ISSN 1996-3343

Asian Journal of Applied Sciences

http://knowledgiascientific.com

Knowledgia SCIENTIFIC
A Place to Publish Outstanding Research

Asian Journal of Applied Sciences 5 (6): 371-383, 2012
ISSN 1996-3343 / DOI: 10.3923/ajaps.2012.371.383

Sample Size Determination for Repeated Measurements using Three Possible Methods of Analysis, POST, CHANGE and ANCOVA, under Various Covariance Structures for Two Groups

[1]V. Chandrasekaran, [2]G. Gopal and [1]W. Basilea
[1]National Institute for Research in Tuberculosis, Chennai 600 031, India
[2]Department of Statistics, University of Madras, Chennai 600 005, India

Corresponding Author: G. Gopal, Department of Statistics, University of Madras, Chennai 600 005, India

ABSTRACT

Many authors have studied the determination of sample size in longitudinal studies under different situations. A statistical methodology for determining the minimum sample size required for within-subjects repeated-measures design, applying Hotelling's T^2 analysis under the general covariance structure exists. This procedure is extended to between-subjects repeated measures design when there are two treatment groups, assuming the correlation structure among the repeated measures are autoregressive or compound symmetry. Three possible methods of analysis POST, CHANGE and ANCOVA are used to determine the sample size under the assumption that the correlation structure is compound symmetry. In this paper, we extend the existing method to obtain minimum sample size assuming that the correlation structure is first order autoregressive or a random effects model.

Key words: Sample size determination, summary statistics, compound symmetry, first order auto regression, random effects

INTRODUCTION

The determination of sample size is an important step before embarking on a research study. A sample that is too small will not possess the required statistical power to identify significant changes when they truly exist, on the other hand, sample sizes larger than required will increase the cost for the research project. Under these circumstances, it becomes imperative to determine the required minimum sample size prior to start of the study with appropriate statistical significance (Machin and Campbell, 1987).

When the dependent variable is a continuous one and is measured at a single time point, the estimation procedures for sample size determination are well founded. The corresponding situation for repeated measurement experiments has not been completely developed.

The absence of autocorrelation of the error terms and zero co-variance between the explanatory variables and the error terms are the basic assumptions in the classical linear regression model. In case of violation of the above two assumptions, various methods for estimating the parameters have been suggested by Olaomi and Ifederu (2008). Their results show that when auto correlation is at $\rho = 0.4$ and when the exponential regressor is significantly correlated at 5% with the auto error terms the Ordinary Least Squares is preferred.

Typically, in a longitudinal study, a correlation structure is assumed among the set of repeated measures captured at well-defined junctures within an individual. The correlation structure

Compound Symmetry (CS) is commonly used, as it is very simple and assumes that the variance at all time points are the same and the correlation between two time points is the same. Fleiss (1986) argues that Compound Symmetry (CS) correlation structure will rarely be satisfied in a repeated measurements experiment. Snedecor and Cochran (1980) feel that this assumption is too restrictive for many real valued situations.

An alternative correlation structure is the First Order Autoregressive, AR(1), which assumes that the correlation between adjacent time-points is the same and the correlation decreases by the power of the number of time intervals between the measures.

The Random-Effects (RE) model provides the basic modeling framework for much of the clinical trials.

The panel data can be approached from a set of similar Randomized Controlled Trials making use of pooling methods to find the efficacy of pharmaceutical regimens. Further, Random Effect model is one of the meaningful techniques when individual studies results are combined. This is a more realistic model as it allows for variation in the true effect across the studies (Antoine *et al*., 2007). The use of random effects allows the longitudinal data to work with Autoregressive (AR) process (Nath and Bhattacharjee, 2011).

It is useful for analyzing longitudinal clinical trials in which there is a sizable number of missing observations, either due to missed visits, loss to follow-up, or death (Albert, 1999). Ware (1985) while discussing about the goodness of fit, mentions that the Random Effects (RE) and Auto Regressive (AR) models introduce strong assumptions about covariance patterns, especially when the number of observations on each subject is large. Hence, in this study we derive an expression for the sample size requirements for repeated measurements experiments under the auto regressive model of order 1 (AR(1)) and Random Effects (RE) model.

Three different formulations of interferon beta (IFNβ) an immunomodulatory agent was compared using random effects in a longitudinal study (Nikfar *et al*., 2010). It has been shown that the asymptotic relative efficiency is more compared to other correlation structures under the assumption of auto regressive correlation structure (Akanda *et al*., 2005).

For sample size calculation in longitudinal studies, two additional quantities are required, namely (1) the number of repeated observation per subject and (2) the correlation among repeated observations which can be estimated from a previous longitudinal study. In this study, we consider the case where the subjects are allocated at random to two treatment groups and measurements on every individual is taken repeatedly at well-defined time points during the course of study.

