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## swpermute: Permutation tests for Stepped-Wedge Cluster-Randomised Trials

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**Abstract.** Permutation tests are useful in stepped-wedge trials to provide robust statistical tests of intervention-effect estimates. However, the Stata command **permute** does not produce valid tests in this setting because individual observations are not exchangeable. We introduce the **swpermute** command that permutes clusters to sequences to maintain exchangeability. The command provides additional functionality to aid users in performing analyses of stepped-wedge trials. In particular, we include the option "withinperiod" that performs the specified analysis separately in each period of the study with the resulting period-specific intervention-effect estimates combined as a weighted average. We also include functionality to test non-zero null hypotheses to aid the construction of confidence intervals. Examples of the application of **swpermute** are given using data from a trial testing the impact of a new tuberculosis diagnostic test on bacterial confirmation of a tuberculosis diagnosis.

 $\label{eq:Keywords: st0001, swpermute, stepped-wedge, cluster-randomised, permutation test, randomization test$ 

 $\bigodot$ yyyy StataCorp LP

### 1 Introduction

Permutation tests are a commonly used non-parametric statistical technique, used to calculate p-values without making distributional assumptions (Pitman (1937), Eden and Yates (1933), Fisher (1960)). In individually randomised trials, they are used because they make no distributional assumptions, provide exact p-values and confidence intervals, and do not rely on large sample approximations (Ernst (2004)); the Stata command permute provides an intuitive and simple way to perform permutation tests in this simple scenario.

While the benefits of permutation tests hold for more complex randomised designs, such as stepped-wedge cluster-randomised trials (SW-CRTs), permute cannot perform a valid test for these complex designs. In a cluster-randomised trial (CRT), the allocation of clusters of individuals, such as villages or hospital wards, is randomised. An SW-CRT is a CRT run over a number of periods. Clusters are randomised to sequences, where each sequence receives the control condition for a different number of periods, and then receive an intervention condition for the remaining periods of the trial (Figure 1). Parametric analysis of SW-CRTs requires specification of the correlation structure over time within cluster. This can be difficult to prespecify and results are sensitive to misspecification (Thompson et al. (2017)), and so permutation tests, which do not require specification of correlation structures, are appealing (Hayes and Moulton (2009), Thompson et al. (2018), Ji et al. (2016), Wang and DeGruttola (2017)).



Figure 1: Schematics of a stepped-wedge cluster-randomised trial. White = time in control condition, Grey = time in intervention condition

Here we introduce a new command, swpermute. The new command allows specification of clustering and allocation to a sequence of intervention conditions to enable use with CRTs in general, but with a particular focus on SW-CRTs. In the next section, we provide an overview of permutation tests for SW-CRTs. In section 3, we outline the syntax of the swpermute command. In section 4, we demonstrate the use of swpermute with two examples.

## 2 Technical details

The **swpermute** command is designed for trials with two treatment conditions; usually, this will be a control and intervention condition, so we will use this terminology throughout this paper. In this section, we will provide a summary of the permutation test, and how this is implemented in **swpermute**.

#### 2.1 Permutation Tests with individual randomisation

Details of the permutation test can be found elsewhere, such as Good (2006): here, we provide a brief summary.

In an individually randomised trial, we have a sample of observations, half of which were collected under a control condition and half under an intervention condition. We are interested in knowing whether the control and intervention conditions result in a different distribution of outcomes. If there is truly no difference between the two conditions, then assignment of observations to each condition is arbitrary, and for any set of assignments of the observations to the control and intervention conditions, we can estimate an intervention effect. By repeating this process for each unique assignment of observations to conditions, we obtain the exact distribution of the intervention effect estimator under the null hypothesis of no effect. The p-value, defined as the probability of the observed data if there is no intervention effect, is then given as the proportion of permuted intervention effects the same as or more extreme than that observed.

#### **Monte-Carlo permutations**

Computational complexity of this process is simplified by randomly sampling a number of permutations from all possible permutations, with or without replacement, a process known as Monte-Carlo permutations (Good (2006)). The p-value calculated may differ when the process is repeated with a different set of permutations.

