Repeated Measures and Sample Size (RMASS) Manual

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Summary:

The RMASS program computes sample size for two-level and three-level mixed-effects linear regression models for the analysis of longitudinal data. Usually, level 1 represents measurement occasion, level 2 represents subject, and level 3 represents center. In some cases, center-level clustering is ignored assuming homogeneity of subjects across centers and in other cases it is not present by design. In such scenarios, we only have two-level representation, i.e. level 1 represents measurement occasion and level 2 represents subject. The sample size determinations in this program are based on the requirements for a test of treatment by time interaction(s) for designs based on either subject-level or cluster-level randomization.

The three-level model allows for random-effects of the time trends at both the subject-level and the center-level. The two-level model which can be viewed as a special case of the three-level model allows for random-effects of the time trends at subject-level. The approach is general with respect to sampling proportions and number of groups, and it allows for differential attrition rates over time.

Table of Contents

A. OVERVIEW

Sample size for longitudinal study depends on the following parameters:
1. The desired level of statistical power (e.g. 80%)
2. The significance level (e.g. 5% for one-sided or two-sided test)
3. Treatment effect size
4. Error variability
5. Number of timepoints and Design matrix

In the case of the three-level model for the analysis of longitudinal data, there are one or two random-effects of time trends at both subject and center-level and randomization can occur at either level. For two-level models there are usually one or two random-effects at the subject-level.

Note: The sample size for the two-level model can be computed by setting the number of centers to 1 in the program and choosing subject-level randomization. The final output contains total sample size for the study.

The details of the two-level and three-level mixed-effects models are presented in the next section.

B. MODELS

Two-level Mixed-effects Model

Let us assume, we have i = 1 to N total number of subjects in two groups and each subject is repeatedly measured for j = 1 to T timepoints. The two-level mixed-effects model accounting for the correlation between repeated observations can be written as,

$$y_{ij} = \beta_{0i} + \beta_{1i}t + \beta_2 G + \beta_3 G \times t + \varepsilon_{ij}$$

$$\text{Outcome}(i,j) = \text{Intercept}(i) + \text{Time}(i) + \text{Group} + \text{Group} \times \text{Time} + \text{Error}(i,j)$$

$$\beta_{0i} = \beta_0 + \gamma_{0i}$$

$$\text{Intercept}(i) = \text{Intercept} + \text{random intercept term}(i)$$

$$\beta_{1i} = \beta_1 + \gamma_{1i}$$

$$\text{Time}(i) = \text{Time} + \text{random slope term}(i)$$

In this model, the joint distribution of random intercept and random slope of time (random intercept term(i) and random slope term(i)) which also capture the correlation within repeated observations is assumed to be multivariate normal with mean 0 and variance covariance matrix V_S.

$$\begin{pmatrix} \gamma_{0i} \\ \gamma_{1i} \end{pmatrix} = MVN\left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \sigma_{\gamma 0}^2 & \sigma_{\gamma 0 \gamma 1} \\ \sigma_{\gamma 0 \gamma 1} & \sigma_{\gamma 1}^2 \end{bmatrix} \right), \text{ where } V_S = \begin{bmatrix} \sigma_{\gamma 0}^2 & \sigma_{\gamma 0 \gamma 1} \\ \sigma_{\gamma 0 \gamma 1} & \sigma_{\gamma 1}^2 \end{bmatrix}$$

In the case of randomized clinical trials (RCTs), the slope of group at baseline (β_2) is assumed to be zero, i.e. the two groups are assumed to have the same response level at randomization time. The primary parameter of interest is the slope of interaction between group and time (β_3). This parameter captures the differences in the linear growth trajectories of two groups over time.

Three-level Mixed-effects Model

Let us assume, we have i = 1 to C with j = 1 to N subjects in each center. Furthermore, each subject is repeatedly measured for k = 1 to T timepoints. Therefore, the three-level mixed-effects model accounting for the correlation between nested observations at each level can be written as,

$$y_{ijk} = \beta_{0ij} + \beta_{1ij}t + \beta_2 G + \beta_3 G \times t + \varepsilon_{ijk}$$

$$\text{Outcome}(i, j, k) = \text{Intercept}(i, j) + \text{Time}(i, j) + \text{Group} + \text{Group} \times \text{Time} + \text{Error}(i, j, k)$$