There are various summary measures in longitudinal study settings that help to bridge the gap between complex statistical methods and inadequate statistical usage. They are Mean, Area Under Curve (AUC), Maximum (Minimum) value, Time to Maximum (Minimum), Regression co-efficient and change between first and last value (Matthews *et al*., 1990) and also summarizing data through a piecewise linear growth curve model (Chandrasekaran *et al*., 2005). Though the choices of summary measures are wide, the main objective in many clinical trials is to determine the average response to treatment over time. This provides three possible methods of analysis as identified by Frison and Pocock (1992). They are:

- **Post-treatment means (POST):** A simple analysis using the mean for each patient's post-treatment measurements as the summary measure
- **Mean changes (CHANGE):** A simple analysis of each patient's difference between mean of post-treatment measurements and mean of baseline measurements, the latter often consisting of just a single baseline value per patient

Analysis of covariance (ANCOVA): Between-patient variations in baseline measurements are taken into account, by using the mean baseline measurement for each patient as covariate in a linear model for treatment comparison of post-treatment means.

As observed by Frison and Pocock (1992), ANCOVA has a smaller variance as compared to POST and CHANGE. Hence, in situations where the main objective is to determine the average response to a particular treatment over time, in comparison to another treatment or placebo, ANCOVA is superior to both, ignoring the pre-treatment data and simply subtracting the post-treatment value from the baseline value for each individual. Also, as pointed out by Senn (1994), ANCOVA is the best of the three methods considered and the only one which produces unbiased estimators in the presence of chance observed imbalance. It does this whether or not the baselines are subject to measurement error. Hence, in this study, sample size determination has been considered in situations where ANCOVA is the method of analysis to summarize the repeated measures data in order to determine the response of a particular treatment over time.

A SIMPLE MODEL AND AN EXAMPLE

In the sample size determination for the model for two treatment groups, let us assume that a randomized clinical trial has two treatment groups (i = A or B) with n_i subjects per group and suppose all patients have p pre-treatment and q post-treatment visits. The quantitative measurement y is observed at every visit for every patient. We adopt the simple model:

$$y_{ist} = \mu_{it} + e_{ist}$$

where, i = A, B; s = 1,2, ... ,n_i; t = 1,2, ... , p, p+1, ... ,p+q; μ_{it} is the underlying true mean response for treatment i at time t. As a result of randomization we can assume $\mu_{At} = \mu_{Bt}$ for the pre-treatment visit and e_{ist} is the individual sth patients 'error' around the mean response μ_{it}.

Let $\sum = \{\sigma_{tl}\}$ be the covariance matrix for all pairs of measurement times t, l. For simplicity we assume this is the same for both the treatments. It is helpful to define three sub matrices:

$$\sum_{post} = \{\sigma_{tl}\} \text{ for } t, l = p+1, \ldots, p+q; \sum_{pre} = \{\sigma_{tl}\} \text{ for } t, l = 1, \ldots, p$$

and:

$$\sum_{mix} = \{\sigma_{tl}\} \text{ for } t = 1, \ldots, p \text{ and } l = p+1, p+2, \ldots, p+q$$

That is:

$$\sum = \begin{bmatrix} \sum_{pre} & | & \sum_{mix} \\ - & - & - \\ \sum_{mix} & | & \sum_{post} \end{bmatrix}$$

The variance formulate for three approaches are:

Post-treatment means (POST):

$$\text{var}\left(\bar{x}_A^{post} - \bar{x}_B^{post}\right) = \left(\frac{1}{n_A} + \frac{1}{n_B}\right)\bar{\sum}_{post}$$

Mean change (CHANGE):

$$\text{var}\left[\left(\bar{x}_A^{post} - \bar{x}_A^{pre}\right) - \left(\bar{x}_B^{post} - \bar{x}_B^{pre}\right)\right] = \left(\frac{1}{n_A} + \frac{1}{n_B}\right)\left(\bar{\sum}_{pre} + \bar{\sum}_{post} - 2\bar{\sum}_{mix}\right)$$

Analysis of covariance (ANCOVA):

$$\text{var}\left(\bar{x}_A^{cov} - \bar{x}_B^{cov}\right) = \left(\frac{1}{n_A} + \frac{1}{n_B}\right)\left(\bar{\sum}_{post} - \frac{\bar{\sum}_{mix}^{2}}{\bar{\sum}_{pre}}\right)$$

