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The *Stata Journal* is published quarterly by the Stata Press, College Station, Texas, USA.

Address changes should be sent to the *Stata Journal*, StataCorp, 4905 Lakeway Drive, College Station, TX 77845, USA, or emailed to sj@stata.com.

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The Stata Journal (2013)
13, Number 1, pp. 77–91

Trial sequential boundaries for cumulative meta-analyses

Branko Miladinovic
Center for Evidence-Based Medicine and Health Outcomes Research
University of South Florida
Tampa, FL
bmiladin@health.usf.edu

Iztok Hozo
Department of Mathematics
Indiana University Northwest
Gary, IN

Benjamin Djulbegovic
Center for Evidence-Based Medicine and Health Outcomes Research
University of South Florida
Tampa, FL

Abstract. We present a new command, `metacumbounds`, for the estimation of trial sequential monitoring boundaries in cumulative meta-analyses. The approach is based on the Lan–DeMets method for estimating group sequential boundaries in individual randomized controlled trials by using the package `ldbounds` in R statistical software. Through Stata's `metan` command, `metacumbounds` plots the Lan–DeMets bounds, z-values, and p-values obtained from both fixed and random-effects cumulative meta-analyses. The analysis can be performed with count data or on the hazard scale for time-to-event data.

Keywords: st0284, metacumbounds, trial sequential analysis, cumulative meta-analysis, information size, Lan–DeMets bounds, monitoring boundary, cumulative z score, heterogeneity

1 Introduction

Randomized controlled trials (RCTs) are the gold standard for making causal inferences regarding treatment effects. Meta-analyses of RCTs increase both the power and the precision of estimated treatment effects. However, there is a risk that a meta-analysis may report false positive results, that is, report a treatment effect when in reality there is none. This is especially true when the pooled estimates are updated with the publication of a new trial in cumulative meta-analyses. A small RCT may result in chance findings and overestimation. To avoid false conclusions, Pogue and Yusuf (1997, 1998) advocated constructing Lan–DeMets trial sequential monitoring boundaries for cumulative meta-analysis. This is analogous to constructing interim treatment sequential monitoring boundaries in a single RCT, where a trial would be terminated if the cumulative z curve

crossed the discrete sequential boundary and a treatment larger than expected occurred. They calculated the optimal information size based on the assumption that participants originated from a single trial.

More recently, Wetterslev et al. (2008) adjusted the method for heterogeneity and labeled it trial sequential analysis (TSA). Their approach accounted for bias and observed heterogeneity in a retrospective cumulative meta-analysis. We implement TSA in Stata under the command `metacumbounds` and with the `ldbounds` package in open-source R statistical software, which calculates bounds by using the Lan–DeMets α spending function approach. `metacumbounds` is the first widely available package to construct monitoring bounds for cumulative meta-analysis for both count data and information in the form of hazard ratios for time-to-event data. Analyzing time-to-event data on the count scale leads to the loss of valuable information, decreases the power, and should be avoided. Tierney et al. (2007) discuss methods for extracting hazard ratios from published data. The option to construct monitoring bounds for cumulative meta-analysis on the hazard scale has not been available in the domain of public software and, to our knowledge, is presented here for the first time. In section 2, we discuss the methodology behind TSA. In section 3, we describe how to install R and the packages needed to implement `metacumbounds`. In section 4, we present the command `metacumbounds`, and in section 5, the command is illustrated with two examples from published literature.

2 Methods

Group sequential analysis for individual RCTs was introduced by Armitage (1969) and Pocock (1977). Gordon Lan and Demets (1983) made the methods for controlling the type I error when interim analyses are conducted more flexible by introducing the z curve and α spending function, which produce either the O'Brien–Fleming or the Pocock type boundaries. Under this method, the progress of a single RCT is measured over time, and the trial is terminated early if the cumulative z curve crosses a discrete sequential boundary. The boundary depends on the number of decision times and the rate at which the prespecified type I error α is spent, independent of the number of future decision times. The probability of terminating a trial early at time t_i is calculated as the proportion of α that should be spent at t_i minus the α already used in the past. We use five different spending functions (Demets and Gordon Lan 1994):

(i) O'Brien–Fleming spending function

$$\alpha(t) = \begin{cases} 0, & t = 0 \\ 2 - 2\Phi(\frac{Z_{\frac{\alpha}{2}}}{\sqrt{t}}), & 0 \ < \ t \ \leq 1 \end{cases}$$