$$\beta_{0ij} = \beta_{0i} + \gamma_{0ij}$$

$$\beta_{1ij} = \beta_{1i} + \gamma_{1ij}$$

$$\text{Intercept}(i, j) = \text{Intercept}(i) + \text{random intercept term}(i, j)$$

$$\text{Time}(i, j) = \text{Time}(i) + \text{random slope term}(i, j)$$

$$\beta_{0i} = \beta_0 + \delta_{0i}$$

$$\beta_{1i} = \beta_1 + \delta_{1i}$$

$$\text{Intercept}(i) = \text{Intercept} + \text{random intercept term}(i)$$

$$\text{Time}(i) = \text{Time} + \text{random slope term}(i)$$

In this model it is assumed that the intercept and slope of time are randomly distributed at subject and center levels. Within center between subjects (WC-BS) heterogeneity is captured by the random-effects at subject-level whereas the variability between centers (BC) is estimated by the random-effects at center-level. Finally, within center within subject (WC-WS) variability is explained by the estimate of error variance. Random intercept and slope of time which capture the correlation within repeated observations of subjects (random intercept term(i,j) and random slope term(i,j)) are assumed to be multivariate normally distributed with mean 0 and variance covariance matrix V_S. Similarly, random intercept and slope of time which capture the correlation within subjects of each center (random intercept term(i) and random slope term(i)) are assumed to be multivariate normally distributed with mean 0 and variance covariance matrix V_C.

$$\begin{pmatrix} \gamma_{0ij} \\ \gamma_{1ij} \end{pmatrix} = MVN \left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \sigma_{\gamma 0}^2 & \sigma_{\gamma 0 \gamma 1} \\ \sigma_{\gamma 0 \gamma 1} & \sigma_{\gamma 1}^2 \end{bmatrix} \right), \text{ where } V_S = \begin{bmatrix} \sigma_{\gamma 0}^2 & \sigma_{\gamma 0 \gamma 1} \\ \sigma_{\gamma 0 \gamma 1} & \sigma_{\gamma 1}^2 \end{bmatrix}$$

$$\begin{pmatrix} \delta_{0i} \\ \delta_{1i} \end{pmatrix} = MVN \left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \sigma_{\delta 0}^2 & \sigma_{\delta 0 \delta 1} \\ \sigma_{\delta 0 \delta 1} & \sigma_{\delta 1}^2 \end{bmatrix} \right), \text{ where } V_C = \begin{bmatrix} \sigma_{\delta 0}^2 & \sigma_{\delta 0 \delta 1} \\ \sigma_{\delta 0 \delta 1} & \sigma_{\delta 1}^2 \end{bmatrix}$$

The primary parameter of interest is the slope of interaction between group and time (β_3). This parameter captures the differences in the linear growth trajectories of two groups over time.

Note: In the case of three-level models, the randomization can occur at subject or center-level. Therefore, the parameter of interest, i.e. slope of the interaction parameter between group and time can be at subject or center-level.

C. CODING OF TIME

We have assumed a linear difference in growth trajectories in the above two and three-level models. However, it is easy to extend these models to incorporate other types of response trajectories using simple transformations. Some of the examples are listed below,

1. Linear, i.e. [0, 1, 2, 3, …, T]
2. Quadratic trend captured using sqrt transformation, i.e. [0, 1, 1.414, 1.732, …, SQRT(T)]
3. Exponential using log transformation, i.e. [0, 0.693, 1.098, …, LOG(T)] (In this case, t starts from 1 instead of 0)
4. Logit using inverse logit function

Therefore, coding of time in these models will depend on the design of study and expected difference between the response trajectories of the two groups. With the help of these transformations, the model still retains its simplicity and the treatment effect can be summarized using a single parameter(β_3).

In certain situations, the observations are collected at certain pre-defined timepoints. For example, consider a study which is designed to assess the primary outcome at baseline, 3 month, 6 month and 12 month follow-ups. In this case, time vector can be coded using two approaches: a) [0, 3, 6, 12], or b) [0, 1, 2, 4]. It can be readily seen that both coding schemes retain the linearity in response. The only difference between the two schemes is that the estimates of the slope parameters for the time trend and group by time trend obtained using the latter case will approximately be three times the estimates obtained using the first time coding scheme.