For a randomized clinical trial all three estimates of the mean treatment difference have the same expected value ($\bar{\mu}_A^{Post}$-$\bar{\mu}_B^{Post}$). It can be seen that among the above variance formulae, the common sample size adjustment is:

$$\left(\frac{1}{n_A} + \frac{1}{n_B}\right)$$

Let the alternative hypothesis be $\bar{\mu}_A^{post}$-$\bar{\mu}_B^{Post}$ = δ. In the conventional approach to power calculation, we define α and β as the type I and type II errors for ANCOVA. It is convenient to assume that sample sizes are sufficiently large and that the normal approximation to the t- distribution can be applied. In that case, for two equals sized treatment groups of size n:

$$n = \frac{2}{\delta^2}\left(\bar{\sum}_{post} - \frac{\bar{\sum}_{mix}^{2}}{\bar{\sum}_{pre}}\right) f(\alpha, \beta) \quad (1)$$

where, $\bar{\Sigma}_{post}$, $\bar{\Sigma}_{mix}$ and $\bar{\Sigma}_{pre}$ are the respective means of the q^2, q×p and p^2 components of the three sub-matrices $\sum_{post}$, $\sum_{mix}$ and $\sum_{pre}$ and $f(\alpha,\beta) = [z(\alpha/2)+z(\beta)]^2$, z(y) is the standardized normal deviate exceeded with probability y and it is to be noted that σ is the within-patients standard deviation. The expression for the sample size formula when using the correlation matrix is:

$$n = \frac{2\sigma^2}{\delta^2}\left(\bar{\psi}_{post} - \frac{\bar{\psi}_{mix}^{2}}{\bar{\psi}_{pre}}\right) f(\alpha, \beta) \quad (2)$$

where $\bar{\Psi}_{post}$, $\bar{\Psi}_{mix}$ and $\bar{\Psi}_{pre}$ are the respective means of the three correlation sub-matrices of q^2, q×p and p^2 components. Using the above expression, Frison and Pocock (1992) derived the sample size under the CS model to be:

$$n = \frac{2\sigma^2}{\delta^2}\left(\frac{1+(p-1)\rho}{p} - \frac{q\rho^2}{1+(q-1)\rho}\right) f(\alpha, \beta)$$

where, the mean of the correlation matrix Ψ_{pre} is:

$$\frac{1}{p^2}[p + (p*(p-1)*\rho)]$$

Mean of the correlation matrix Ψ_{post} is:

$$\frac{1}{q^2}[q + (q*(q-1)*\rho)]$$

and, Mean of the correlation matrix $\Psi_{mix = \rho}$.

On substitution of these quantities in (2), one gets the required sample size n, under the assumption of CS covariance structure. The same method is adopted for the determination of the sample size under the random effects first order auto regressive and random effects models.

The covariance matrix for random effects model (RE): Let $y_{ij} = \alpha_i + \beta_j + u_{ij}$, where y_{ij} is the observation on the ith individual on occasion j, α_i is the individual effect, β_j is the occasion effect and u_{ij} is random error. However, the α_i are randomly selected from a distribution of individual effects and constitute a random effect. Then the model becomes:

$$y_{ij} = \alpha + \alpha_i + \beta_j + u_{ij} \; (i = 1, 2, \ldots, n; \; j = 1, 2, \ldots, p)$$

and the generalization of this in matrix form is:

$$y_i = Z_i b_i + X_i \beta + e_i$$

Here, the b_i are random effects, yielding a combined contribution to y_i via the design matrix Z_i and β is a vector of fixed effects. Such models are sometimes called two-stage models because the e_i, refer to within-individual variation (stage 1) and the b_i refer to between-individual variation (stage 2). Models with this general form have now become popular. An early expositions to this type of modeling is form the work of Laird and Ware (1982). We can generalize this supposing that $E(b_i) = 0$, $E(e_i) = 0$, $var(b_i) = B_i$, $var(e_i) = E_i$ and that b_i and e_i are independent.
Then:

$$\Sigma_{pi} = var(y_i) = var(Z_i b_i) + var(e_i) = Z_i B_i Z'_i + E_i$$

where, bi and ei are multivariate normal.

The correlation matrix under the Random effects model is:

$$\sum = Z\phi Z' + \sigma^2 I$$

where, the matrix Z has (p+q) rows and I columns of treatment groups (two) and $\phi = i X_i$ is the dispersion matrix. For example, the covariance matrix for 7×7 (7 repeated value) the matrix of $\sum_{pre}$ are:

$$\begin{pmatrix} (\phi_{11}+1\phi_{12})+1(\phi_{12}+1\phi_{22})+\sigma^2 & (\phi_{11}+1\phi_{12})+2(\phi_{12}+1\phi_{22}) & (\phi_{11}+1\phi_{12})+3(\phi_{12}+1\phi_{22}) \\ (\phi_{11}+2\phi_{12})+1(\phi_{12}+2\phi_{22}) & (\phi_{11}+2\phi_{12})+2(\phi_{12}+2\phi_{22})+\sigma^2 & (\phi_{11}+2\phi_{12})+3(\phi_{12}+2\phi_{22}) \\ (\phi_{11}+3\phi_{12})+1(\phi_{12}+3\phi_{22}) & (\phi_{11}+3\phi_{12})+2(\phi_{12}+3\phi_{22}) & (\phi_{11}+3\phi_{12})+3(\phi_{12}+3\phi_{22})+\sigma^2 \end{pmatrix}$$

The mean of $\sum_{pre}$ are:

$$\frac{1}{pp}\left[(pp)\phi_{11}+2p\phi_{12}\left(\frac{p(p+1)}{2}\right)+\phi_{22}\left(\frac{p(p+1)}{2}\right)^2+p\sigma^2\right]$$