(ii) Pocock spending function

$$\alpha(t) = \begin{cases} 0, & t = 0 \\ \alpha \ln\{1 + (e-1)t\}, & 0 \ < \ t \ \leq 1 \end{cases}$$

(iii) Alpha × time

$$\alpha(t) = \begin{cases} 0, & t = 0 \\ \alpha t, & 0 < t \leq 1 \end{cases}$$

(iv) Alpha × time$^{1.5}$

$$\alpha(t) = \begin{cases} 0, & t = 0 \\ \alpha t^{1.5}, & 0 < t \leq 1 \end{cases}$$

(v) Alpha × time^2

$$\alpha(t) = \begin{cases} 0, & t = 0 \\ \alpha t^2, & 0 < t \leq 1 \end{cases}$$

Pogue and Yusuf (1997) extended the methodology to cumulative meta-analysis, where its progress is monitored as the relevant information is accrued over time. The total number of observed patients in the cumulative meta-analysis is defined as the accrued information size (AIS). Assuming that the information size (that is, the sample size) needed is at least equal to the sample size required in an individual RCT, given the prespecified type I error α and power $(1-\beta)$, then the required a priori anticipated information size (APIS) based on a prespecified intervention effect is defined as

$$\text{APIS} = \frac{4\nu}{\mu^2}(Z_{\frac{\alpha}{2}} + Z_\beta)^2$$

Here μ is the intervention effect and ν its variance, assuming equal size between the intervention and control groups. For count data and the event rates in the control and experimental groups p_c and p_e, $\mu = p_c - p_e$ and $\nu = p^*(1-p^*)$, where $p^* = (p_c + p_e)/2$. The a priori relative risk reduction (RRR) is defined as $\text{RRR} = 1 - p_e/p_c$.

If we use the results of Lachin and Foulkes (1986), the required APIS for time-to-event data and assumed hazard ratio HR_0, expected censoring rate w (that is, loss to follow-up), and average survival rate across studies S is given by

$$\text{APIS} = \frac{(Z_{\frac{\alpha}{2}} + Z_\beta)^2}{(1-w)(1-S)} \left(\frac{\text{HR}_0 + 1}{\text{HR}_0 - 1}\right)^2$$

Individual RCTs may be biased. It is well accepted that trials with a high risk of bias due to inadequate randomization sequence generation, intention-to-treat analysis, allocation concealment, masking, or reported incomplete outcome data may overestimate intervention effects. RRR and low-bias information size (LBIS) are thus calculated by applying the intervention effects from low-bias trials only. Combining trials as if participants came from one mega-trial may bias the results because of heterogeneity. To account for uncertainty induced by heterogeneity, we must adjust (multiply) information size by $1/(1-I^2)$ to calculate the low-bias heterogeneity-adjusted information size (LBHIS). Note that I^2 is heterogeneity defined as

$$I^2 = \frac{(Q - k + 1)}{Q}$$

and Q is Cochran's homogeneity statistic. Once the information size is calculated, while the new trials are published and meta-analyses are updated, the monitoring bounds can be updated over time as well. Brok et al. (2008) present a set of examples of two-sided TSA for four different cumulative z curves (see figure 1).

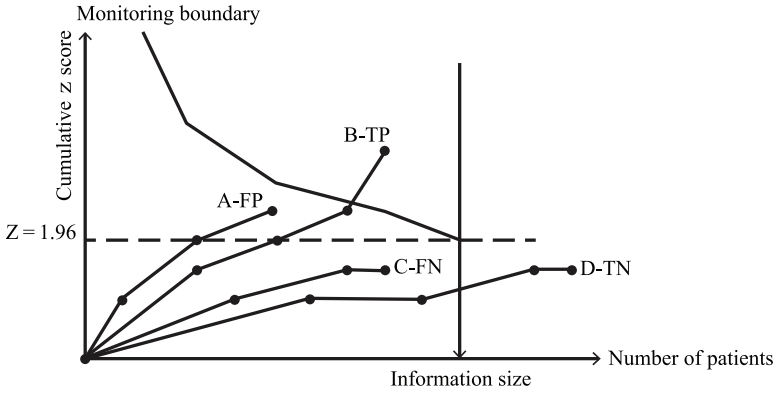


Figure 1. Examples of the upper half of two-sided TSA

(A) Crossing of $Z = 1.96$ provides a significant result but a spurious effect because the z curve does not cross the monitoring boundary. This is a false positive result.

(B) Crossing of the monitoring boundary before reaching the information size provides for firm evidence of effect. This is a true positive result.