D. DEFINITIONS OF PARAMETERS FOR THE SOFTWARE

i)   Slope Parameter

Slope parameter of interaction between group by time can be also defined in terms of mean difference at any timepoint, i.e.

$$\text{Slope Parameter} = \frac{\text{Expected Mean Difference between the two groups at given time t}}{\text{Timepoint difference between time t and baseline}}$$

ii)   Effect Size

$$\text{Effect Size} = \frac{\text{Expected Mean Difference between the two groups at given time t}}{\text{Sqrt of variance at a particular time t}}$$

iii) Variance at Timepoint t

Variance at timepoint t
= variance of random intercept at center-level + variance of random intercept at subject-level
+ variance of random slope of time at center-level $\times Time^2$
+ variance of random slope of time at subject-level $\times Time^2$
+ 2 × covariance of random intercept and of random slope of time at center-level × Time
+ 2 × covariance of random intercept and of random slope of time at subject-level × Time
+ Error variance

Alternatively, the slope parameter can be defined in terms of effect size as

$$\text{Slope Parameter} = \frac{\text{Effect Size} \times \text{Sqrt of variance at a particular time t}}{\text{Timepoint difference between time t and baseline}}$$

iv) Proportion of Subjects in Group 1

$$\text{Proportion of Subjects in Group 1} = \frac{\text{Total number of subjects in each Center of Group 1}}{\text{Total number of subjects in each Center}}$$

v) Attrition Vector

Each row entry of this vector contains fraction of subjects that drop out between timepoints t and t+1.

For example, if the study contains 4 timepoints and the attrition vector is specified as [0.05, 0.10, 0.07], i.e. 0.05 fraction drop out between timepoints 1-2, 0.10 drop out between timepoints 2-3 and 0.07 drop out between timepoints 3-4, then the total number of subjects that are present at timepoint 2 will be 0.95N, the total number of subjects that are present at timepoint 3 will be 0.90 x 0.95N = 0.855N, and the total number of subjects that are present at the last timepoint 4 will be 0.93 x 0.90 x 0.95N = 0.79715N.

Alternatively,
Proportion of subjects that are present at timepoint 1 = 0.05N
Proportion of subjects that are present at timepoints 1 and 2 = 0.10 x 0.95N = 0.095N
Proportion of subjects that are present at timepoints 1, 2 and 3 = 0.07 x 0.90 x 0.95N = 0.05985N
And proportion of subjects that are present at timepoints 1, 2, 3 and 4 = 0.79715N

vi) Error Variance Structure

In the case of the two-level mixed-effects model, the most common assumption is that the two observations of same subjects are independent given the information about the random subject effect. This restriction can be relaxed and the error in the model can be allowed to be correlated.

Various choices of error variance covariance are available as a part of the software:
1. Compound Symmetry in which all correlations are set to a constant.
2. Auto Regressive model with lag 1 which allows the correlations to decrease with respect to power of absolute timepoint difference.
3. Toeplitz with M number of correlated lags allows the correlations to be only function of lags.

Both the Compound Symmetry and Auto Regressive model with lag 1 only require the specification of the error variance and correlation term. Toeplitz with M number of correlated lags also requires the specification of the number of correlated lags.

vii) Variance Covariance Matrix of Random-Effects V_S and V_C

The variance covariance of random-effects at center-level and subject-level can be estimated using a pilot data. If prior data is not available then an approximation can be obtained using the definition of Intra Class Correlation (ICC) or Variation Partition Coefficient (VPC).

In order to obtain the estimate of the random intercept variance, random slope of time variance and correlation between random intercept and random slope of time at subject and center-level, VPC needs to be specified at least for 3 different timepoints at each level along with the error variance. If VPC is assumed to be constant over time then the model will only contain random intercept terms. In this scenario, the variance of random slope of time and correlation between random intercept and random slope of time are assumed to be 0, and VPC is nothing but ICC.