Matrix of $\sum_{mix}$:

$$\begin{pmatrix} (\phi_{11}+1\phi_{12})+4(\phi_{12}+1\phi_{22}) & (\phi_{11}+1\phi_{12})+5(\phi_{12}+1\phi_{22}) & (\phi_{11}+1\phi_{12})+6(\phi_{12}+1\phi_{22}) & (\phi_{11}+1\phi_{12})+7(\phi_{12}+1\phi_{22}) \\ (\phi_{11}+2\phi_{12})+4(\phi_{12}+2\phi_{22}) & (\phi_{11}+2\phi_{12})+5(\phi_{12}+2\phi_{22}) & (\phi_{11}+2\phi_{12})+6(\phi_{12}+2\phi_{22}) & (\phi_{11}+2\phi_{12})+7(\phi_{12}+2\phi_{22}) \\ (\phi_{11}+3\phi_{12})+4(\phi_{12}+3\phi_{22}) & (\phi_{11}+3\phi_{12})+5(\phi_{12}+3\phi_{22}) & (\phi_{11}+3\phi_{12})+6(\phi_{12}+3\phi_{22}) & (\phi_{11}+3\phi_{12})+7(\phi_{12}+3\phi_{22}) \end{pmatrix}$$

The mean of $\sum_{mix}$ are:

$$\frac{1}{pq}\left[(pq)\phi_{11}+\phi_{12}\left[\left(\frac{qp(p+1)}{2}\right)+p\left(\frac{(p+q)(p+q+1)}{2}-\frac{p(p+1)}{2}\right)\right]+\phi_{22}\begin{pmatrix}\frac{p(p+1)}{2}*\\ \left(\frac{(p+q)(p+q+1)}{2}-\frac{p(p+1)}{2}\right)\end{pmatrix}\right]$$

Matrix of $\sum_{post}$:

$$\begin{pmatrix} (\phi_{11}+4\phi_{21})+(\phi_{12}+4\phi_{22})+\sigma^2 & (\phi_{11}+4\phi_{21})+2(\phi_{12}+4\phi_{22}) & (\phi_{11}+4\phi_{21})+3(\phi_{12}+4\phi_{22}) & (\phi_{11}+4\phi_{21})+4(\phi_{12}+4\phi_{22}) \\ (\phi_{11}+5\phi_{21})+(\phi_{12}+5\phi_{22}) & (\phi_{11}+5\phi_{21})+2(\phi_{12}+5\phi_{22})+\sigma^2 & (\phi_{11}+5\phi_{21})+3(\phi_{12}+5\phi_{22}) & (\phi_{11}+5\phi_{21})+4(\phi_{12}+5\phi_{22}) \\ (\phi_{11}+6\phi_{21})+(\phi_{12}+6\phi_{22}) & (\phi_{11}+6\phi_{21})+2(\phi_{12}+6\phi_{22}) & (\phi_{11}+6\phi_{21})+3(\phi_{12}+6\phi_{22})+\sigma^2 & (\phi_{11}+6\phi_{21})+4(\phi_{12}+6\phi_{22}) \\ (\phi_{11}+7\phi_{21})+(\phi_{12}+7\phi_{22}) & (\phi_{11}+7\phi_{21})+2(\phi_{12}+7\phi_{22}) & (\phi_{11}+7\phi_{21})+3(\phi_{12}+7\phi_{22}) & (\phi_{11}+7\phi_{21})+4(\phi_{12}+7\phi_{22})+\sigma^2 \end{pmatrix}$$

Mean of $\sum_{post}$ is:

$$\frac{1}{qq}\begin{bmatrix}(pp)\phi_{11}+q\phi_{12}\left[\left(\frac{(p+q)(p+q+1)}{2}-\frac{p(p+1)}{2}\right)+\frac{q(q+1)}{2}\right]+q\sigma^2\\ +\phi_{22}\left(\left(\frac{(p+q)(p+q+1)}{2}-\frac{p(p+1)}{2}\right)*\left(\frac{q(q+1)}{2}\right)\right)\end{bmatrix}$$

The general form of $\sigma^2_t = \phi_{11}+t\,\phi_{12}+t(\phi_{12}+i\,\phi_{22})+\sigma^2$; $i = 1, 2, \ldots, p+q$ and $\sigma_{ij} = (\phi_{11}+i\,\phi_{12})+j\,(\phi_{12}+i\,\phi_{22})$; $i, j = 1, 2, \ldots, p+q$; $i \neq j$.

On substitution of these quantities in (1) we get the sample size n, under the assumption of random effects.