#### **Constructing Confidence Intervals**

Confidence intervals are created by finding the boundaries of hypothesised intervention effects that lead to two-sided p-values less than the  $\alpha$  level. One way to identify the confidence limits is to test several hypothesised intervention effects to see whether the p-value is larger or smaller than  $\alpha$ .

A hypothesised intervention of  $\theta = \theta_A$  is tested by first subtracting  $\theta_A$  from observations collected in the intervention condition, then running the permutation test as described above to get a p-value (Good (2006), Rigdon and Hudgens (2015)). The random number seed should be set to the same seed as the original analysis so that one set of permutations are used throughout the analysis, allowing the confidence intervals and p-value to coincide with one another.

# 2.2 Extending permutation tests to stepped-wedge cluster-randomised trials

Two assumptions are required for permutation tests to be valid.

Firstly, permutation tests test equivalence of distributions between the conditions. This means they will return a small p-value if either the mean or variance of outcomes differ. The effect of an intervention varying between observations is an example of the latter.

Secondly, permutation tests assume exchangeability of observations. This means that any assignment of observations to the conditions is equally likely. In the context of SW-CRTs, exchangeability holds for the assignment of clusters to sequences but will not hold at the individual observation level. Clusters should therefore be permuted between sequences. The permute command permutes individual observations, so is not a valid test for SW-CRTs. The swpermute command permutes clusters to sequences so is valid for SW-CRTs (as well as CRTs with other designs).

# 2.3 Selecting an intervention effect estimator for a stepped-wedge trial

Permutation tests provide a p-value and confidence intervals for a given intervention effect estimator. A key design feature of all SW-CRTs is that the intervention effect is confounded with time. Therefore, the chosen estimator must account for this confounding either by adjusting for period effects, or by conditioning on periods.

To adjust for period effects, generalised linear models or generalised linear mixed models can be utilised (Bellan et al. (2015), Ji et al. (2016), Wang and DeGruttola (2017)).

To condition on period, the analysis can be conducted within each period with resulting within-period estimates combined as a weighted average. More details of this method, also known as a vertical analysis, are given in Thompson et al. (2018). Any analysis that can be used for a parallel CRT could be used within each period, for example Thompson et al. (2018) suggested using a cluster-level analysis in each period.

The overall intervention effect estimate can be estimated more accurately by using appropriate weights for each period (Hayes and Moulton (2009)). Periods can be weighted by the imbalance in the number of clusters in the control and intervention conditions (Matthews and Forbes (2017)), or by the precision of within-period estimates (Thompson et al. (2018)).

## 3 The swpermute Command

In this section, we describe the swpermute command.

The swpermute command runs a permutation test for SW-CRTs using any analysis,

specified by the user, to estimate the intervention effect. The algorithm identifies sequences in the data and permutes clusters between these sequences. Like the permute command, swpermute performs Monte-Carlo permutations with replacement. The specified analysis can be run either across all periods in the study or within each period with results combined as a weighted average. Users can specify hypothesised intervention effects to construct confidence intervals.

#### 3.1 Data requirements

The swpermute command requires specification of a clustering variable identified in cluster(), a period variable identified in period(), and an intervention variable identified in intervention(): together these variables define the design of the trial. The intervention must be specified as a binary variable where 0 and 1 represent the control and intervention conditions, respectively. All observations within each value of cluster() must have the same value of intervention() in each period() or the command will return an error. If the intervention variable contains missing values for all observations in a period in a cluster, then this is assumed to be part of the sequence, for example as a washout period, and the missing value will be permuted. Otherwise, observations with intervention() missing will be excluded from the analysis.

The data should be in long format, with observations in each period given in different rows of the data.

#### 3.2 Syntax

The syntax of the swpermute command is as follows:

```
swpermute exp , cluster(varname) period(varname) intervention(varname)
  [ reps(#) left|right strata(varlist) saving(filename, ...) null(numlist)
   outcome(varname) withinperiod weightperiod(weightperiod) nodots
   level(#) seed(#) ] : command
```

exp specifies the result to be collected from results stored by the execution of command. Examples are  $r(mu_1) - r(mu_2)$  the mean difference estimated by ttest, or \_b[varname] a coefficient estimate from a regression model.

