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A menu-driven facility for complex sample size calculation in randomized controlled trials with a survival or a binary outcome: Update

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Abstract. Royston and Babiker (2002) presented a menu-driven Stata program for the calculation of sample size or power for complex clinical trial designs under a survival time or binary outcome. In the present article, the package is updated to Stata 8 under the new name **ART**. Furthermore, the program has been extended to incorporate noninferiority designs and provides more detailed output. This package is the only realistic sample size tool for survival studies available in Stata.

Keywords: st0013_1, sample size, power, randomized controlled trial, multiarm designs, survival analysis

1 Introduction

Royston and Babiker (2002) presented a menu-driven Stata program for the calculation of sample size or power for complex clinical trial designs under a survival time or binary outcome. The features of this program include multiarm trials, an arbitrary time-to-event distribution, nonproportional hazards, nonuniform rates of patient entry, loss to follow-up and treatment changes from allocated treatment. In the present article, the program is updated to operate under the new Stata 8 dialog interface. Additionally, its name has been changed to **ART**–**Analysis of Resources for Trials**. This note also reports some further improvements to the software.

A brief summary of the underlying calculations can be found in Royston and Babiker (2002). A full report on the methodology and its performance in particular with respect to loss to follow-up, nonproportional hazards and crossover is given by Barthel et al. (2005).

2 New design of menu and dialogs

All features are available from the newly designed **ART** menu and associated dialogs. As before, on completion of the calculations, the command line that generated the results will be displayed in the Review window. For reproducibility of the calculations, we suggest that the user open a log file before executing the commands via the dialog that will hence save the command line. This log file can then be edited to produce a do-file to repeat the calculations, if desired.

When `artmenu` has been executed using `artmenu on`, a new item, **ART**, will appear on the system menu bar under **User**. This menu may be turned off by typing `artmenu off`. **ART** contains the following two items:

- **Survival outcomes** sets up all design parameters, including advanced options such as loss to follow-up and crossover for survival time trials.
- **Binary outcomes** sets up design parameters for trials with a binary outcome under a simple design.

Since no considerable changes have been made to the **Binary outcomes** facility, this article will concentrate on the changes made to **Survival outcomes**, and readers are referred to the original article by Royston and Babiker (2002) for further information on trials with binary outcomes.

2.1 Survival outcomes — Panel 1 tab

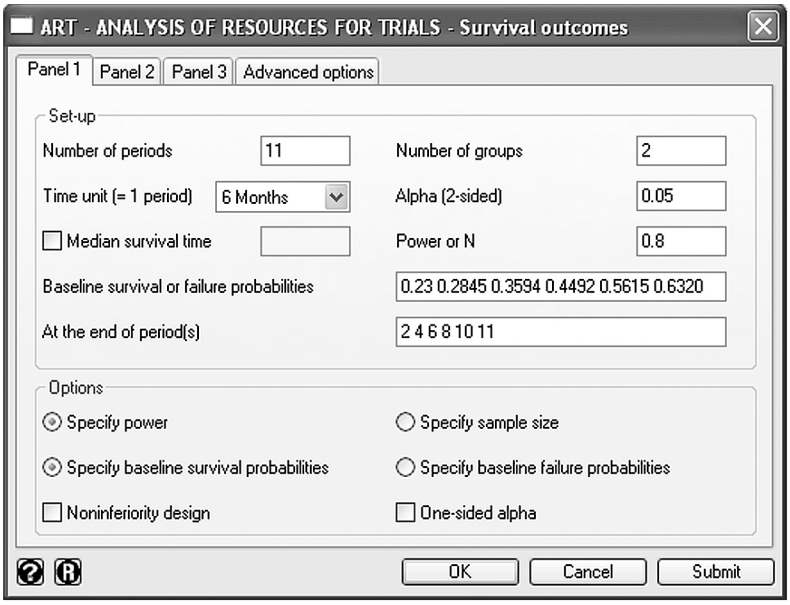

Figure 1: A completed Panel 1 screen for survival outcomes

Figure 1 illustrates the new dialog window for **Survival outcomes**. The Panel 1 tab requires the input of the basic trial set-up. The main change from the old dialog is the input of the survival/failure probabilities. These can now be input by either specifying median survival in a particular period or by filling in the cumulative probabilities at the end of periods as illustrated in figure 1. Furthermore, the actual time units of periods, such as years, may be specified. The choice of these does not have any impact on the

sample size calculations themselves but is displayed in the final output to remind the user of the time scale assumed.