Correlation structure for first order autoregressive model (AR(1)): Assume that the correlation matrix has a first-order autoregressive structure, which is consistent with the observation that the correlations exhibit the ρ, ρ^2, ρ^3 pattern required under the AR(1) structure. From the covariance matrix, the correlation matrix is obtained by removing the constant variance, σ^2. Under the auto regressive model of order 1 for pre treatment p and post treatment q, the correlation matrix is given as:

$$\begin{bmatrix}
1 & \rho & \cdots & \rho^{p-1} & | & \rho^{p} & \rho^{p+1} & \cdots & \rho^{p+q-1} \\
\rho & 1 & \cdots & \rho^{p-2} & | & \rho^{p-1} & \rho^{p} & \cdots & \rho^{p+q-2} \\
\vdots & \vdots & \cdots & \vdots & | & \vdots & \vdots & \cdots & \vdots \\
\rho^{p-1} & \rho^{p-2} & \cdots & 1 & | & \rho & \rho^{2} & \cdots & \rho^{q} \\
\hline
\rho^{p} & \rho^{p-1} & \cdots & \rho & | & 1 & \rho & \cdots & \rho^{q-1} \\
\rho^{p+1} & \rho^{p} & \cdots & \rho^{2} & | & \rho & 1 & \cdots & \rho^{q-2} \\
\vdots & \vdots & \cdots & \vdots & | & \vdots & \vdots & \cdots & \vdots \\
\rho^{p+q-1} & \rho^{p+q-2} & \cdots & \rho^{p} & | & \rho^{p-1} & \rho^{p-2} & \cdots & 1
\end{bmatrix}$$

Hence, we arrive at the following:

Mean of the correlation matrix Ψ_{pre} is:

$$\frac{1}{p^2}\left[p + 2\left(\sum_{i=1}^{p-1} i \;\; \rho^{p-i}\right)\right]$$

Mean of the correlation matrix Ψ_{post} is:

$$\frac{1}{q^2}\left[q + 2\left(\sum_{i=1}^{q-1} i \;\; \rho^{q-i}\right)\right]$$

Mean of the correlation matrix Ψ_{mix} is:

$$\frac{1}{pq}\left(\frac{(1-\rho^{q})(1-\rho^{p})\rho}{(1-\rho)^2}\right)$$

Substitution of these quantities in (2), we get the required sample size n, under the assumption of first order auto regressive covariance structure.

RESULT AND DISCUSSION

Table 1-4 provide the minimum number of subjects required in each treatment group, assuming equal allocation, under the CS and AR(1) correlation model, for a one sided test at α and β for $\Delta = .1\ (.1).1$, $\rho = 0\ (.1).9$ for p (pre-treatment) = 1 and 3 and q (post-treatment) = 3 (2)9. The greatest difficulty lies in choosing an appropriate values for Δ and σ but this problem applies to any power calculation with quantitative data expressed as means. Note that σ here is the between-patients standard deviation.

Table 1: Sample required in each treatment group, assuming equal allocation, for the AR(1) correlation structure (pre-treatment p = 1), for a two-sided test at $\alpha = 0.05$ and $\beta = 0.20$ for selected values of p (No. of post-treatment repeated), ρ and $\Delta = (\sigma/\delta)$

		Standardized $\Delta = 2*(\sigma^2/\delta^2)$								
Repeated	ρ	4	6	8	10	12	14	16	18	20
4	0.1	12	18	24	30	36	42	48	54	60
	0.2	13	20	27	34	40	47	54	60	67
	0.3	15	22	30	37	44	52	59	66	74
	0.4	16	24	32	40	48	56	64	72	80
	0.5	17	25	33	42	50	58	66	75	83
	0.6	17	25	33	42	50	58	67	75	83
	0.7	16	23	31	39	47	54	62	70	78
	0.8	13	19	26	32	39	45	52	58	64
	0.9	8	12	16	20	24	28	32	36	40
6	0.1	7	11	15	18	22	26	30	33	37
	0.2	9	13	17	22	26	30	34	39	43
	0.3	10	15	20	25	30	35	40	45	50
	0.4	11	17	23	29	34	40	46	51	57
	0.5	13	19	26	32	39	45	52	58	64
	0.6	14	21	28	35	42	49	56	64	71
	0.7	15	22	29	37	44	51	59	66	73
	0.8	14	21	27	34	41	48	55	62	69
	0.9	10	15	19	24	29	34	39	44	49
8	0.1	5	8	11	13	16	19	21	24	27
	0.2	6	9	13	16	19	22	25	28	32
	0.3	7	11	15	19	22	26	30	34	37
	0.4	9	13	18	22	26	31	35	40	44
	0.5	10	16	21	26	31	36	41	47	52
	0.6	12	18	24	30	36	42	48	54	60
	0.7	13	20	27	34	40	47	54	60	67
	0.8	14	21	28	34	41	48	55	62	69
	0.9	11	16	22	27	33	38	44	49	55
10	0.1	4	6	8	10	13	15	17	19	21
	0.2	5	7	10	12	15	17	20	22	25
	0.3	6	9	12	15	18	21	24	27	30
	0.4	7	11	14	18	21	25	29	32	36
	0.5	9	13	17	21	26	30	34	39	43
	0.6	10	15	21	26	31	36	41	46	51
	0.7	12	18	24	30	36	42	48	55	61
	0.8	13	20	27	34	40	47	54	60	67
	0.9	12	18	24	30	36	41	47	53	59