- cluster(varname) specifies the variable identifying the clusters. cluster() is required and must be a numeric variable. Observations with cluster() missing will be excluded from the analysis.
- period(varname) specifies the variable identifying the periods. period() is required and must be a numeric variable. Observations with period() missing will be excluded from the analysis.

intervention(varname) specifies the variable identifying the intervention assignment.

intervention() is required and must be a binary variable. Treatment of missing values is described above.

- reps(#) specifies the number of permutations to perform. The default is reps(500).
- left|right requests that one-sided p-values be computed. If left is specified, the p-value reported is the proportion of permutations where exp gives a value less than or equal to the observed value. If right is specified, the p-value reported is the proportion of permutations where exp gives a value greater than or equal to the observed value. The default is two-sided p-values, where the p-value reported is the proportion of permutations where exp is the same or further from zero than the observed value.
- strata(varlist) specifies that the permutations be performed within each stratum defined by the values of varlist. This option should be used if randomisation of clusters was stratified (Ernst (2004)).
- saving(filename, ...) creates a Stata file (.dta file) consisting of a row for each permutation for each value in null(). The file consists of three variables containing the null() value being tested, the observed value of exp for that null value, and values of exp for each permutation. A new filename is required unless replace is specified. The option double specifies that results should be stored in double precision, the default is to store results as float. The option every(#) writes results to file every # permutations. This will allow recovery of partial results should the command not complete running.
- null(numlist) specifies a list of values to test as the null hypothesis. For each value specified, the value will be subtracted from the variable specified in outcome() if the variable defined in intervention() is equal to 1. The permutation test is run on this modified dataset to calculate a p-value. The random number seed is reset for each value tested. This option should only be used with cluster-period level or continuous outcomes. The null values are assumed to be on the same scale as the outcome (e.g. risk differences if the outcomes are cluster-period risks). Ratios such as risk ratios, or odds ratios should be given on the log scale. The default is null(0). When values other than the default are specified the option outcome(varname) is required.
- outcome(varname) specifies the variable identifying the outcome. This option is only required when null(numlist) is specified with numlist != 0. outcome() is assumed to be on the same scale as the values specified in null(). For example, outcome() should contain risks if null() gives risk differences, or log risks if null() gives log risk ratios.
- withinperiod specifies that a within-period analysis should be performed. *command* is run within each unique value of the variable specified in period() and the resulting values of *exp* are combined as a weighted average using the weights specified in weightperiod().

weightperiod(weightperiod) specifies the weights to be used if withinperiod is speci-

fied. This option is only required when withinperiod is specified and is one of the following:

weightperiod(none): each period is given equal weight, so the weight  $w_j = 1$  for all periods j.

weightperiod(N): periods are weighted by the number of clusters in the control and intervention conditions as:

$$w_j = \left(\frac{1}{s_{oj}} + \frac{1}{s_{1j}}\right)^{-1}$$

where  $s_{0j}$  and  $s_{1j}$  are the numbers of clusters in the control condition and intervention condition respectively in period j. This is the default and is recommended if the total variance is not expected to vary between periods (Matthews and Forbes (2017)).

weightperiod(variance  $exp_2$ ): each period is weighted by the inverse of the statistic  $exp_2$  stored by the execution of *command*. That is

$$w_j = exp_{2j}^{-1}$$

 $exp_{2j}$  is assumed to be the variance of the estimate from the jth period. This specification is suggested by Thompson et al. (2018) when the variance of the outcome is expected to vary between periods.

- nodots suppresses display of the dots at the completion of each permutation. By default, one . is displayed for each successful permutation. A red x is displayed if command returns an error or if the statistic in exp is missing for a permutation.
- level(#) specifies the confidence level, as a percentage, for the confidence interval of the p-value. The default is level(95) or as set by set level; see [U] 20.7 Specifying the width of confidence intervals.

seed(#) sets the random-number seed. Specifying this option is equivalent to typing:

set seed #

prior to calling swpermute. If no seed is specified, swpermute will return different results each time it is run due to the random selection of permutations.

