RACE 616 Advance Statistical Analysis in Medical Research

Survival Analysis

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Section for Clinical Epidemiology & Biostatistics, Faculty of Medicine Ramathibodi Hospital

Part II

Sample size estimation for time to event outcome

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Sample size estimation

Test for difference

H_0: $Median_1 = Median_2 = Median_3 = \ldots Median_k$

H_a: $Median_1 \neq Median_2 \neq Median_3 \neq \ldots Median_k$

Or

H_0: $HR1_1 = HR_2 = HR_3 = \ldots HR_{k=} 1$

H_a: $HR1_1 \neq HR1_2 \neq HR_3 \neq \ldots HR_k \neq 1$

Requirement of basic information

- Median survival/disease-free time for
  - Control (reference) group
  - Treatment group/s that investigator needs to detect OR
- Hazard ratio/s that investigator needs to detect
- Possible loss to follow-up rate in that setting
- Setting alpha, beta, ratio

Software

- PS can perform only 2 groups
- STATA can perform 2-6 groups
  - artsurv (via artmenu)

- Ex1. As for AIDS defining illness, suppose that investigators wish to conduct the study with 5-year period. The recruitment period is ~ 1 year and the follow-up time ranges from 4 - 5 years. The primary outcome of interest is time to death. The research question is whether median survival time between PCP and Tbc groups are different. Previous study provided information that median survival time of PCP was ~ 24 months. How large a sample size should investigator expect to enrol to detect difference at least 6 months.

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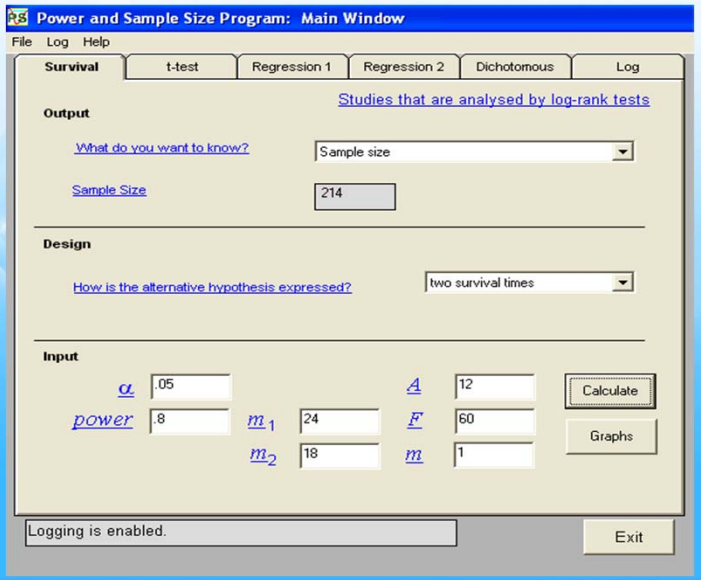
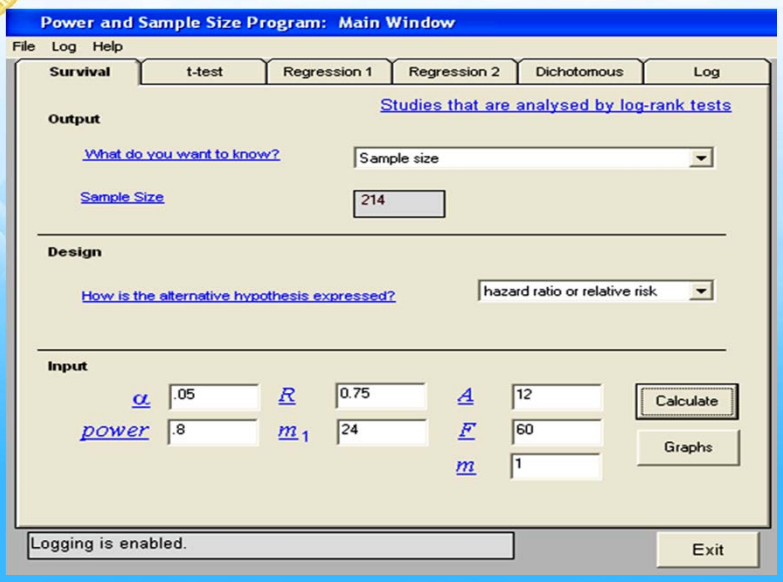
Set

- alpha = 0.05
- Beta = 0.8
- Ratio 1:1
- Median
  - Tbc ~ 18
  - HR = Median(Tb)/ Median(PCP) = 0.75
- Numbers of period = 5
- Time unit = 1 year
- Patient recruitment period (Accrual time) =1 year