2.2 Survival outcomes — Panel 2 tab

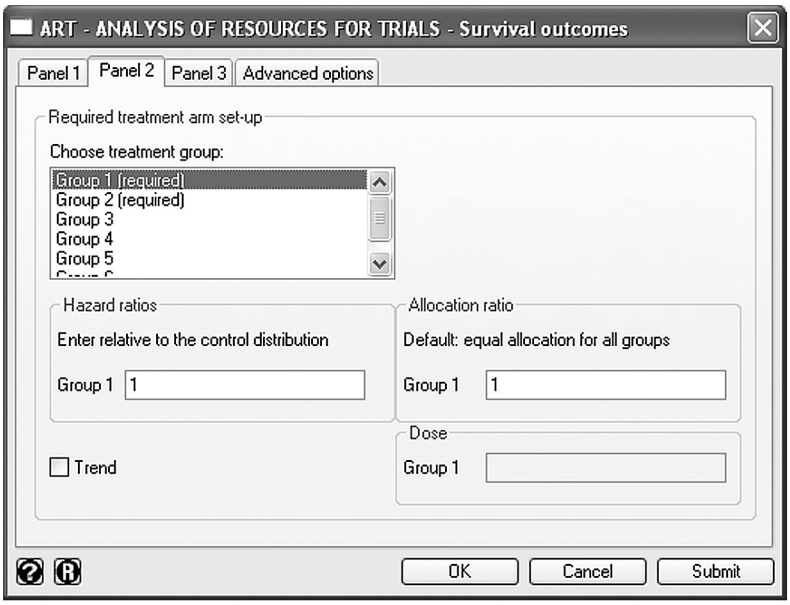

Figure 2: Panel 2 screen completed for a two arm trial

Hazard ratios for each treatment group relative to group 1, as well as allocation ratios, may be entered on the Panel 2 tab, as illustrated in figure 2. Only one value per treatment group needs to be entered for the hazard ratio if these are assumed constant over time. In the case of nonproportional hazards, one value may be entered for each period of the trial. If for a given group fewer hazard ratios are entered than the number of periods, the remaining hazard ratios are taken to have the same value as the last specified hazard ratio. In addition, if no hazard ratio is specified for a particular group, its value in a given period is taken to be the geometric mean of the hazard ratios specified for the same period across all the groups for which a value has been entered. When a test for trend is chosen, the dose may be entered for each treatment group.

2.3 Survival outcomes — Panel 3 tab

The Panel 3 tab, which is illustrated in figure 3, requires the input of patient recruitment options and the selection of the analysis method from the dropdown list. The input methods are similar to those of the original dialog.