Intra Class Correlation

ICC is defined as percentage of variance explained at higher level in comparison to total variance. The assumption for ICC is that the random slope variances of time at subject and center-level are 0.

$$\text{ICC (at subject-level)} = \frac{\text{Variance at subject-level}}{\text{Total Variance}}$$

$$\text{Variance at subject-level} = \text{Random Intercept at subject-level} + \text{Random Intercept Variance at center-level}$$

$$\text{ICC (at center-level)} = \frac{\text{Variance at center-level}}{\text{Total Variance}}$$

$$\text{Variance at center-level} = \text{Random Intercept Variance at center-level}$$

$$\text{Total Variance} = \text{Error Variance} + \text{Random Intercept Variance at subject-level} + \text{Random Intercept Variance at center-level}$$

Variation Partition Coefficient

There are various definitions of VPC in literature. It is based on the generalization of ICC where we assume slope of time parameter also vary randomly along with the intercept. For this manual, we have presented the most intuitive extension of ICC. Note that unlike ICC, VPC is a function of time and can be reported at various timepoints.

$$\text{VPC (at subject-level)} = \frac{\text{Variance at subject-level}}{\text{Total Variance}}$$

$$\text{Variance at subject-level}$$
$$= \begin{pmatrix} \text{Variance Random Intercept at subject-level} \\ + \text{Variance Random Slope of time at subject-level} \times \text{Time}^2 \\ + 2 \times \text{Covariance of random intercept and random slope of time at subject-level} \times \text{Time} \end{pmatrix}$$
$$+ \begin{pmatrix} \text{Variance Random Intercept at center-level} \\ + \text{Variance Random Slope of time at center-level} \times \text{Time}^2 \\ + 2 \times \text{Covariance of random intercept and random slope of time at center-level} \times \text{Time} \end{pmatrix}$$

$$\text{VPC (at center-level)} = \frac{\text{Variance at center-level}}{\text{Total Variance}}$$

$$\text{Variance at center-level}$$
$$= \begin{pmatrix} \text{Variance Random Intercept at center-level} \\ + \text{Variance Random Slope of time at center-level} \times \text{Time}^2 \\ + 2 \times \text{Covariance of random intercept and random slope of time at center-level} \times \text{Time} \end{pmatrix}$$

$$\text{Total Variance}$$
$$= \text{Variance Random Intercept at center-level} + \text{Variance Random Intercept at subject-level}$$
$$+ \text{Variance Random Slope of time at center-level} \times \text{Time}^2$$
$$+ \text{Variance Random Slope of time at subject-level} \times \text{Time}^2$$
$$+ 2 \times \text{Covariance of random intercept and random slope of time at center-level} \times \text{Time}$$
$$+ 2 \times \text{Covariance of random intercept and random slope of time at subject-level} \times \text{Time}$$
$$+ \text{Error Variance}$$

Illustration of ICC vs VPC and the observed trajectories of subjects:
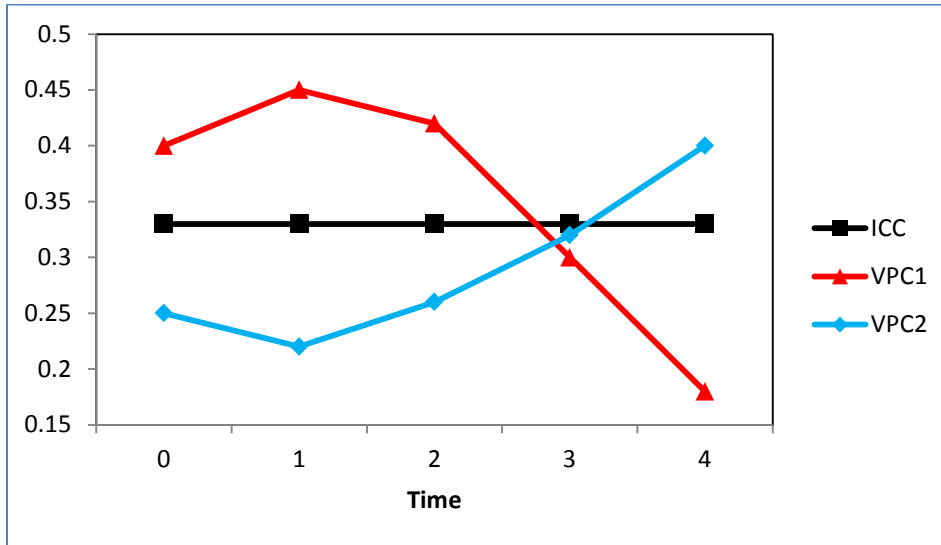