Median survival time



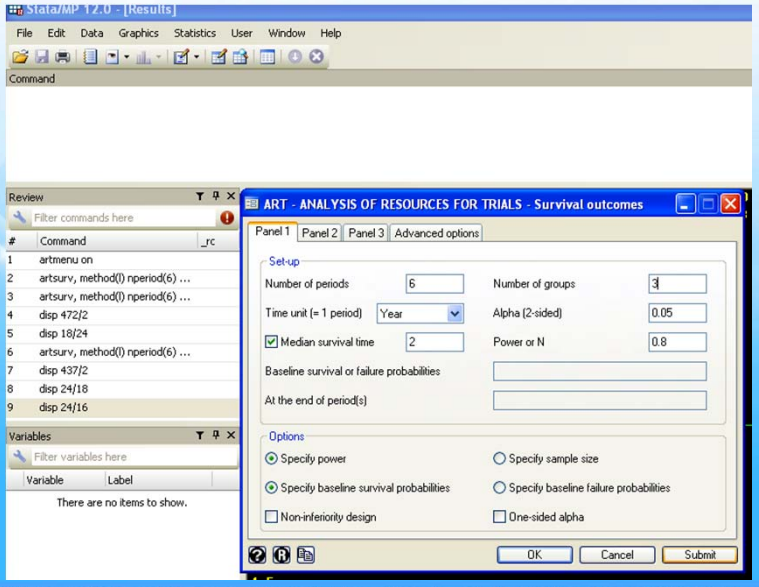
Base on HR



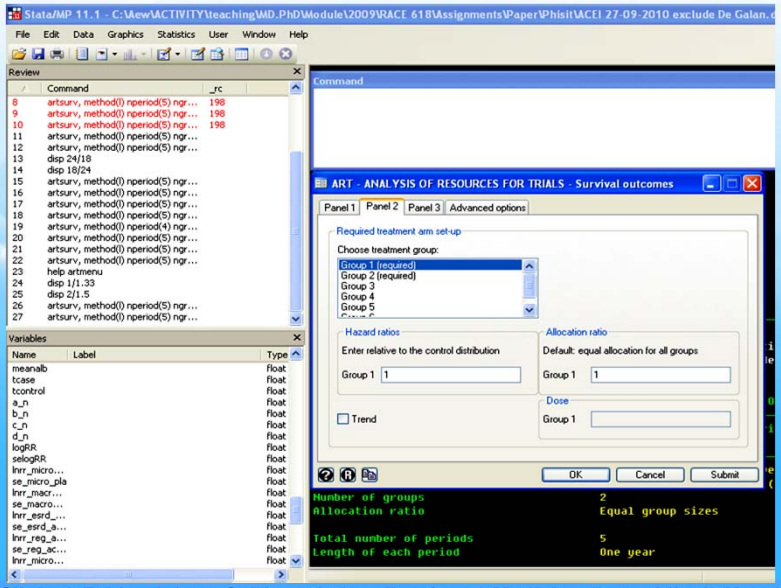
More than 2 groups

- Additional one more group is interested, i.e., Cryptococal meningitis group. Median survival time of this group is at least ~ 8 months shorter than PCP group. The incidence of Crypto is ~ 2 times higher than the PCP.
- Artsurv in STATA