Table 2: Sample required in each treatment group, assuming equal allocation, for the AR(1) correlation structure (pre-treatment p = 0), for a two-sided test at $\alpha = 0.05$ and $\beta = 0.20$ for selected values of p (No. of post-treatment repeated), ρ and $\Delta = (\sigma/\delta)$

		Standardized $\Delta = 2*(\sigma^2/\delta^2)$								
Repeated	ρ	4	6	8	10	12	14	16	18	20
4	0.1	9	14	18	23	28	32	37	41	46
	0.2	11	16	21	27	32	37	42	48	53
	0.3	12	18	25	31	37	43	49	55	61
	0.4	14	21	28	35	42	50	57	64	71
	0.5	16	24	33	41	49	57	65	73	81
	0.6	19	28	37	47	56	65	75	84	94
	0.7	21	32	43	54	64	75	86	96	107
	0.8	24	37	49	61	73	86	98	110	122
	0.9	28	42	56	70	84	97	111	125	139
6	0.1	6	9	12	16	19	22	25	28	31
	0.2	7	11	15	18	22	26	29	33	37
	0.3	9	13	17	22	26	30	35	39	44
	0.4	10	16	21	26	31	36	41	47	52
	0.5	12	19	25	31	37	43	49	56	62
	0.6	15	22	30	37	44	52	59	67	74
	0.7	18	27	36	44	53	62	71	80	89
	0.8	21	32	43	54	64	75	86	97	107
	0.9	26	39	52	65	78	91	104	117	130
8	0.1	5	7	9	12	14	16	19	21	24
	0.2	6	8	11	14	17	20	22	25	28
	0.3	7	10	13	17	20	24	27	30	34
	0.4	8	12	16	20	24	28	32	37	41
	0.5	10	15	20	25	30	35	40	44	49
	0.6	12	18	24	30	36	43	49	55	61
	0.7	15	23	30	38	45	53	61	68	76
	0.8	19	29	38	48	57	67	76	86	96
	0.9	24	37	49	61	73	86	98	110	122
10	0.1	4	6	8	9	11	13	15	17	19
	0.2	5	7	9	11	14	16	18	20	23
	0.3	5	8	11	14	16	19	22	25	27
	0.4	7	10	13	17	20	23	27	30	33
	0.5	8	12	16	21	25	29	33	37	41
	0.6	10	15	21	26	31	36	41	46	51
	0.7	13	20	26	33	39	46	53	59	66
	0.8	17	26	34	43	51	60	69	77	86
	0.9	23	34	46	57	69	80	92	103	115

The sample size under covariance structure in CS is less when ρ is large. In AR (1) the sample size increases with increase in post-treatment. Besides, when $\Delta = 0.2$ irrespective of whether the pre-treatment is taken, the sample size generally tends to start from around 200, leave alone the number of post-treatment visits (q); also when $\Delta = 0.6$ the sample size usually begins with 25. When $\rho = 0.3$ with the same $\Delta = 0.2$ and $p = 3$, the sample size decreases in both (AR(1) and CS models. When $p = 3$ and $\Delta = 0.6$ in AR(1) with $\rho = 0.3$ and $\rho = 0.9$ in CS model, the sample size decreases.

Table 3: Sample required in each treatment group, assuming equal allocation, for the CS correlation structure (pre-treatment p = 1), for a two-sided test at α 0.05 and β = 0.20 for selected values of p (No. of post-treatment repeated), ρ and Δ = (σ/δ)

		Standardized Δ = 2*(σ²/δ²)								
Repeated	ρ	3	5	7	9	11	13	15	18	21
3	0.1	9	3	22	28	34	40	46	55	65
	0.2	10	3	24	30	37	44	51	61	71
	0.3	11	4	25	32	39	46	53	63	74
	0.4	10	3	24	31	38	45	52	63	73
	0.5	10	3	23	30	36	43	49	59	69
	0.6	9	3	21	27	32	38	44	53	62
	0.7	7	2	17	22	27	32	37	44	51
	0.8	5	2	13	16	20	23	27	32	38
	0.9	3	1	7	9	11	13	15	18	20
5	0.1	6	11	15	19	23	28	32	38	45
	0.2	8	13	18	23	28	33	38	46	53
	0.3	8	14	19	25	30	36	41	50	58
	0.4	9	14	20	26	31	37	43	51	60
	0.5	8	14	19	25	30	36	41	50	58
	0.6	8	13	18	23	28	33	38	46	53
	0.7	6	11	15	19	23	28	32	38	45
	0.8	5	8	11	14	17	21	24	28	33
	0.9	3	4	6	8	10	11	13	16	18
7	0.1	5	9	12	16	19	22	26	31	36
	0.2	7	11	15	20	24	28	38	39	46
	0.3	7	12	17	22	27	32	41	44	51
	0.4	8	13	18	23	28	33	43	46	54
	0.5	8	13	18	23	28	33	41	46	53
	0.6	7	12	16	21	26	31	38	42	49
	0.7	6	10	14	18	22	26	32	36	42
	0.8	4	7	10	13	16	19	24	27	31
	0.9	2	4	6	7	9	11	13	15	17
9	0.1	5	8	11	14	17	20	23	27	32
	0.2	7	10	14	18	22	26	29	35	41
	0.3	7	11	16	20	25	30	34	41	48
	0.4	8	12	17	22	27	31	36	44	51
	0.5	8	12	17	22	27	31	36	43	51
	0.6	7	11	16	20	25	29	34	40	47
	0.7	6	10	13	17	21	25	29	35	40
	0.8	4	7	10	13	16	19	22	26	30
	0.9	2	4	6	7	9	10	12	14	17