Trajectory of subjects corresponding to ICC, VPC1 and VPC2 will appear approximately as follows:
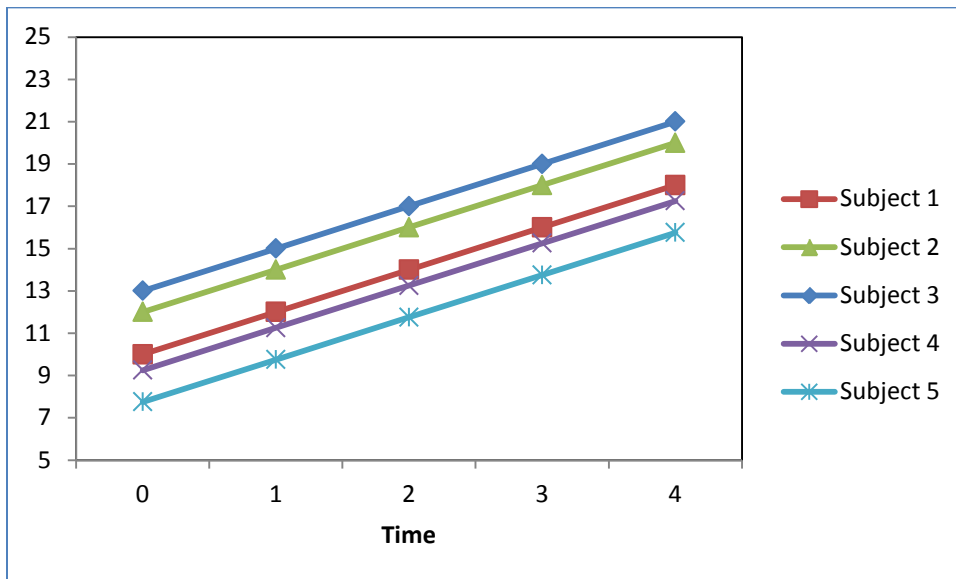
ICC represents no variation in slopes. Hence, expected response of all the subjects will only show variability with respect to the intercept. The slopes of the subjects will be approximately parallel.
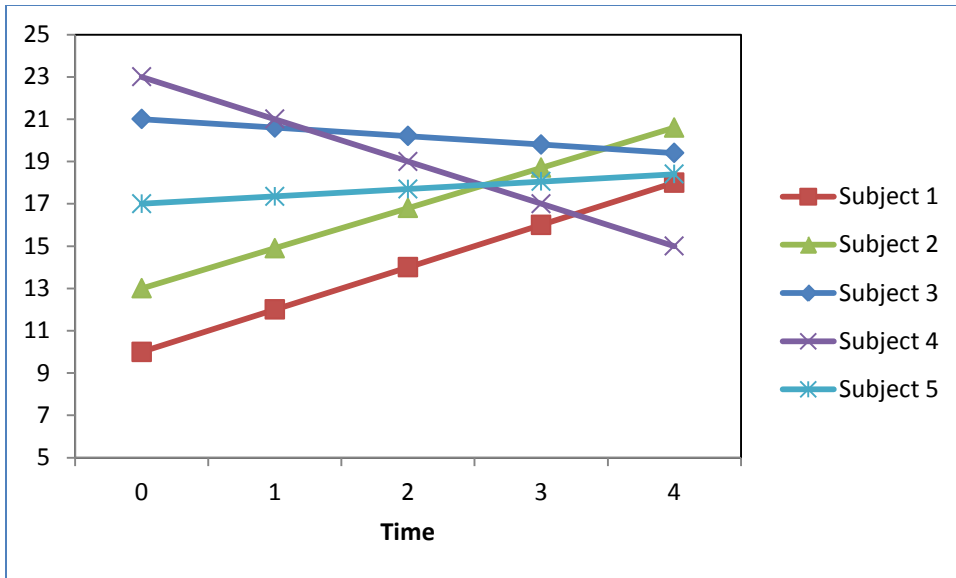
The expected response for the subject will appear to be converging for VPC1, i.e. the variability in slopes will decrease over time.
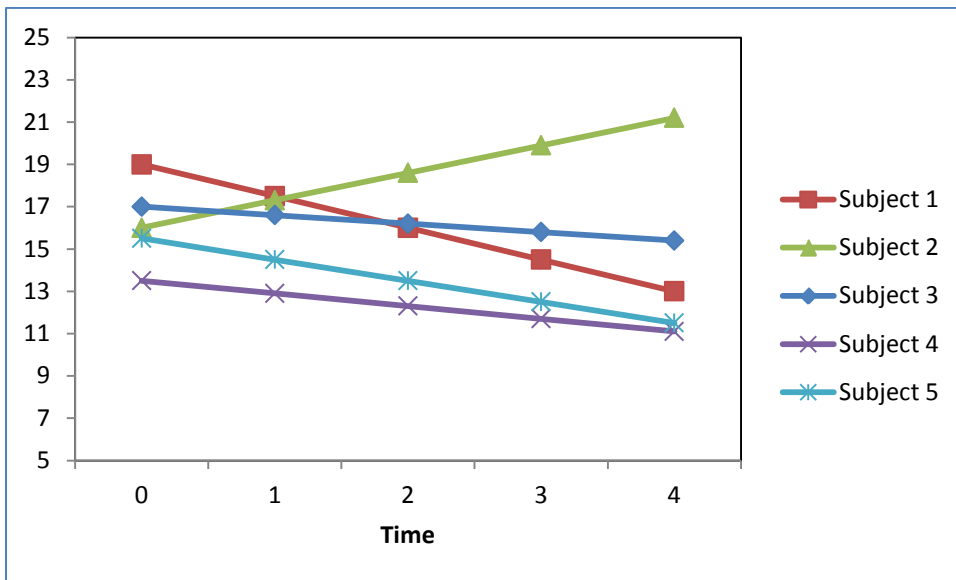
The expected response for the subject will appear to be diverging for VPC2, i.e. the variability in slopes will increase over time.