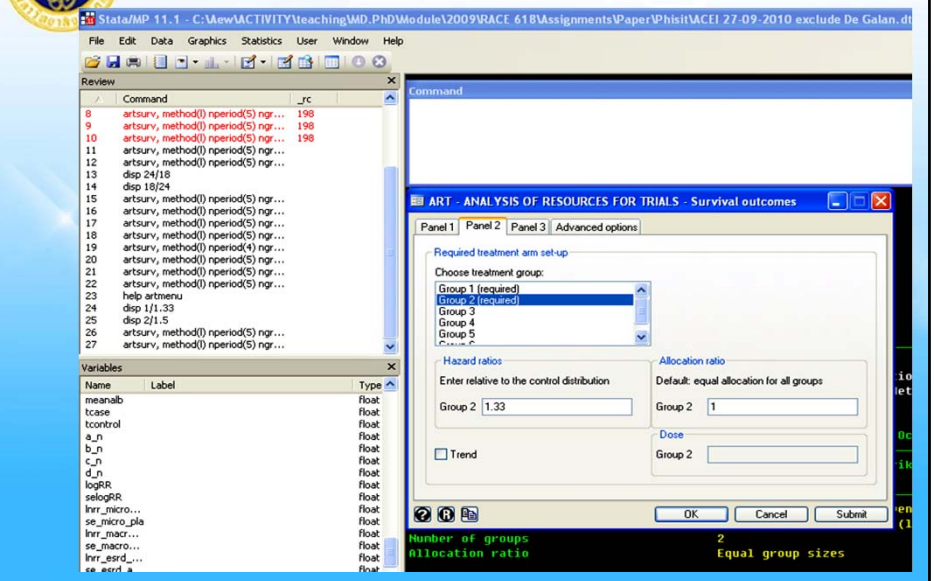
artmenu on Panel 1



Panel 2 group 1



Panel 2 group 2



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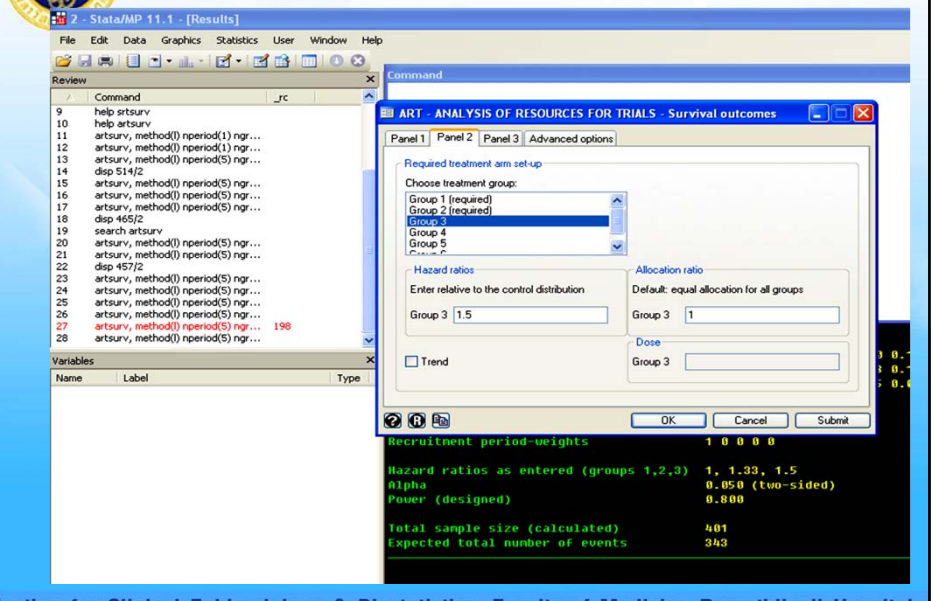
Panel 2 group 3



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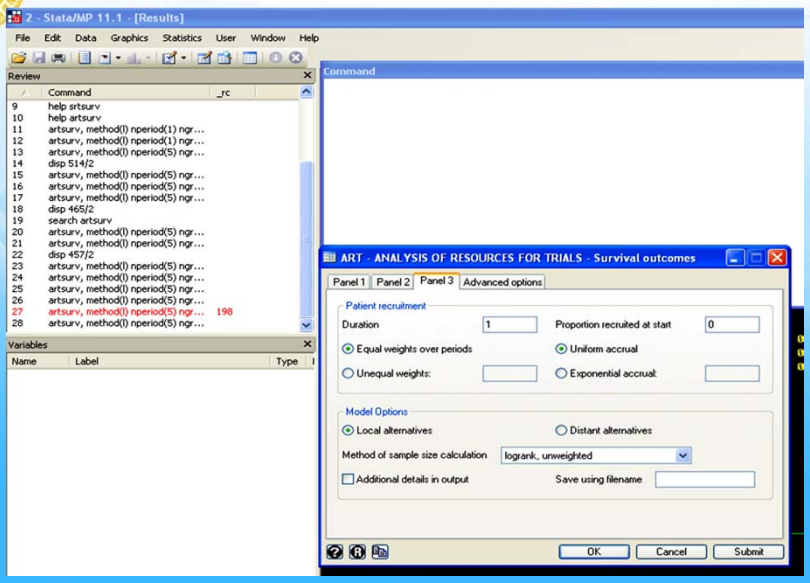
Panel 3



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 ART - ANALYSIS OF RESOURCES FOR TRIALS       (version 1.0.7, 19 October 2009)
-------------------------------------------------------------------------------
A sample size program by Abdel Babiker, Patrick Royston & Friederike Barthel,
MRC Clinical Trials Unit, London NW1 2DA, UK.
-------------------------------------------------------------------------------
Type of trial                           Superiority - time-to-event outcome
Statistical test assumed                Unweighted logrank test (local)
Number of groups                        3
Allocation ratio                        Equal group sizes
Global test