#### 3.3 Stored results

swpermute stores the following in r():

Scalars	
$r(N_cluster)$	number of clusters
$r(N_strata)$	number of strata if strata option has been used
r(obs_value)	value of <i>exp</i> observed in the data
$r(N_reps)$	number of permutations
Matrices	
r(design)	a matrix of 0 and 1 values showing the design of the SW-CRT
r(obs_period)	value of <i>exp</i> observed in the original data within each period if
	a within-period analysis is specified
r(p)	p-values with their confidence intervals for each null value

#### 3.4 The Dialog Box

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The swpermute command can be used both as a coded command, and through a dropdown dialog box as shown in the appendix. To install the dialog box run the following commands:

- . window menu append submenu "stUser" "&Cluster RCTs"
- window menu append item "Cluster RCTs" "Permute for stepped-wedge trials (&swpermute)" "db swpermute"
- . window menu refresh

Running these commands from within Stata will only install the dialog box for the current session of Stata. To install the menus permanently, place the above commands into your profile.do file. See [U] [GSW] B.3, [U] [GSM] B.1, or [U] [GSWU] B.1 Executing commands every time Stata is started for more details on how to do this.

## 4 Example

To demonstrate the use of swpermute we will use data from an SW-CRT conducted in Brazil that assessed the impact of switching to a new tuberculosis (TB) diagnostic test called Xpert MTB/RIF from the standard test, sputum smear microscopy. We will focus on a secondary outcome of the proportion of patients with a bacterial confirmation of their TB diagnosis (Trajman et al. (2015)). These examples use real trial data, but the data cannot be provided with the command. Instead, a simulated dataset is included that closely mimics the characteristics of these trial data, but will not reproduce these example results.

The trial included 14 laboratories (clusters). At initiation of the study, all laboratories were using sputum smear microscopy to diagnose TB. Following a month of baseline data collection, the Xpert test was rolled out to two randomly assigned laboratories each month, so that 7 months later, all laboratories were using the Xpert test. The dataset contains 3,924 patients; their type of diagnosis was recorded as either clinical (with a negative test or no test done), or bacterially confirmed. The Xpert test was used to

diagnose 2,147 (55%) patients. Across both trial arms 2,833 (72%) had a confirmed TB diagnosis.

The output below describes the dataset.

Contains data obs: vars: size:	from TBd 3,924 6 27,468	iagnostic.dt	a	5 Oct 2018 15:33
variable name	storage type	display format	value label	variable label
lab patientid	byte int	%8.0g %9.0g		ID of laboratory
study_month	byte	%8.0g		Study month
arm	byte	%8.0g	armlbl	Intervention status
fav_outcome	byte	%10.0g	favoutlbl	
				Treatment outcome of individual
confirmed	byte	%11.0g	confirmedl	bl
				Laboratory confirmation of TB diagnosis

Sorted by: lab study\_month

. list in 1/5

	lab	patien~d	study_~h	arm	fav_outc~e	confirmed
1.	1	1	1	smear	favourable	unconfirmed
2.	1	2	1	smear	poor	confirmed
3.	1	3	1	smear	favourable	confirmed
4.	1	4	1	smear	poor	confirmed
5.	1	5	1	smear	favourable	confirmed

Each row gives the diagnosis type, confirmed, of a patient. lab identifies which laboratory they were diagnosed in and so assigns the patient to a cluster. study\_month identifies which month of the study they were diagnosed in, and arm identifies whether the laboratory was using smear microscopy or the Xpert diagnostic at the time of diagnosis.

We will explore two analyses with permutation tests: the first will use a generalised linear mixed model with a permutation test, the second will demonstrate a within-period analysis.

#### 4.1 Example 1: Generalised linear mixed model

A mixed-effect logistic regression, adjusting for period effects as a fixed categorical variable and with a random intercept for cluster, can be used in combination with a permutation test to analyse this trial, as shown below.

```
swpermute _b[arm], cluster(lab) period(study_month) intervention(arm) /*
           */ reps(1000) seed(20255) nodots: /*
>
           */ melogit confirmed i.study_month arm || lab :
Monte Carlo permutation results
     command:
                melogit confirmed i.study_month arm || lab :
   statistic:
                _b[arm]
      design:
                                                              6
                                                                    7
                                                                           8
                 freq
                             1
                                   2
                                          3
                                                 4
                                                       5
                                                              0
                                                                    0
                     2
                            0
                                   0
                                          0
                                                0
                                                       0
                                                                           1
                     2
                            0
                                   0
                                          0
                                                              0
                                                0
                                                       0
                                                                    1
                                                                           1
                     2
                            0
                                   0
                                          0
                                                0
                                                       0
                                                              1
                                                                    1
                                                                           1
                     2
                            0
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                                                                    1
                                                                           1
                     2
                            0
                                   0
                                          0
                                                1
                                                       1
                                                              1
                                                                    1
                                                                           1
                     2
                            0
                                   0
                                          1
                                                1
                                                              1
                                                                           1
                                                       1
                                                                    1
                     2
                            0
                                   1
                                                              1
                                                                    1
                                                                           1
                                          1
                                                1
                                                       1
statistic
                 obs_value
                                null
                                            с
                                                              p [95% Conf. Interval]
                                                     n
                   .4155579
                                            2
                                                  1000
                                                       0.0020
                                                                 .0002423
                                                                              .0072058
     _b[arm]
                                   0
```