viii) Minimum Number of Centers in the Case of Center-level Randomization

For center-level randomization, there is lower limit to number of centers which depends on the following parameters:

- Variance of Center Slope
- Slope of Group × Time
- Power
- Type I error rate
- Proportions allocated to each group

Hence, the number of centers cannot be arbitrarily reduced by increasing the number of subjects in each center. Please refer to the manuscript: Roy et. al. (2007).

E. RMASS PROGRAM SCREENSHOTS

Randomization Tab
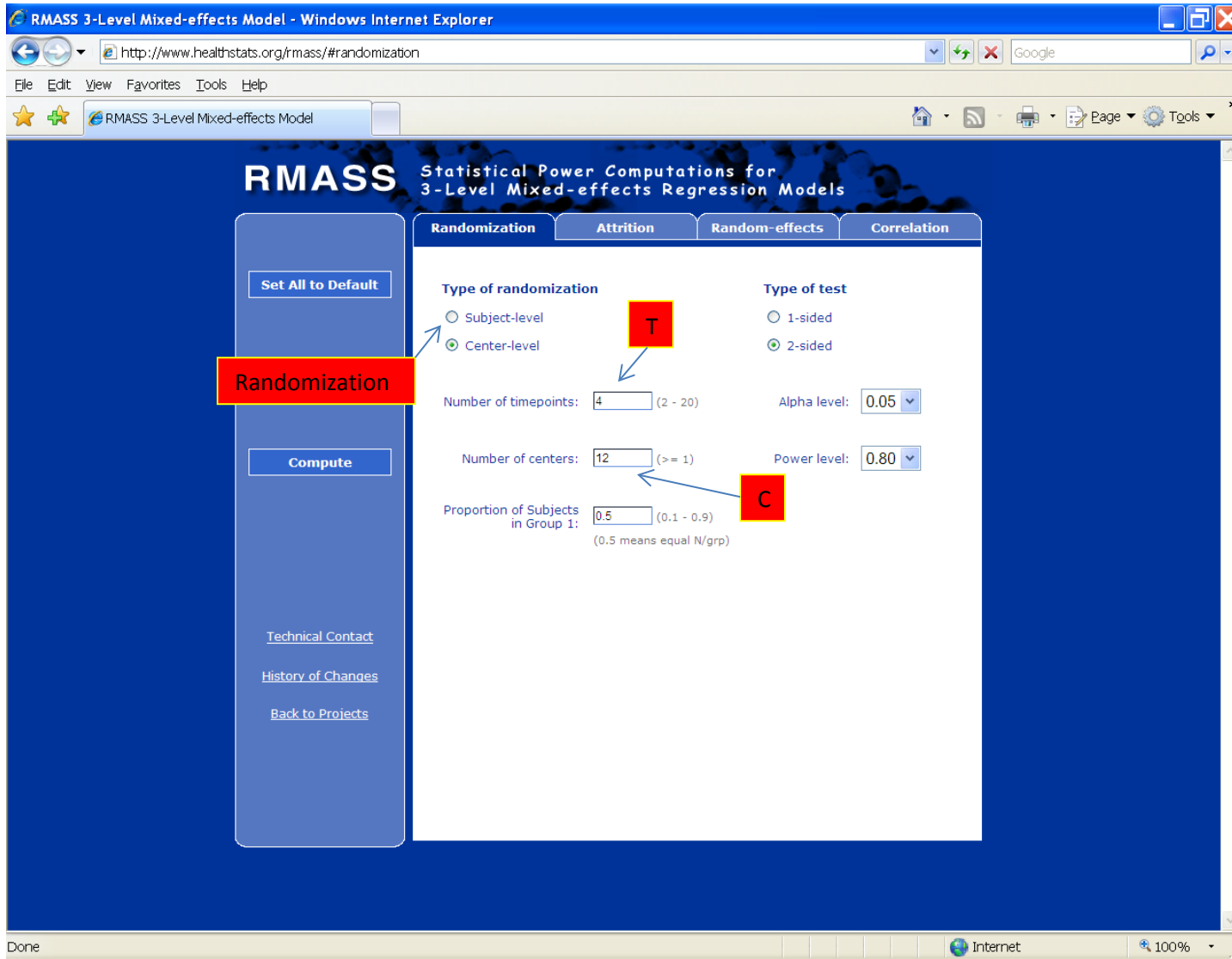
Attrition Tab

Random-Effects and Parameters Tab

Correlation Tab

Screenshot content: RMASS 3-Level Mixed-effects Model - Windows Internet Explorer

URL: http://www.healthstats.org/rmass/#correlation

RMASS — Statistical Power Computations for 3-Level Mixed-effects Regression Models

Tabs: Randomization | Attrition | Random-effects | **Correlation**

Set All to Default

Correlation structure of errors   Error variance: 0.576
- ⦿ all correlations equal
- ◯ stationary AR1
- ◯ toeplitz (banded) matrix
  - 1   # of correlated lags

Correlation terms
  1: 0.000

Compute

In this example all correlations between the errors at different timepoints are assumed to be equal and are set to 0.

After entering and reviewing all the parameters on the 4 program tabs, click **Compute** to see the results.

Technical Contact

History of Changes

Back to Projects

12

F. EXAMPLES

Three-level Model

Estimates available from previous study:

NIMH Schizophrenia Collaborative Study

- Nine Clinical Research Centers.
- Three active drugs vs Placebo. Drugs were Chlorpromazine, Fluphenazine and Thiordidazine.
- 6 weeks of Follow-up.
- Hedeker and Gibbons considered data for 220 subjects assigned to Chlorpromazine or Placebo.