Total number of periods                 6
Length of each period                   One year

Baseline median survival time           2 years
Survival probs per period (group 1)     0.707 0.500 0.354 0.250 0.177 0.125
Survival probs per period (group 2)     0.631 0.398 0.251 0.158 0.100 0.063
Survival probs per period (group 3)     0.595 0.354 0.210 0.125 0.074 0.044
Number of recruitment periods           1
Number of follow-up periods             5
Method of accrual                       Uniform
Recruitment period-weights              1 0 0 0 0 0

Hazard ratios as entered (groups 1,2,3) 1, 1.33, 1.5
Alpha                                   0.050 (two-sided)
Power (designed)                        0.800

Total sample size (calculated)          377
Expected total number of events         341
-------------------------------------------------------------------------------
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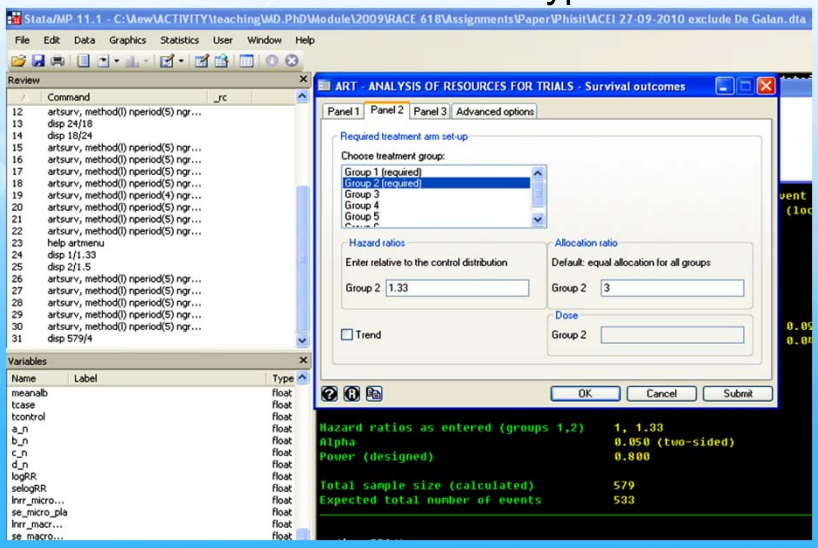
Tbc is ~ 3 times more prevalent than PCP,

ratio PCP:Tbc: Cryp=1:3:1



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Type of trial                           Superiority - time-to-event outcome
Statistical test assumed                Unweighted logrank test (local)
Number of groups                        3
Allocation ratio                        1.00:3.00:1.00
Global test

Total number of periods                 6
Length of each period                   One year

Baseline median survival time           2 years
Survival probs per period (group 1)     0.707 0.500 0.354 0.250 0.177 0.125
Survival probs per period (group 2)     0.631 0.398 0.251 0.158 0.100 0.063
Survival probs per period (group 3)     0.595 0.354 0.210 0.125 0.074 0.044
Number of recruitment periods           1
Number of follow-up periods             5
Method of accrual                       Uniform
Recruitment period-weights              1 0 0 0 0 0

Hazard ratios as entered (groups 1,2,3) 1, 1.33, 1.5
Alpha                                   0.050 (two-sided)
Power (designed)                        0.800

Total sample size (calculated)          608
Expected total number of events         553
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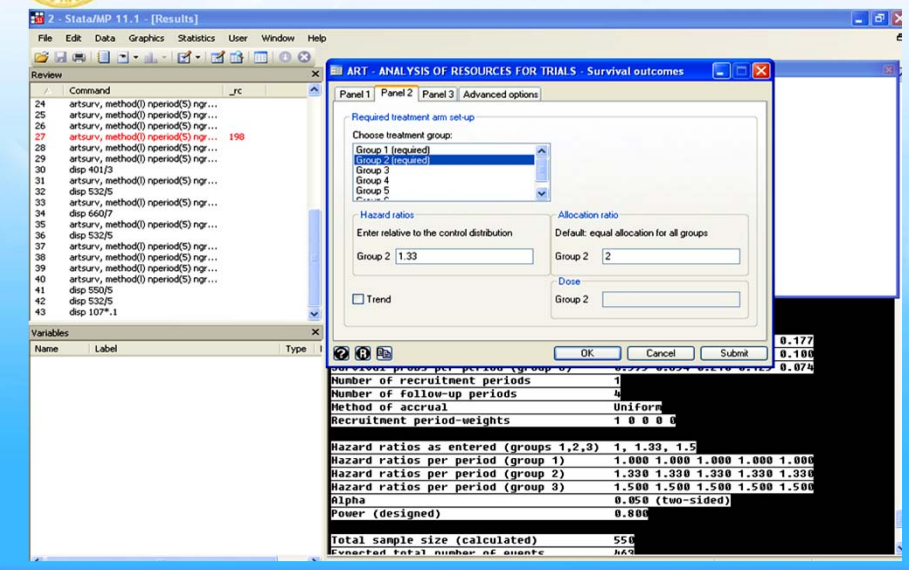
Allocation ratio 1:2:2