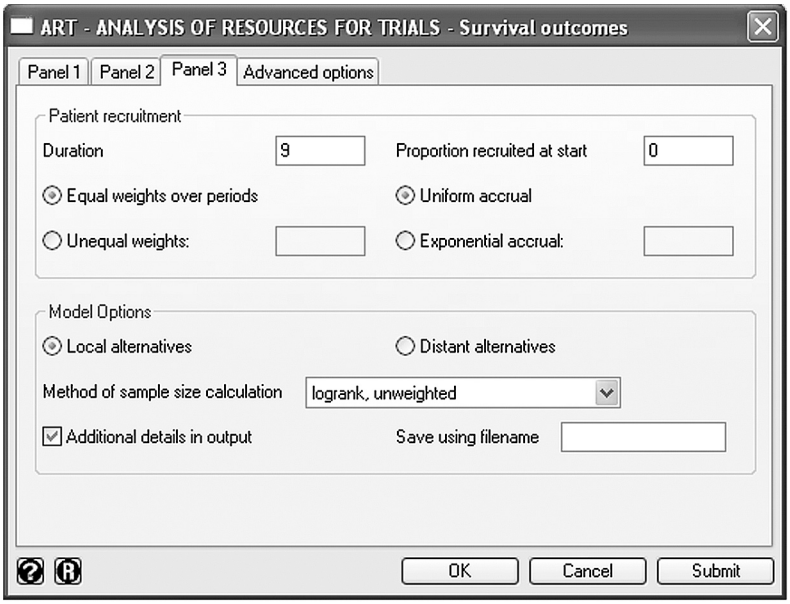

Figure 3: A completed Panel 3 screen illustrating input of recruitment options

The default method of computation is the unweighted logrank test under local alternatives. This implies that sample sizes are derived under the assumption that hazard ratios between treatment groups are not far from 1. However, simulations have shown that the improvements in terms of accuracy gained by computing sample size under distant alternatives are minimal. The user may save the probabilities and hazard ratios used in the calculations to a new file by filling in the **Save using filename** box.

2.4 Survival outcomes — Advanced options tab

The last part of the dialog window for **ART** shown in figure 4 allows the input of loss to follow-up and crossover for each of the treatment groups in the trial, as specified in the Panel 1 tab, in a similar manner to the input of survival probabilities and hazard ratios in figures 1 and 2.

The user may choose to `Specify target group on crossover` or to `Specify hazard ratios postwithdrawal`. The first option assumes that patients withdrawing from treatment of a particular group will receive the treatment regimen of the target group and hence take on that hazard after crossing over. If the second option is chosen, a postwithdrawal hazard ratio function relative to the hazard of the control arm failure time distribution needs to be entered for each arm that is subject to crossover. Similar to the hazard ratios between groups entered in the Panel 2 tab (see figure 2), as many values as there are periods may be entered.

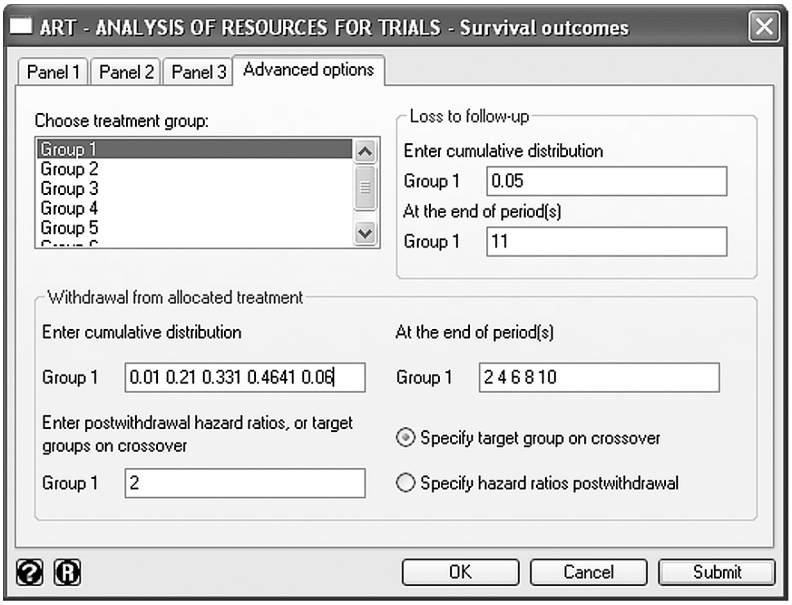

Figure 4: Advanced options for survival outcomes

2.5 Output

The output illustrated below corresponds to the inputs illustrated in figures 1–4. The main improvement from the previous version concerns the level of detail available in the output in terms of the parameters used for the sample size calculation.

In this trial, we chose to compare two treatment groups with a hazard ratio of 0.7 in favor of the experimental treatment group. The total running time of the trial was taken to be 5.5 years with 4.5 years of accrual. Loss to follow-up and crossover were specified as illustrated in figure 4. Further information on these parameters was obtained by choosing the detailed output option on the Panel 3 tab. Sample size was calculated for a power of 80% and a 5% two-sided significance level.