(C) z curve not crossing $Z = 1.96$ indicates absence of evidence; that is, the meta-analysis included fewer patients than the required information size. This is a false negative result.

(D) Lack of predefined effect even though the information size is reached. This is a true negative result.

The monitoring boundary typically moves right and down over time. However, it may move right and up if the event rate decreases, intervention effect increases, or heterogeneity increases. In the context of LBIS and LBHIS, crossing of the monitoring bounds before the information size is reached indicates that high-bias risk trials find a larger intervention effect compared with low-bias risk trials.

3 R statistical software

R statistical software is an open-source package that may be downloaded free of charge at http://www.r-project.org. To use `metacumbounds`, after installing R, the user needs to install the R packages `foreign` (to read and write Stata data files) and `ldbounds` (to compute group sequential bounds by using the Lan–Demets method with either

the O'Brien–Fleming or the Pocock spending functions). The package `ldbounds` is based on the Fortran code `ld98` by Reboussin et al. (2000). Statistical packages can be downloaded from the Comprehensive R Archive Network from a multitude of mirror websites within R. This is done by selecting **Packages > Install package(s)...** and then the mirror site closest to the user (figure 2 outlines the steps). The USA(MD) Comprehensive R Archive Network mirror highlighted in figure 2 is at the United States National Cancer Institute (http://watson.nci.nih.gov/cran_mirror/).

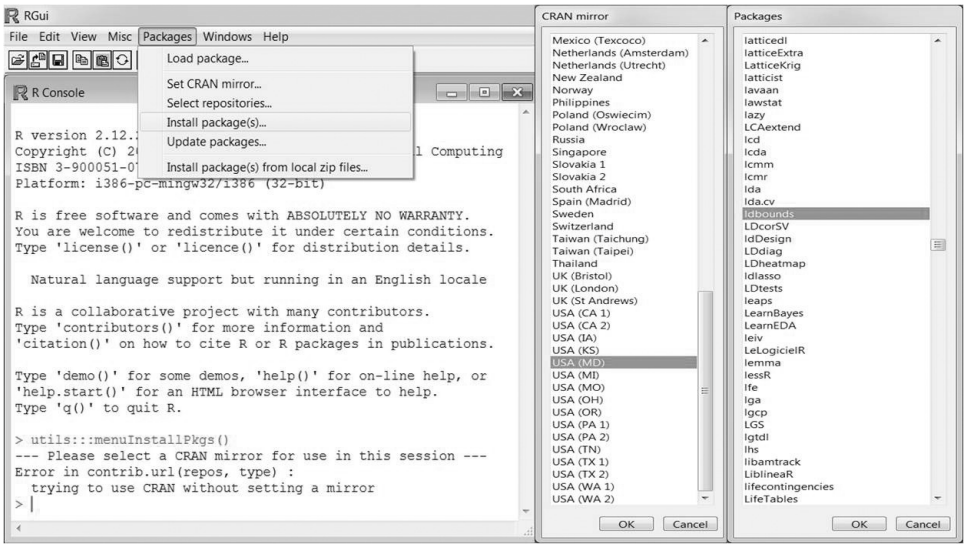


Figure 2. `ldbounds` installation description

Note that R does not have to be running when Stata is executing the `metacumbounds` command. The Stata program `rsource` is used to run R from inside Stata. It works by running the `Rterm.exe` program and may be downloaded from within Stata by typing `ssc install rsource`.

4 The metacumbounds command

4.1 Syntax for metacumbounds

Our command `metacumbounds` assumes that Stata's `metan` command (Harris et al. 2008) has been installed. Because of the complexity of the syntax and to facilitate its implementation, we have included the dialog-box file `metacumbounds.dlg`, which should be placed in the active Stata directory.

`metacumbounds` *varlist* [*if*] [*in*], `data(count|loghr)` `effect(f|r)`
`spending(`*string*`)` `rdir(`*string*`)` `is(ais|apis|lbis|lbhis)` [`id(`*strvar*`)`
`surv(#)` `loss(#)` `lbid(`*varname*`)` `stat(rr|or|rd)` `wkdir(`*string*`)`
`kprsrce(`*string*`)` `alpha(#)` `beta(#)` `graph` `rrr(#)` `listRout` `listRin` `keepR`
graph_options]

where *varlist* contains either count data or log hazard-ratios, their standard errors, and trial sample size.