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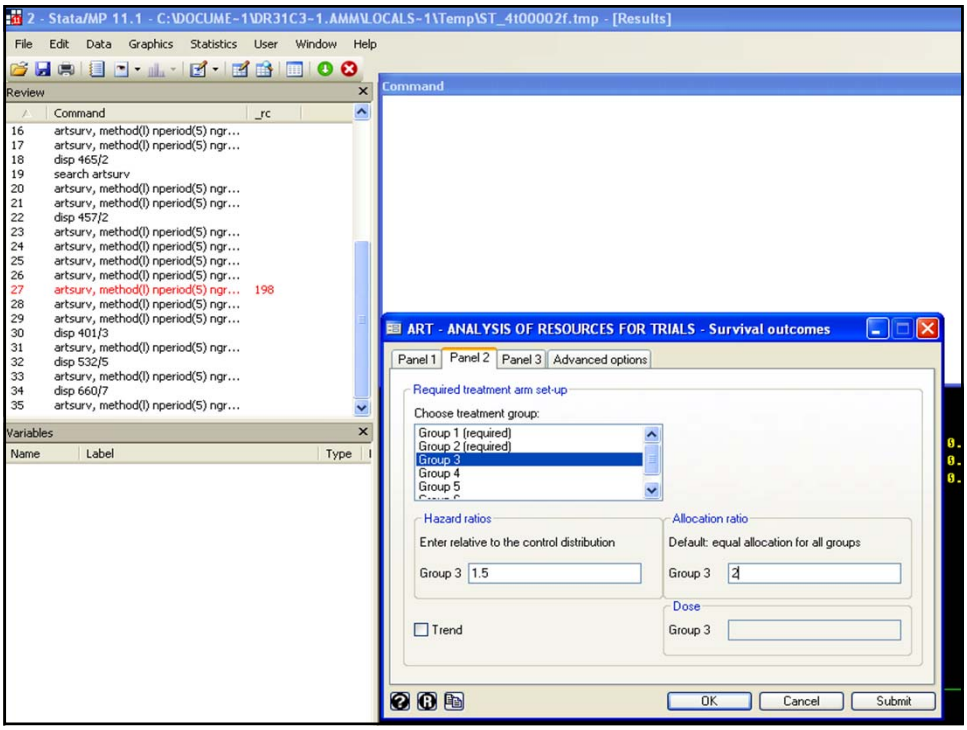

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Type of trial                           Superiority - time-to-event outcome
Statistical test assumed                Unweighted logrank test (local)
Number of groups                        3
Allocation ratio                        1.00:2.00:2.00
Global test

Total number of periods                 6
Length of each period                   One year

Baseline median survival time           2 years
Survival probs per period (group 1)     0.707 0.500 0.354 0.250 0.177 0.125
Survival probs per period (group 2)     0.631 0.398 0.251 0.158 0.100 0.063
Survival probs per period (group 3)     0.595 0.354 0.210 0.125 0.074 0.044
Number of recruitment periods           1
Number of follow-up periods             5
Method of accrual                       Uniform
Recruitment period-weights              1 0 0 0 0 0

Hazard ratios as entered (groups 1,2,3) 1, 1.33, 1.5
Alpha                                   0.050 (two-sided)
Power (designed)                        0.800