Note: confidence interval is with respect to p p-value is two-sided

swpermute shows the design-pattern matrix of the trial to allow users to check that sequences have been correctly identified. Each row represents a unique sequence of allocations observed within the data, each column represents a period. For each sequence and period, a 0 or 1 is shown representing the intervention condition of clusters in that sequence in that period. The left-most column shows the number of clusters assigned to each sequence.

The table below this gives the results of the permutation test. First, we see the intervention effect estimate observed in the data (obs\_value), then the null hypothesis being tested (null). The third column (c) gives the number of permutations with a value of *exp* the same or more extreme than the observed value and the fourth column (n) gives the total number of permutations successfully completed.

The intervention effect estimate is the value estimated by the melogit command (odds ratio =  $\exp(0.42) = 1.52$ ).

Only 2/1000 permutations gave a result the same or more extreme than that observed, giving the p-value 2/1000 = 0.002 shown in column 5 (p). This analysis suggests that there is strong evidence that the Xpert test increases the odds of a confirmed diagnosis.

The last two columns give a two-sided 95% confidence interval for the p-value that indicates the level of uncertainty around the p-value from the random selection of permutations. In this example, the interpretation of the p-value does not substantively change for values within this interval. Where interpretation would alter for different values within the interval, the analysis should be rerun with a larger number of permutations.

# 4.2 Example 2: Within-period analysis and generating confidence intervals

In our second example, we will use a within-period analysis to calculate the difference in the risk (the proportion) of a confirmed diagnosis using a cluster-level analysis within each period, and we show how to construct confidence intervals.

First, we calculate the proportion of confirmed diagnoses in each cluster-period by collapsing the data. We run swpermute with regress as the *command* to calculate a risk difference and its variance. We select the withinperiod option to run the regression within each period, and set the period weights as variance weights.

. collapse (mean) risk\_confirmed = confirmed , by(lab study\_month arm) swpermute \_b[arm], cluster(lab) period(study\_month) intervention(arm) /\* \*/ seed(9845) withinperiod weightperiod(variance \_se[arm]^2) nodots /\* > > \*/ reps(1000): regress risk\_confirmed arm Warning: study\_month = 1 not included in analysis. Clusters all in one condition Warning: study\_month = 8 not included in analysis. Clusters all in one condition Monte Carlo permutation results command: regress risk\_confirmed arm statistic: \_b[arm] design: 7 8 freq 1 2 3 4 5 6 2 0 0 0 0 0 0 0 1 2 0 0 0 0 0 0 1 1 2 0 0 0 0 0 1 1 1 2 0 0 0 0 1 1 1 1 2 0 0 0 1 1 1 1 1 2 0 0 1 1 1 1 1 1 2 0 1 Within period Estimates and Weights: Estimate Weight study\_month:2 0.0401 0.0581 study\_month:3 0.0998 0.1787 study\_month:4 0.0334 0.1329 study\_month:5 0.1512 0.1835 study\_month:6 0.1362 0.2714 study\_month:7 0.0909 0.1753 statistic obs\_value null с n p [95% Conf. Interval] .1052611 1000 0.0500 .0373354 \_b[arm] 0 50 .0653905

Note: confidence interval is with respect to p p-value is two-sided

We are warned that study month 1 and study month 8 are not included in this analysis. All clusters are in the same condition during these periods, so an intervention effect cannot be calculated.