Frison and Pocock (1992) have observed that in simple designs where there is only one post treatment reading and no pre-treatment reading, the POST analysis requires around n = 100 in each group. Increasing the number of post-treatment reading has some effect on decreasing n but with no use of pre-treatment reading n remains at around 75 even with q = 8. The CHANGE analysis with p = 1 pre-treatment (a two-sample t-test comparing mean change) leads to a required n around 60 for q = 1 post-treatment measurement, which can be reduced to n<40 if q is increased

Table 4: Sample required in each treatment group, assuming equal allocation, for the CS correlation structure (pre-treatment p = 0), for a two-sided test at α 0.05 and β = 0.20 for selected values of p (No. of post-treatment repeated), ρ and Δ = (σ/δ)

		Standardized Δ = 2*(σ²/δ²)								
Repeated	ρ	3	5	7	9	11	13	15	18	21
4	0.1	9	3	22	28	35	41	47	57	66
	0.2	11	4	26	33	41	48	55	66	77
	0.3	13	4	29	38	46	55	63	76	88
	0.4	14	5	33	43	52	62	71	85	100
	0.5	16	5	37	47	58	68	79	95	111
	0.6	17	6	41	52	64	75	87	104	122
	0.7	19	6	44	57	70	82	95	114	133
	0.8	21	7	48	62	75	89	103	123	144
	0.9	22	7	52	66	81	96	111	133	155
6	0.1	7	11	15	20	24	29	33	40	46
	0.2	9	14	20	26	31	37	43	51	60
	0.3	10	17	24	31	38	45	52	63	73
	0.4	12	21	29	37	45	53	62	74	86
	0.5	14	24	33	43	52	62	71	85	100
	0.6	16	27	38	48	59	70	81	97	113
	0.7	18	30	42	54	66	78	90	108	126
	0.8	20	33	46	60	73	86	100	119	139
	0.9	22	36	51	65	80	94	109	131	153
8	0.1	5	9	13	16	20	23	27	33	38
	0.2	7	12	17	22	27	32	37	45	52
	0.3	9	16	22	28	35	41	47	57	66
	0.4	12	19	27	35	42	50	58	69	81
	0.5	14	23	32	41	50	59	68	81	95
	0.6	16	26	36	47	57	67	78	93	109
	0.7	18	29	41	53	65	76	88	106	123
	0.8	20	33	46	59	72	85	98	118	137
	0.9	22	36	51	65	79	94	108	130	152
10	0.1	5	8	11	14	17	21	24	28	33
	0.2	7	11	16	21	25	30	34	41	48
	0.3	9	15	21	27	33	39	45	54	63
	0.4	11	18	26	33	41	48	55	66	77
	0.5	13	22	31	40	48	57	66	79	92
	0.6	15	25	36	46	56	66	76	92	107
	0.7	17	29	41	52	64	75	87	104	122
	0.8	19	32	45	58	71	84	97	117	136
	0.9	22	36	50	65	79	94	108	130	151

to 4 or more post-treatment measurements. The superiority of ANCOVA is illustrated by a further fall in sample size. For instance, with p = 1 and q>4 we can reduce n to below 30 if ANCOVA is used.

It is often possible to have more than one pre-treatment visit in a repeated measures design (all pre-treatment visits occurring before randomization) and here we consider the improved efficiency for both ANCOVA and CHANGE. Of course the time lapses between pre-treatment

measurements may affect the correlation structure. The more widespread use of such power calculation formulae may add greatly to a sensible choice of n, p and q in repeated measures designs. While the compound symmetry assumption is unlikely to be true, it is often not wildly off the mark and so use of these simple formulae should give an adequate estimate of order of magnitude for n. A plausible value of ρ in the range 0.5 to 0.75 should usually be appropriate. Perhaps the greatest difficulty lies in choosing an appropriate value for δ/σ but this problem applies to any power calculation with quantitative data expressed as means. Note that σ here is the between-patient standard deviation, although the ANCOVA and CHANGE analyses are within-patient in essence (Frison and Pocock, 1992).