Total sample size (calculated)          499
Expected total number of events         457
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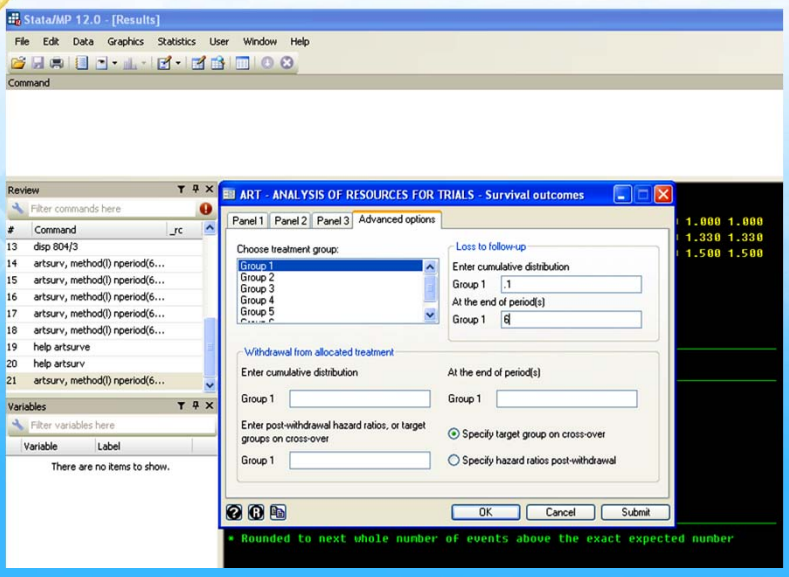
Group 1,2,3: loss to FU



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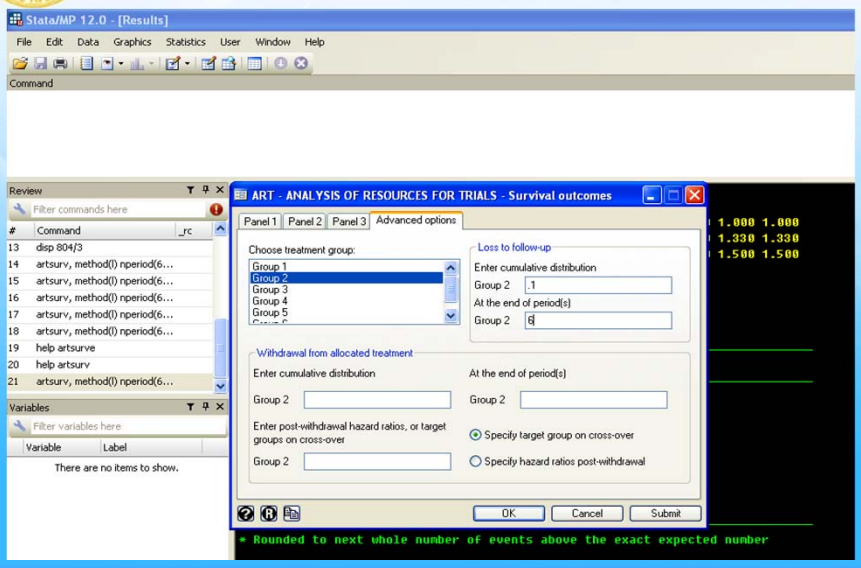
Group 2



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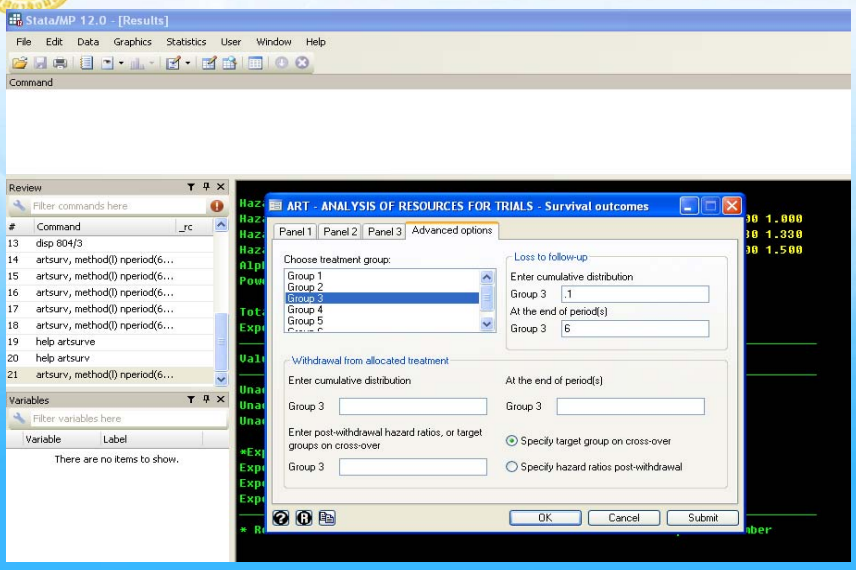
Group 3