4.2 Options

`data(count|loghr)` specifies whether the analysis is done for count data or on the log-hazard scale for time-to-event outcomes. Under the `data(count)` option, the user can specify effect size based on risk ratio, odds ratio, or risk difference. For both `data(count)` and `data(loghr)`, the output is on the natural scale. `logrr` or `logor` may equally be used under the `loghr` option in the unlikely event that the count data are unavailable, in which case the survival rate S and loss to follow-up are both equal to 0. `data()` is required.

`effect(f|r)` specifies whether fixed- or random-effects estimates are used in the output and graph. If the fixed-effects model is chosen and heterogeneity I^2 is greater than 30%, then a warning message is displayed. The pooling method used is the inverse variance method (`fixedi` and `randomi` in `metan`). `effect()` is required.

`spending(`*string*`)` specifies the spending function that is calculated by `ldbounds` in R. `spending(1)` computes O'Brien–Fleming type bounds. `spending(2)` computes Pocock type bounds. `spending(3)` computes bounds of type αt. `spending(4)` computes bounds of type $\alpha t^{1.5}$. `spending(5)` computes bounds of type αt^2. `spending()` is required.

`rdir(`*string*`)` lists the path of the directory where the binary files for R can be found. `rdir()` is required.

`is(ais|apis|lbis|lbhis)` specifies the method to be used for calculation size. `is()` is required.

`ais` represents the simple accrued information size—the fraction of the total number of participants in the meta-analysis used up to that point. The assumed a priori RRR (RRR = `rrr()`) is used to determine the power of the test for given alpha and given (actual) sample size.

`apis` represents the a priori information size and means that the total sample size will be calculated so that the trial has the a priori intervention effect (RRR = `rrr()`) on the incidence rate in the control group (which is calculated from the provided trial data). The incidence rate for the experimental group is calculated using this RRR. The RRR is given by the user, as are alpha and beta. These variables are then used to determine the sample size (APIS).

`lbis` represents the low-bias information size and means that the total sample size will be calculated using the incidence rate of only those trials for which the low-bias ID variable is greater than 0. If LBIS = 1, then the trial has low bias. If LBIS = 0, then the trial does not have low bias, it has high bias. The intervention effect (RRR) is now calculated from the incidence rates of both control and experimental groups for only those trials for which the low-bias ID variable is greater than 0. For this RRR and for user-specified alpha and beta, we calculate the required sample size and call it LBIS.

`lbhis` (low-bias heterogeneity-adjusted information size) is the same as `lbis` except adjusted for heterogeneity; that is, LBHIS = LBIS$/(1 - I^2)$, where I^2 is the heterogeneity index of this group of trials for the given statistic.

`id(`*strvar*`)` is a character variable used to label the studies. If the data contain a labeled numeric variable, then the `decode` command can be used to create a character variable.

`surv(#)` for hazard-ratio data specifies the overall average survival rate and is defined on [0, 1).

`loss(#)` for hazard-ratio data specifies the percent of patients lost to follow-up and is defined on [0, 1).

`lbid(`*varname*`)` specifies whether each study is low risk for bias (coded 1) or high risk for bias (coded 0) under `is(lbis)` or `is(lbhis)`.

`stat(rr|or|rd)` for count data specifies the effect size (risk ratio, odds ratio, or risk difference) to be pooled.

`wkdir(`*string*`)` is the directory where all the files should be saved.

`kprsrce(`*string*`)` saves the R source file after the program is completed.

`alpha(#)` specifies the type I error. # must be between 0 and 1.

`beta(#)` specifies the type II error. # must be between 0 and 1.

`graph` requests a graph.

`rrr(#)` specifies the trial a priori intervention effect size (RRR) to calculate APIS. For LBIS and LBHIS, `rrr()` is calculated from low-bias trials only.

`listRout` lists the R output on the Stata screen.

`listRin` lists the R source file on the Stata screen.

`keepR` keeps the R source file.

graph_options are overall graph options. `shwRRR` and `pos()` allow for the addition and position of the RRR, α, and power on the graph; `xtitle(`*string*`)` and `ytitle(`*string*`)` add labels to the x and y axes; `title(`*string*`)` and `subtitle(`*string*`)` add the title and subtitle to the graph. The dialog box makes performing TSA easier.

5 Examples

5.1 Example 1: Effects of artery catheter tip position in the newborn

Wetterslev et al. (2008) performed TSA with data from a systematic review by Barrington (2000). One of the review's aims was to determine whether the position (high versus low) of the tip of an umbilical arterial catheter led to clinical vascular compromise. Out of five total trials, only one was found to have adequate allocation concealment and was considered low bias (table 1). The author reported that high-placed catheters were found to produce a significantly lower incidence of clinical vascular complications with RRR = 47% (95% confidence interval (CI); [37%–56%]).