In most practical circumstances the bias of ANCOVA should be small. Having more than one pre-treatment measurement will reduce this bias further, since it is approximately proportional to 1/p. In many repeated measures trials the analysis is complicated by missing values and patient withdrawals. In summary statistics approach it is relatively easy to define sensible criteria for coping with occasional missing values. However, patient withdrawals provoke greater problems since they are often associated with informative censoring (Wu and Bailey, 1989).

In the summary statistics approach to analysis of repeated measures we confirm the well known result that ANCOVA is superior to both ignoring pre-treatment reading and simply subtracting pre-treatment readings for each individual (Fleiss, 1986).

It is noted that the parameters will not be unbiased when there is correlation among responses. In this respect, Nugraha (2011) has proved that the MLE on mixed logit model is precise in estimating the parameters in a discrete model like GEE. When there are many parameters in the model, the concept of subsetting has been used to eliminate the parameters which are redundant and close to zero (Ojo *et al*., 2008).

Maximum likelihood estimates of the covariance parameters, listed in the order; Φ_{11}, Φ_{21}, Φ_{22} and σ^2. Note that neither Φ_{21} nor Φ_{22} is statistically different from zero. If Φ_{21} and Φ_{22} are both zero, then the random effects covariance structure $Z\Phi Z'+I$ reduces to the compound symmetry structure (Dixon, 1992).

CONCLUSION

It has been observed that for repeated measures design, ANCOVA is the best of the three summary methods considered-POST, CHANGE and ANCOVA. It gives the most unbiased estimator in the presence of chance observed imbalance. In many longitudinal studies, the covariance structure either assumes the Auto Regressive or Random Effect (RE) structure. Hence, the procedure to estimate sample size for such kind of longitudinal studies with the covariance structure of the outcome variables as AR or RE structure is very much useful to the practitioners.

REFERENCES

Akanda, M.A.S., M. Khanam and M.A. Islam, 2005. Comparison of goodness-of-fit tests for GEE modeling with binary responses to diabetes mellitus. J. Applied Sci., 5: 1214-1218.

Albert, P.S., 1999. Tutorial in Biostatistics longitudinal data analysis (repeated measures) in clinical trials. Stat. Med., 18: 1707-1732.

Antoine, R., A. Sahai and P. Chami, 2007. Meta analysis of panel data generated by a set of randomized controlled trials. J. Applied Sci., 7: 951-957.

Chandrasekaran, V., G. Gopal and A. Thomas, 2005. Summarizing data through a piecewise linear growth curve model. Stat. Med., 24: 1139-1151.

Dixon, W.J., 1992. Statistical Software Manual: To Accompany. University of California Press, Oxford, UK., Page: 1504.

Fleiss, J.L., 1986. The Design and Analysis of Clinical Experiments. Wiley, New York.

Frison, L. and S.J. Pocock, 1992. Repeated measures in clinical trials: Analysis using mean summary statistics and its implication for design. Stat. Med., 11: 1685-1704.

Laird, N.M. and J.H. Ware, 1982. Random-effects models for longitudinal data. Biometrics, 38: 963-974.

Machin, D. and M.J. Campbell, 1987. Statistical Tables for the Design of Clinical Trials. Blackwell Scientific Publications, UK.

Matthews, J.N.S., D.G. Altman, M.J. Campbell and P. Royston, 1990. Analysis of serial measurements in medical research. Brit. Med. J., 300: 230-235.

Nath, D.C. and A. Bhattacharjee, 2011. A Bayesian Approach for Autoregressive Models in Longitudinal Data Analysis: An Application to Type 2 Diabetes Drug Comparison Asian J. Applied Sci., 4: 640-648.

Nikfar, S., R. Rahimi and M. Abdollahi, 2010. A systematic review on the efficacy of interferon β in relapsing remitting multiple sclerosis: Comparison of different formulations. Int. J. Pharmacol., 6: 638-644.

Nugraha, J., 2011. Mixed Logit Model on Multivariate Binary Response using Maximum Likelihood Estimator and Generalized Estimating Equations Asian J. Mathe. Stat., 4: 113-127.

Ojo, J.F., T.O. Olatayo and O.O. Alabi, 2008. Forecasting in subsets autoregressive models and autoprojective models. Asian J. Scientific Res., 1: 481-491.

Olaomi, J.O. and A. Ifederu, 2008. Understanding estimators of linear regression model with AR(1) error which are correlated with exponential regressor. Asian J. Math. Stat., 1: 14-23.

Senn, S., 1994. Letter to the editor. Stat. Med., 13: 197-198.

Snedecor, G.W. and W.G. Cochran, 1980. Statistical Methods. 7th Edn., Iowa State University Press, Iowa, USA., ISBN-10: 0-81381560-6, Pages: 507.

Ware, J.H., 1985. Linear models for the analysis of longitudinal studies. Am. Statist., 39: 95-101.

Wu, M.C. and K.R. Bailey, 1989. Estimation and comparison of changes in the presence of informative right censoring: Conditional linear model. Biomet., 45: 939-955.