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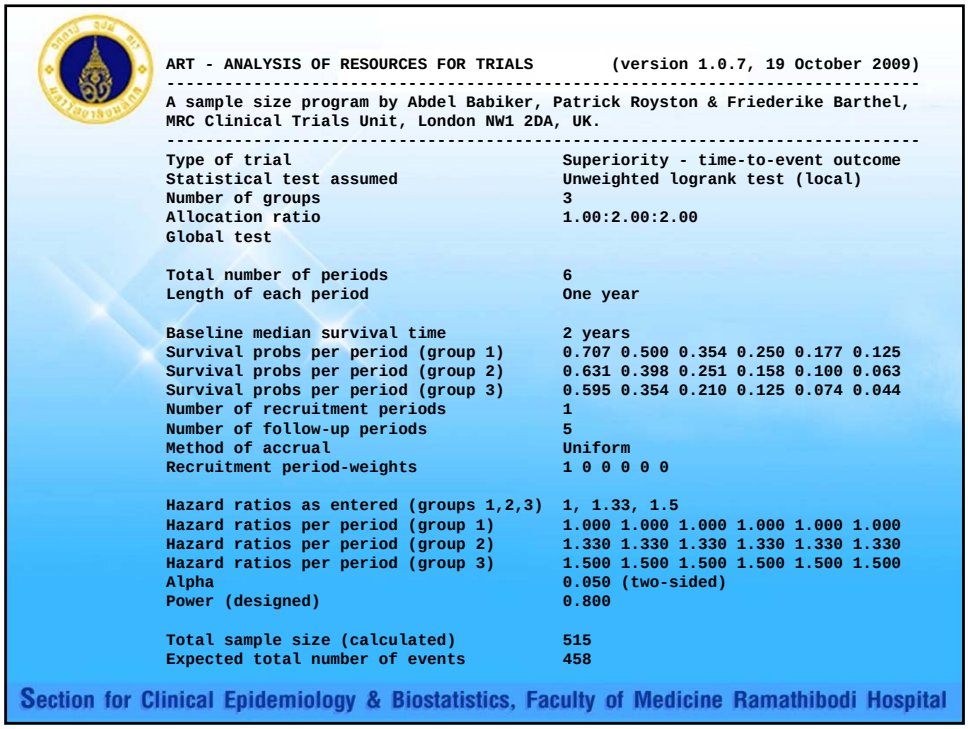

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MRC Clinical Trials Unit, London NW1 2DA, UK.
------------------------------------------------------------------------------
Type of trial                              Superiority - time-to-event outcome
Statistical test assumed                   Unweighted logrank test (local)
Number of groups                           3
Allocation ratio                           1.00:2.00:2.00
Global test

Total number of periods                    6
Length of each period                      One year

Baseline median survival time              2 years
Survival probs per period (group 1)        0.707 0.500 0.354 0.250 0.177 0.125
Survival probs per period (group 2)        0.631 0.398 0.251 0.158 0.100 0.063
Survival probs per period (group 3)        0.595 0.354 0.210 0.125 0.074 0.044
Number of recruitment periods              1
Number of follow-up periods                5
Method of accrual                          Uniform
Recruitment period-weights                 1 0 0 0 0 0

Hazard ratios as entered (groups 1,2,3)    1, 1.33, 1.5
Hazard ratios per period (group 1)         1.000 1.000 1.000 1.000 1.000 1.000
Hazard ratios per period (group 2)         1.330 1.330 1.330 1.330 1.330 1.330
Hazard ratios per period (group 3)         1.500 1.500 1.500 1.500 1.500 1.500
Alpha                                      0.050 (two-sided)
Power (designed)                           0.800