The command displays a list of effect estimates and weights for each period in the study. Greatest weight is given to study month 6, despite the imbalance in clusters in the control and intervention conditions. This is because there was less variability in the cluster-level outcomes during this period leading to a lower variance for the estimated intervention effect.

The observed value in the table of results is the weighted average of these periodspecific estimates. The percentage of patients with a confirmed diagnosis was 10.5%higher in patients diagnosed with the Xpert test compared to patients diagnosed with smear microscopy, and there is some evidence against the intervention having no effect (p=0.05).

Next, we demonstrate the construction of 95% confidence intervals. Initial estimate of the confidence interval boundaries can be found by assuming that the intervention effect estimate follows a normal distribution and using the p-value to estimate a standard error as follows:

```
. * Estimate standard error
. display .1052611 / invnorm( 1 - 0.0500 / 2 )
.05370563
.
. * Initial lower bound of 95% CI:
. display .1052611 - 1.96 * .0537
9.100e-06
. * Initial upper bound of 95% CI:
. display .1052611 + 1.96 * .0537
.2105131
```

Permutation tests are conducted to test these initial values. An example is shown below for the initial proposed upper boundary; the dialog boxes shown in the appendix replicate this example.

Warning: study\_month = 1 not included in analysis. Clusters all in one condition
Warning: study\_month = 8 not included in analysis. Clusters all in one condition
Monte Carlo permutation results

command: statistic: design:	regress _b[arm]	s risk_co	onfirme	ed arm					
0	freq	1	2	3	4	5	6	7	8
	2	0	0	0	0	0	0	0	1
	2	0	0	0	0	0	0	1	1
	2	0	0	0	0	0	1	1	1
	2	0	0	0	0	1	1	1	1
	2	0	0	0	1	1	1	1	1
	2	0	0	1	1	1	1	1	1
	2	0	1	1	1	1	1	1	1

Within period Estimates and Weights:

	Estimate	Weight						
study_month:2	0.0401	0.0581						
study_month:3	0.0998	0.1787						
study_month:4	0.0334	0.1329						
study_month:5	0.1512	0.1835						
study_month:6	0.1362	0.2714						
study_month:7	0.0909	0.1753						
statistic	obs_value	null	с	n	р	[95% 0	conf.	Interval]
_b[arm]	.1052611	.211	26	1000	0.0260	.0170	528	.0378651

Note: confidence interval is with respect to  $\ensuremath{p}$  p-value is two-sided

Depending on the p-value, the proposed boundary value is either increased or decreased until the boundary value with p > 0.05 is identified. To identify the lower boundary in our example, the initial estimate was 0.00, which gives p=0.0500, so we tested a null value of -0.001 to see if a smaller value also fell with the 95% confidence interval. This has p=0.048, so the lower boundary is 0.00. For the upper boundary, the initial estimate of 0.211 gave p=0.026, well outside the 95% confidence interval. A null of 0.20 gave p=0.045, null=0.197 gave p=0.054, null=0.198 gave p=0.051, and lastly null=0.199 gave p=0.047: the largest value within the 95% confidence interval is 19.8%. Therefore our 95% confidence interval is (0.0%, 19.8%).

## 5 Concluding remarks

swpermute is an extension of the Stata command permute that permutes clusters between sequences and can perform within-period analyses. We also incorporated functionality to test non-zero null hypotheses to facilitate the construction of confidence intervals. Although this command has been designed for use with SW-CRTs, it can also be used with other trial designs such as parallel and crossover CRTs.

The command does, however, have limitations. Testing non-zero null hypothesis values is only available for continuous outcomes (including cluster-period level summaries). For other outcome types, the process involves manipulating the dataset to such a degree that we felt it was safer for the user to perform this themselves. For example, with a binary outcome, a risk difference cannot simply be subtracted from the outcome of 0 or 1. Whilst we have incorporated stratification of randomisation by a list of variables, some randomisation strategies, such as restricted randomisation, cannot be captured in this way (Moulton (2004)). It is a limitation of permutation tests generally that confidence intervals construction is computationally intensive.

swpermute facilitates the use of robust analysis methods for an SW-CRT, making complex analysis easier to perform.

## 6 Acknowledgments

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## Appendix: Dialog boxes to run the example in section 4.2

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