Table 1. High versus low catheter position for clinical vascular compromise

Study	High (n/N)	Low (n/N)	Low bias
Harris (1978)	3/18	12/18	no
Mokrohisky (1978)	9/33	26/40	no
Stork (1984)	12/85	25/97	no
Kempley (1992)	34/162	66/146	no
UACTSG (1992)	77/481	130/489	yes

For LBIS and LBHIS to be calculated, the low-bias ID variable needs to be specified. In their analysis, Wetterslev et al. (2008) assumed RRR = 15% based on clinical significance. Figure 3 provides a screenshot of the dialog box used to perform the TSA analysis, which confirms the results from the systematic review in figure 4(a)–(c). The figure also displays the actual power achieved given the information size. Trial sequential monitoring boundary (TSMB) for AIS and APIS detected three potentially spurious p-values; TSMB for LBIS and LBHIS detected two potentially spurious levels.

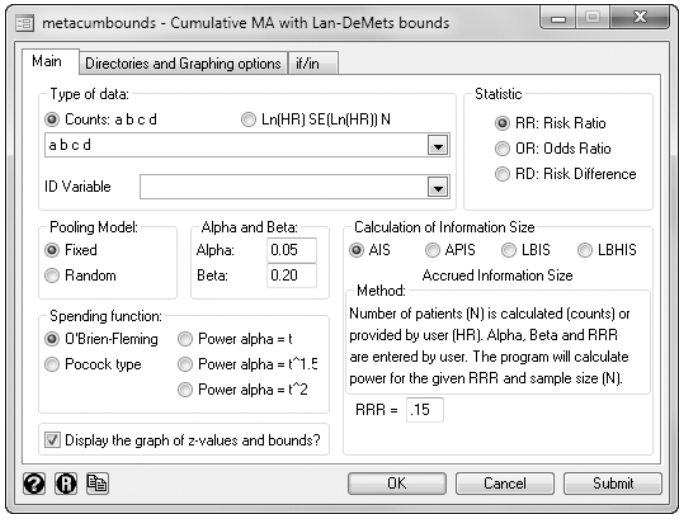
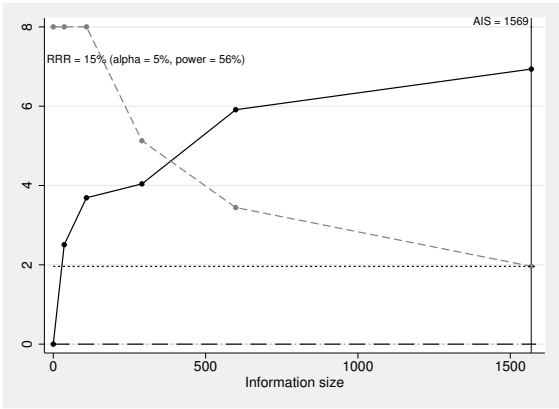
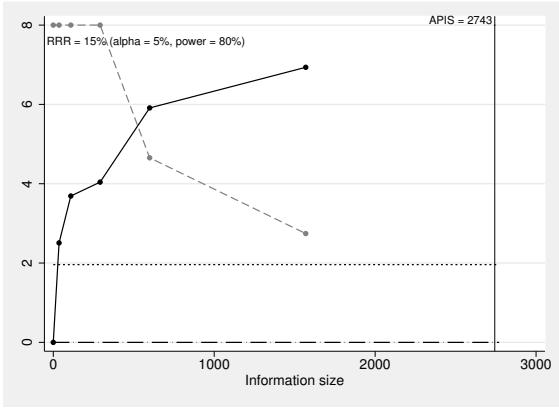


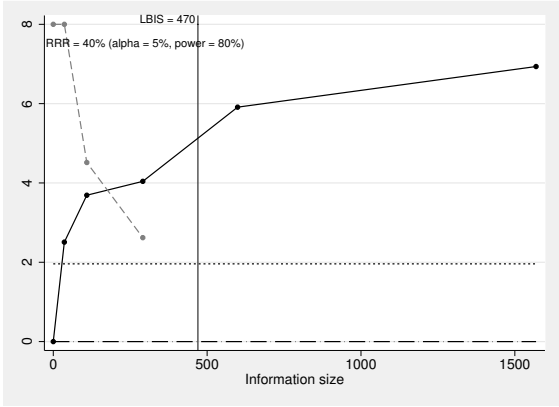
Figure 3. Dialog box used to create figure 4



(a) Results showing three potentially spurious p-values for AIS of 1,569 patients.