- Severity of Illness as continuous outcome.
- **Model was fit using sqrt of week to linearize the time-response function.**

		Estimate	SE	P-value
Intercept		5.335	0.122	0.001
Treatment		0.057	0.097	0.557
Week		-0.327	0.079	0.001
Treatment by Week		-0.643	0.077	0.001
Within subject error variance		0.576	0.030	
Subject	Intercept Variance	0.304	0.057	
	Slope Variance	0.229	0.032	
	Covariance	0.043	0.030	
Center	Intercept Variance	0.069	0.041	
	Slope Variance	0.015	0.012	
	Covariance	-0.026	0.018	

Time for this example is coded as SQRT(T), where T is [0, 1 week, 3 weeks and 6 weeks].
Hence, T = [0, 1, 1.73, 2.44].

Subject-level Randomization

   a. Power = 80%, Type I error = 0.05 (2-sided test) with no attrition

       Number of Timepoints = 4
       Alpha level = 0.050 (2-sided)
       Power level = 0.800
       Proportion of Subjects in Group 1 = 0.500
       Number of Centers = 6
       Total # of Subjects per Center = **6**
       Time Pt Values = 0.000 1.000 1.730 2.440
       Mean Diffs = 0.000 0.643 1.112 1.569
       Stand. Devs. = 0.974 1.108 1.318 1.576
       Effect Sizes = 0.000 0.580 0.844 0.995

       Hence, the total number of subjects = 6 x 6 = 36
       And the total number of subjects per group = 36/2 = 18

   b. Power = 95%, Type I error = 0.05 (2-sided test) with no attrition

       Number of Timepoints = 4
       Alpha level = 0.050 (2-sided)
       Power level = 0.950
       Proportion of Subjects in Group 1 = 0.500
       Number of Centers = 6
       Total # of Subjects per Center = **9**
       Time Pt Values = 0.000 1.000 1.730 2.440
       Mean Diffs = 0.000 0.643 1.112 1.569
       Stand. Devs. = 0.974 1.108 1.318 1.576
       Effect Sizes = 0.000 0.580 0.844 0.995