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ART - ANALYSIS OF RESOURCES FOR TRIALS (version 1.0.4, 13 January 2005)

A sample size program by Abdel Babiker, Patrick Royston & Friederike Barthel,
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Type of trial                          Superiority - time-to-event outcome
Statistical test assumed               Unweighted logrank test (local)
Number of groups                       2
Allocation ratio                       Equal group sizes

Total number of periods                11
Length of each period                  6 months
Cum. event probs per period (group 1)  0.123 0.230 0.259 0.287 0.324 0.359
                                        0.406 0.449 0.509 0.561 0.632
Cum. event probs per period (group 2)  0.087 0.167 0.190 0.211 0.240 0.268
                                        0.306 0.341 0.392 0.438 0.503
Number of recruitment periods          9
Number of follow-up periods            2
Method of accrual                      Uniform
Recruitment period-weights             1 1 1 1 1 1 1 1 0 0

Hazard ratios as entered (groups 1,2)  1, 0.7
Hazard ratios per period (group 1)     1.000 1.000 1.000 1.000 1.000 1.000
                                        1.000 1.000 1.000 1.000 1.000
Hazard ratios per period (group 2)     0.700 0.700 0.700 0.700 0.700 0.700
                                        0.700 0.700 0.700 0.700 0.700
Alpha                                  0.050 (two-sided)
Power (designed)                       0.800

Total sample size (calculated)         825
Expected total number of events        287

Values given below apply to each group at the end of the trial

Unadjusted event probs (groups 1,2)     0.632, 0.503
Unadjusted loss to follow-up probs      0.050, 0.050
Unadjusted crossover probabilities     0.068, 0.098

Expected proportions of event           0.392, 0.303
Expected proportions lost to follow-up  0.022, 0.024
Expected proportions of crossover      0.026, 0.072
```

The first part of the output gives an overview of the trial parameters chosen by the user at the time of filling in the dialog menu. A detailed display of the cumulative event probabilities as well as the hazard ratios over each of the periods in the trial allows the user to check that the trial design was entered correctly. Sample size and number of events needed for the trial design are given towards the end. The second part of the output provides further information regarding the expected performance in all treatment groups by the end of trial, in particular with regards to loss to follow-up and crossover proportions in all arms.

3 Other changes to ART

The new design of the dialog menu exploiting features introduced in Stata 8 and more detailed output are the main improvements to **ART**. In addition, the sample size calculations may now be performed for noninferiority designs. This option may be specified on the Panel 1 tab (see figure 1). Furthermore, the program now allows for the choice of a one-sided alpha which may also be specified on the Panel 1 tab. Finally, the help files have been updated. In some instances, the user may want to run several calculations with similar parameters and, in this case, does not require the header given in the output for each of the calculations. To suppress this output, the option `nohead` may be added at the end of the command line.

In summary, users should find the new version easier to use and more informative than the first release. The validity of the calculations has been checked via extensive simulation studies of which some details are provided in Barthel et al. (2005).

4 References

Barthel, F. M.-S., A. Babiker, P. Royston, and M. K. B. Parmar. 2005. Evaluation of sample size and power for multi-arm survival trials allowing for nonproportional hazards, loss to follow-up and crossover. *Statistics in Medicine* submitted.

Royston, P. and A. Babiker. 2002. A menu-driven facility for complex sample size calculation in randomized controlled trials with a survival or a binary outcome. *Stata Journal* 2(2): 151–163.

About the Authors

Friederike Barthel is studying for a PhD at University College London and is based at the UK Medical Research Council Clinical Trials Unit. She currently works on sample size issues, particularly concerning multistage trials, and treatment covariate interaction designs.

Patrick Royston is a medical statistician of 25 years of experience, with a strong interest in biostatistical methodology and in statistical computing and algorithms. At present, he works in clinical trials and related research issues in cancer. Currently, he is focusing on problems of model building and validation with survival data, including prognostic factors studies, on parametric modeling of survival data and on novel trial designs.

Abdel Babiker is head of the HIV division of the MRC Clinical Trials Unit in London, UK.