(b) Results showing three potentially spurious p-values for APIS of 2,743 patients.



(c) Results showing three potentially spurious p-values for LBIS of 470 patients. Note that because LBIS equals LBHIS, results for the latter are the same.

Figure 4. TSA on the effects of umbilical artery catheter position in newborns

```
. use example1
. metacumbounds a b c d, data(count) effect(f) id(study) alpha(0.05) beta(0.20)
> is(AIS) stat(rr) graph spending(1) rrr(.15) kprsrce(StataRsource.R)
> rdir(C:\Program Files\R\R-2.12.2\bin\i386) shwRRR pos(10)
> xtitle(Information size)
Isquare =  0.00%
Cumulative fixed-effects meta-analysis of 5 studies  with Lan-DeMets bounds
---------------------------------------------------------------

                Cumulative
Trial          estimate(rr)     z    P val     partN      UB
Harris_1978           0.250   2.508  0.012        36   8.000
Mokrohisky_1978       0.371   3.691  0.000       109   8.000
Stork_1984            0.436   4.041  0.000       291   5.128
Kempley_1992          0.452   5.911  0.000       599   3.445
UACTSG_1992           0.525   6.936  0.000      1569   1.962
```

5.2 Example 2: Neoadjuvant chemotherapy for invasive bladder cancer

Advanced Bladder Cancer Meta-analysis Collaboration (2011) conducted individual patient data meta-analysis to study whether neoadjuvant chemotherapy improves survival in patients with invasive bladder cancer. They concluded that the hazard ratio for all trials, including single-agent cisplatin, tended to favor neoadjuvant chemotherapy with RRR = 11% (95% CI; [2%–19%]) (the results were reported on the hazard scale as HR = 0.89; 95% CI; [81%–98%]). All 10 trials were found to have adequate allocation concealment and were considered low bias (see table 2). Because $I^2 = 0\%$, fixed- and random-effects meta-analyses produce identical TSMBs, and LBIS equals LBHIS.

Table 2. Neoadjuvant chemotherapy for invasive bladder cancer

Study	Neoadjuvant (n/N)	Local (n/N)	HR [95% CI]	Low bias
Raghavan (1991)	34/41	37/55	1.43 [0.88, 2.31]	yes
Wallace (1991)	59/83	50/76	1.11 [0.76, 1.61]	yes
Martinez (1995)	43/62	38/59	1.02 [0.66, 1.57]	yes
Malmstrom (1996)	68/151	84/160	0.77 [0.56, 1.06]	yes
Cortesi (unpub)	43/82	41/71	0.91 [0.6, 1.40]	yes
Bassi (1999)	53/102	60/104	0.93 [0.64, 1.35]	yes
MRC/EORTC (1999)	275/491	301/485	0.85 [0.72, 1]	yes
Sherif (2002)	79/158	90/159	0.86 [0.64, 1.16]	yes
Sengelov (2002)	70/78	60/75	1.06 [0.75, 1.50]	yes
Grossman (2003)	98/158	108/159	0.77 [0.58, 1.01]	yes

Figure 5 provides a screenshot of the dialog box used to perform the analysis. Using the estimated average survival rate of $S = 40\%$ and assuming $w = 0\%$ loss to follow-up, we found that TSA confirms the results from the systematic review for AIS [figure 6(a)–

(c)]. TSMB crosses the z curve for AIS of 2,809 patients. The TSA confirms the results for the systematic review of APIS = 1,990 under assumed RRR = 15%, $\alpha = 0.05$, and power$(1 - \beta) = 0.8$. However, the results of the systematic review do not hold under estimated LBIS = LBHIS = 4,418. There was one spurious p-value (Grossman trial) under LBIS and LBHIS estimates.