       Hence, the total number of subjects = 6 x 9 = 54
       And the total number of subjects per group = 54/2 = 27

   c. Power = 95%, Type I error = 0.05 (2-sided test) with attrition of 5% between timepoints

       Number of Timepoints = 4
       Alpha level = 0.050 (2-sided)
       Power level = 0.950
       Proportion of Subjects in Group 1 = 0.500
       Number of Centers = 6
       Total # of Subjects per Center = **10**
       Proportion with t Observations = 0.05 0.05 0.05 0.86
       Time Pt Values = 0.000 1.000 1.730 2.440
       Mean Diffs = 0.000 0.643 1.112 1.569
       Stand. Devs. = 0.974 1.108 1.318 1.576
       Effect Sizes = 0.000 0.580 0.844 0.995

       Hence, the total number of subjects = 6 x 10 = 60
       And the total number of subjects per group = 60/2 = 30
       Note: the attrition only changes the total sample size by 3 per group (compare with case b).

Center-level Randomization

   d. Number of Centers = 6 with Power = 95%, Type I error = 0.05 (2-sided test) with attrition of 5% between timepoints

      Number of Timepoints = 4
      Alpha level = 0.050 (2-sided)
      Power level = 0.950
      Proportion of Subjects in Group 1 = 0.500
      Number of Centers = 6
      Total # of Subjects per Center = **14**
      Proportion with t Observations = 0.05 0.05 0.05 0.86
      Time Pt Values = 0.000 1.000 1.730 2.440
      Mean Diffs = 0.000 0.643 1.112 1.569
      Stand. Devs. = 0.974 1.108 1.318 1.576
      Effect Sizes = 0.000 0.580 0.844 0.995

      Hence, the total number of subjects = 6 x 14 = 84
      And the total number of subjects per group = 84/2 = 42
      Note: the number of subjects for center-level randomization increases drastically in comparison to subject-level randomization (compare with case c).

   e. Number of Centers = 4 with Power = 95%, Type I error = 0.05 (2-sided test) with attrition of 5% between timepoints

      Number of Timepoints = 4
      Alpha level = 0.050 (2-sided)
      Power level = 0.950
      Proportion of Subjects in Group 1 = 0.500
      Number of Centers = 4
      Total # of Subjects per Center = **27**
      Proportion with t Observations = 0.05 0.05 0.05 0.86
      Time Pt Values = 0.000 1.000 1.730 2.440
      Mean Diffs = 0.000 0.643 1.112 1.569
      Stand. Devs. = 0.974 1.108 1.318 1.576
      Effect Sizes = 0.000 0.580 0.844 0.995

      Hence, the total number of subjects = 4 x 27 = 108
      And the total number of subjects per group = 108/2 = 54
      Note: More subjects are required when the number of centers is lower (compare with case d).

Two-level Model

The sample size for two-level mixed-effects models can be computed by setting the number of centers = 1 and choosing subject-level randomization. The variance covariance matrix of center-level is automatically changed to a 0 matrix and it does not play any role in the final sample size computation. The results are in terms of total sample size N. The sample sizes in each group are equal to N × proportion of subjects in group1 and N × (1 − proportion of subjects in group1), respectively.

f. Power = 80%, Type I error = 0.05 (2-sided test) with no attrition

Number of Timepoints = 4
Alpha level = 0.050 (2-sided)
Power level = 0.800
Proportion of Subjects in Group 1 = 0.500
Number of Centers = 1
Total # of Subjects per Center = 31
Time Pt Values = 0.000 1.000 1.730 2.440
Mean Diffs = 0.000 0.643 1.112 1.569
Stand. Devs. = 0.938 1.081 1.292 1.546
Effect Sizes = 0.000 0.595 0.861 1.015

Hence, the total number of subjects = 31
And the total number of subjects per group = 31/2 approximately 16
Note: The number of subjects only changed slightly (compare with case a).

References

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Hedeker D, Gibbons RD, Waternaux C. Sample size estimation for longitudinal designs with attrition: Comparing time-related contrasts between two groups. *Journal of Educational and Behavioral Statistics.* 1999; 24:70-93.