1}\left(X_{js}\theta_{is}\right) = \frac{\exp\left(X_{js}\theta_{is}\right)}{1+\exp\left(X_{js}\theta_{is}\right)}$$

X_{js} is the *jth* row of X_s (design matrix for the *sth* subpopulation)

θ_{is} p-vector $(k=1,...,p)$ of parameters for *ith* individual, *sth* subpopulation

$$\theta_{isk} = \theta_{sk} + b_{isk} \qquad b_{isk} \sim N(0,\omega_{sk}) \qquad \Omega_s = diag\left[\omega_{sk},...,\omega_{sp}\right]$$

Define $n \times p$ matrices J_{is} and Z_{is} where $J_{ijs} = \frac{\partial p_{ijs}}{\partial \theta_{isk}}$ $Z_{ijs} = \frac{\partial p_{ijs}}{\partial b_{isk}}$

The approximate covariance matrix is given by

$$V_{is} \approx Z_{is}\Omega_s Z_{is}^T + W_{is} \qquad W_{is} = diag\left[p_{ijs}(1-p_{ijs}),..., p_{ins}(1-p_{ins})\right]$$

Assuming the same sampling design in all subject and sample size N in each of the S subpopulations

The Fisher information matrix and covariance matrix are given by

$$F(\hat{\theta}) = N\sum_{s=1}^{S} J_s^T V_s^{-1} J_s \qquad \text{cov}(\hat{\theta}) = \left[N\sum_{s=1}^{S} J_s^T V_s^{-1} J_s\right]^{-1} = N^{-1}\Omega_{MB}$$

The hypothesis for consideration can be expressed as

$$H_0 : H\theta = h_0 \quad \text{vs.} \quad H_1 : H\theta \neq h_0$$

A Wald test statsitics can be derived as $Q_w = N\left(H\hat{\theta}-h_0\right)^T\left[H\Omega_{MB}H^T\right]\left(H\hat{\theta}-h_0\right)$ which is asymptotically distributed as a $\chi^2_{(h),\lambda}$ distribution with a noncentrality parameter given by $\lambda \approx N\left(H\hat{\theta}-h_0\right)^T\left[H\Omega_{MB}H^T\right]\left(H\hat{\theta}-h_0\right)$

If α and γ type I and II errors respectively, power associated with Q_w is

$$1-\gamma = \int_{\chi^2_{(h),1-\alpha}}^{\infty} f(x;h,\lambda)dx$$

$\chi^2_{(h),1-\alpha}$ is the critical value from the central $\chi^2_{(h)}$ distribution and $f(x;h,\lambda)dx$ is the probability density function of the $\chi^2_{(h),\lambda}$ distribution

Example

Two groups $(S=2)$: placebo $(s=1)$ and treatment $(s=2)$

$$logit(p_{js}) = \theta_{s1} + \theta_{s2}t_{js}$$

t_{js} is time in days and $\theta_s = \left[\theta_{s1}, \theta_{s2}\right]$ $(p=2)$

Hypothesis is based on slope parameter and is of the form

$$H_{\theta_{s2},0} : \theta_{12} = \theta_{22} \quad \text{vs.} \quad H_{\theta_{s2},1} : \theta_{12} \neq \theta_{22}$$

Three models were considered : random intercept only (RIO), random slope only (RSO) and random intercept and slope (RIS)

For all models $\theta_{11} = \theta_{21} = -3.4, \theta_{12} = 0.3, \theta_{22} = 0.5$

RIO : $\omega_{21} = \omega_{22} = 0, \omega_{11} = \omega_{21} = 1$

RSO : $\omega_{11} = \omega_{21} = 0, \omega_{12} = \omega_{22} = 0.01$

RIS : $\omega_{11} = \omega_{21} = 1, \omega_{12} = \omega_{22} = 0.01$

Sample size allocation (placebo/d rug) : 50/50, 60/40 and 70/30

Sampling times (13 times) = 0,1,...,12 days (2 designs : S1 and S2)

S1 : All subjects sampled at all time points

S2 : 25% subjects sampled at all time points, 25% sampled at first 9 time points and 50% sampled at first 5 time points

Minumum sample size required were obtained using $\alpha = 0.05$ and 0.01 and $1-\gamma = 0.8$ and 0.9 (power)

Using parameter estimates and sample sizes estimated, power of the designs were obtained by simulation in NONMEM (using laplace approximation)

Results

Results of sample size (power)

α	$1-\lambda$	50/50		60/40	70/30
		S1	S2	S1	S1
RIO					
0.05	0.8	50 (0.81)	108 (0.82)	52 (0.83)	62 (0.85)
	0.9	66 (0.91)	144 (0.91)	70 (0.91)	82 (0.93)
0.01	0.8	72 (0.80)	160 (0.82)	77 (0.80)	90 (0.81)
	0.9	92 (0.91)	204 (0.90)	99 (0.90)	115 (0.93)
RSO					
0.05	0.8	58 (0.79)	122 (0.78)	60 (0.81)	70 (0.81)
	0.9	76 (0.91)	164 (0.91)	80 (0.90)	94 (0.91)
0.01	0.8	84 (0.78)	182 (0.80)	90 (0.78)	105 (0.81)
	0.9	108 (0.87)	232 (0.88)	114 (0.91)	133 (0.90)
RIS					
0.05	0.8	58 (0.80)	132 (0.78)	60 (0.79)	70 (0.88)
	0.9	76 (0.88)	178 (0.89)	80 (0.89)	94 (0.90)
0.01	0.8	84 (0.75)	196 (0.79)	90 (0.77)	104 (0.80)
	0.9	108 (0.88)	250 (0.88)	113 (0.88)	133 (0.90)

Conclusion

✓A method for calculating sample size for population PD experiments involving repeated dichotomous observations based on analysis by mixed effects modelling has been presented

✓The expressions have been extended to account for unbalanced allocation of sample size and sampling times between and within subgroups

✓The results showed good agreements between empirical power and power obtained by simulation in NONMEM

✓The method can be extended to ordered categorical responses involving more than two responses

[1]Zeger *et al* (1988) Biometrics, [2]Yane *et al* (2001) J.Pharmacokinet.Pharmacodyn., [3]Rochon (1998) Stat.Med.,[4] Lui (1991) Stat.Med., [5]Jung & Ahn (2005) Stat.Med.