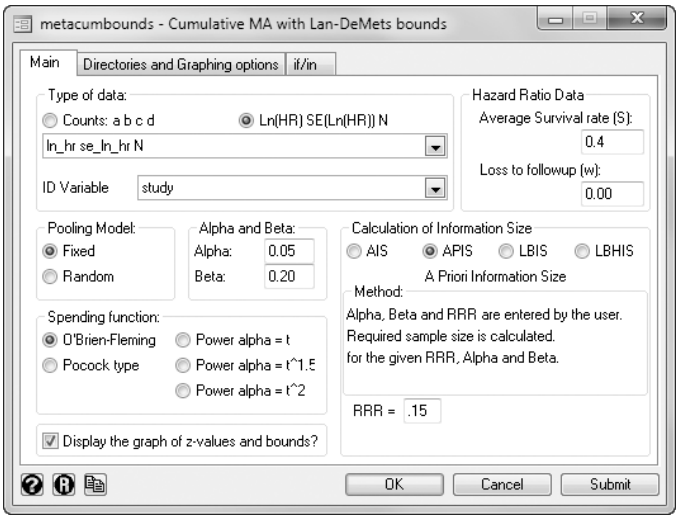
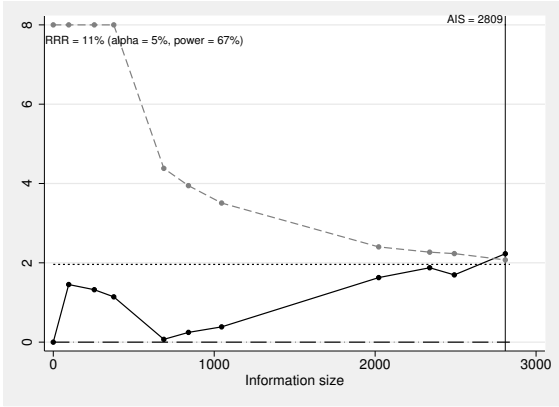
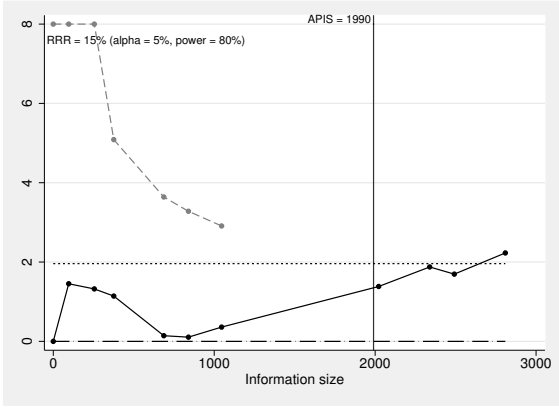


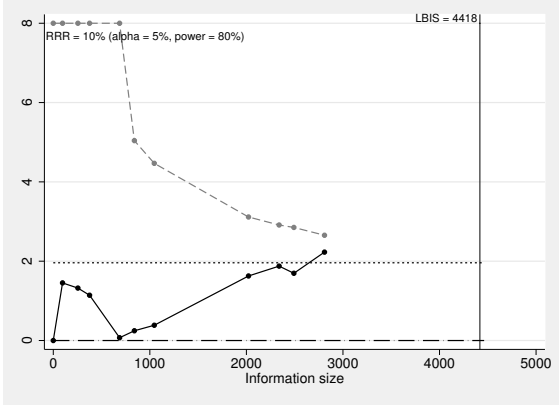
Figure 5. Dialog box used to create figure 6



(a) Results showing that TSMB crosses z curve for AIS of 2,809 patients.



(b) Results for APIS of 1,990 patients.



(c) Results for LBIS of 4,418 patients. Note that because LBIS equals LBHIS, results for the latter are the same.

Figure 6. TSA on the effects of neoadjuvant chemotherapy for invasive bladder cancer

```
. use example2
. metacumbounds ln_hr se_ln_hr N, data(loghr) effect(r) id(study) surv(0.40)
> loss(0.00) alpha(0.05) beta(0.20) is(APIS) graph spending(1) rrr(.15)
> kprsrce(StataRsource.R) rdir(C:\Program Files\R\R-2.12.2\bin\i386\)
> shwRRR pos(10) xtitle(Information size)
Isquare =  0.00%
Cumulative random-effects meta-analysis of 10 studies  with Lan-DeMets bounds
------------------------------------------------------------------
```

Trial	Cumulative estimate()	z	P val	partN	UB
Raghavan_1991	1.430	1.453	0.146	96	8.000
Wallace_1991	1.221	1.322	0.186	255	8.000
Martinez_1995	1.153	1.142	0.253	376	5.087
Malmstrom_1996	1.019	0.143	0.887	687	3.640
Cortesi_1997	0.989	0.106	0.915	840	3.281
Bassi_1999	0.971	0.360	0.719	1046	2.910
MRC_EORTC_1999	0.917	1.384	0.166	2022	.
Sherif_2002	0.903	1.876	0.061	2339	.
Sengelov_2002	0.915	1.696	0.090	2492	.
Grossman_2003b	0.897	2.229	0.026	2809	.

6 Discussion

We presented a command, `metacumbounds`, for the implementation of TSA in Stata, which we recommend to minimize the risk of random error when performing cumulative meta-analyses. This way, the risk of finding a difference in treatment effects where no difference exists is minimized. The command uses a package for constructing Lan–Demets bounds in an open-source R statistical software.

`metacumbounds` can be implemented by using either fixed- or random-effects meta-analysis. It can incorporate heterogeneity in the calculation of boundaries. The method can be applied with count data or on the hazard scale for time-to-event data; TSA for both has not been available in the domain of public software. In addition to the subgroup analysis, funnel plots and meta-regression, the plot of the cumulative z curve, and monitoring boundaries, APIS and LBIS (or LBHIS in the presence of heterogeneity) should be a standard supplement to any meta-analysis.

7 Acknowledgment

The `rsource` program we used to run the R statistical software through Stata was developed by Roger Newson of the Imperial College London.

8 References

Advanced Bladder Cancer Meta-analysis Collaboration. 2011. Neoadjuvant cisplatin for advanced bladder cancer. *Cochrane Database of Systematic Reviews* 6: CD001426.

Armitage, P. 1969. Sequential analysis in therapeutic trials. *Annual Review of Medicine* 20: 425–430.

Barrington, K. J. 2000. Umbilical artery catheters in the newborn: Effects of position of the catheter tip. *Cochrane Database of Systematic Reviews* 2: CD000505.

Brok, J., K. Thorlund, C. Gluud, and J. Wetterslev. 2008. Trial sequential analysis reveals insufficient information size and potentially false positive results in many meta-analyses. *Journal of Clinical Epidemiology* 61: 763–769.

Demets, D. L., and K. K. Gordon Lan. 1994. Interim analysis: The alpha spending function approach. *Statistics in Medicine* 13: 1341–1352.

Gordon Lan, K. K., and D. L. Demets. 1983. Discrete sequential boundaries for clinical trials. *Biometrika* 70: 659–663.

Harris, R. J., M. J. Bradburn, J. J. Deeks, R. M. Harbord, D. G. Altman, and J. A. C. Sterne. 2008. metan: Fixed- and random-effects meta-analysis. *Stata Journal* 8: 3–28.

Lachin, J. M., and M. A. Foulkes. 1986. Evaluation of sample size and power for analyses of survival with allowance for nonuniform patient entry, losses to follow-up, noncompliance, and stratification. *Biometrics* 42: 507–519.

Pocock, S. J. 1977. Group sequential methods in the design and analysis of clinical trials. *Biometrika* 64: 191–199.

Pogue, J. M., and S. Yusuf. 1997. Cumulating evidence from randomized trials: Utilizing sequential monitoring boundaries for cumulative meta-analysis. *Controlled Clinical Trials* 18: 580–593.

———. 1998. Overcoming the limitations of current meta-analysis of randomised controlled trials. *Lancet* 351: 47–52.

Reboussin, D. M., D. L. DeMets, K. Kim, and K. K. G. Lan. 2000. Computations for group sequential boundaries using the Lan–DeMets spending function method. *Controlled Clinical Trials* 21: 190–207.

Tierney, J. F., L. A. Stewart, D. Ghersi, S. Burdett, and M. R. Sydes. 2007. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 8: 16.

Wetterslev, J., K. Thorlund, J. Brok, and C. Gluud. 2008. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. *Journal of Clinical Epidemiology* 61: 64–75.

About the authors

Branko Miladinovic is an assistant professor of biostatistics in the Center for Evidence-Based Medicine at the University of South Florida. His recent research has focused on meta-analysis and extreme value distributions in both frequentist and Bayesian settings.

Iztok Hozo is a professor of mathematics and actuarial sciences at Indiana University Northwest. His research interests include medical decision making, acceptable regret theory, and meta-analysis.

Benjamin Djulbegovic is a distinguished professor of medicine and oncology at the University of South Florida and the H. Lee Moffitt Cancer Center and Research Institute. He is also the Director of the Center for Evidence-Based Medicine and the Associate Dean for Clinical Research at the University of South Florida. His major academic interests lie in the areas of evidence-based medicine, decision analysis, clinical reasoning, systematic reviews and meta-analysis and comparative effectiveness research, the ethics of clinical trials, practice guidelines, outcomes research, the impact of clinical trials, and the role of uncertainty in medicine.