Total sample size (calculated)             515
Expected total number of events            458
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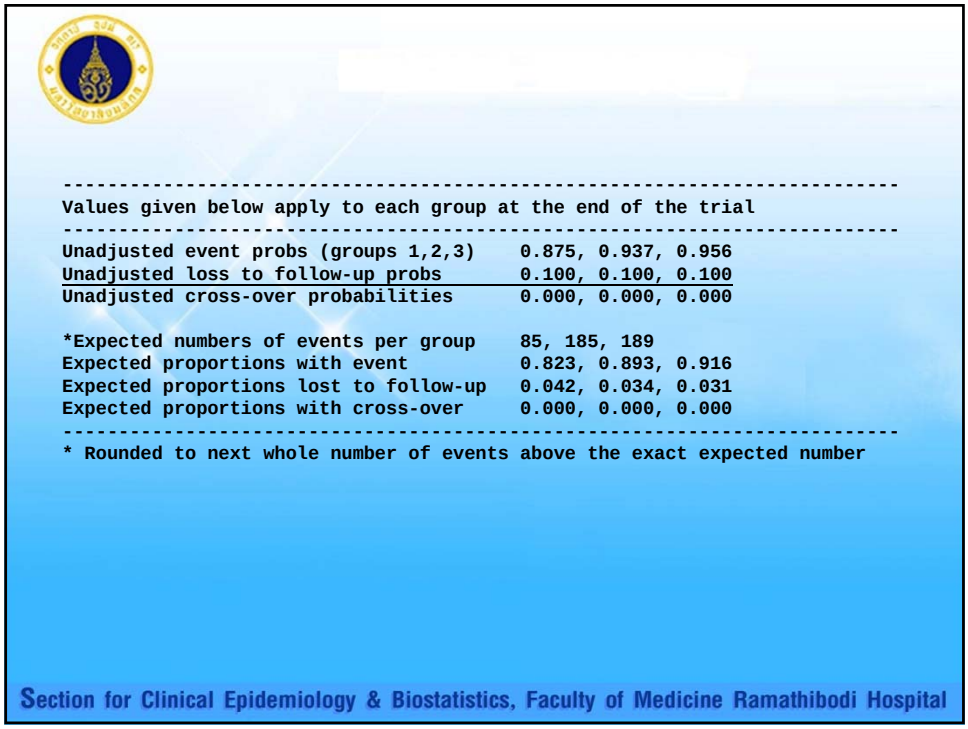

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------------------------------------------------------------------------------
Values given below apply to each group at the end of the trial
------------------------------------------------------------------------------
Unadjusted event probs (groups 1,2,3)     0.875, 0.937, 0.956
Unadjusted loss to follow-up probs        0.100, 0.100, 0.100
Unadjusted cross-over probabilities       0.000, 0.000, 0.000

*Expected numbers of events per group     85, 185, 189
Expected proportions with event           0.823, 0.893, 0.916
Expected proportions lost to follow-up    0.042, 0.034, 0.031
Expected proportions with cross-over      0.000, 0.000, 0.000
------------------------------------------------------------------------------
* Rounded to next whole number of events above the exact expected number
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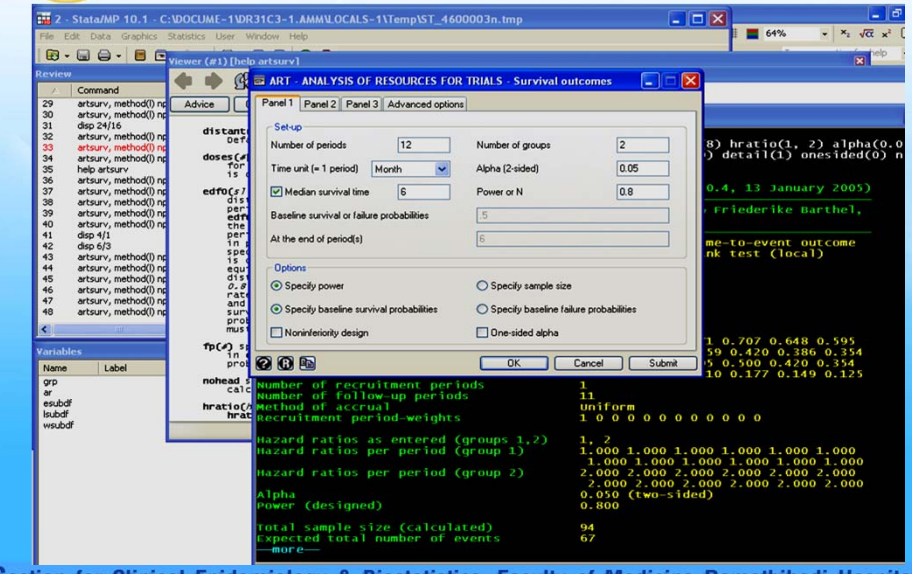
- Exercise 2. Investigators would like to conduct a randomised control trial which aim to assess recovery rates between treatments (i.e., Prednisolone and Acyclovir plus Prednisolone) in Bell's palsy patients. The primary outcome of interest is time since receiving treatment to disease recovery, which is defined as House-Brackman score ≤ 2. Since Acyclovir is more expensive than Prednisolone, investigators thus set a ratio of 2:1 for Prednisolone versus Acyclovir. Previous studies reported that median time to disease recovery was ~ 4-6 months for Prednisolone group. Adding Acyclovir should be able to shorten the median recovery time and it will be clinically significant if the median time to recovery can be only~ 3-4 months. How large is the sample size if the study period is 12 months & recruitment period is 6 months?

- Alpha = 0.05
- Beta = 0.2
- Ratio 2:1
- Median(Pred) = 6 months

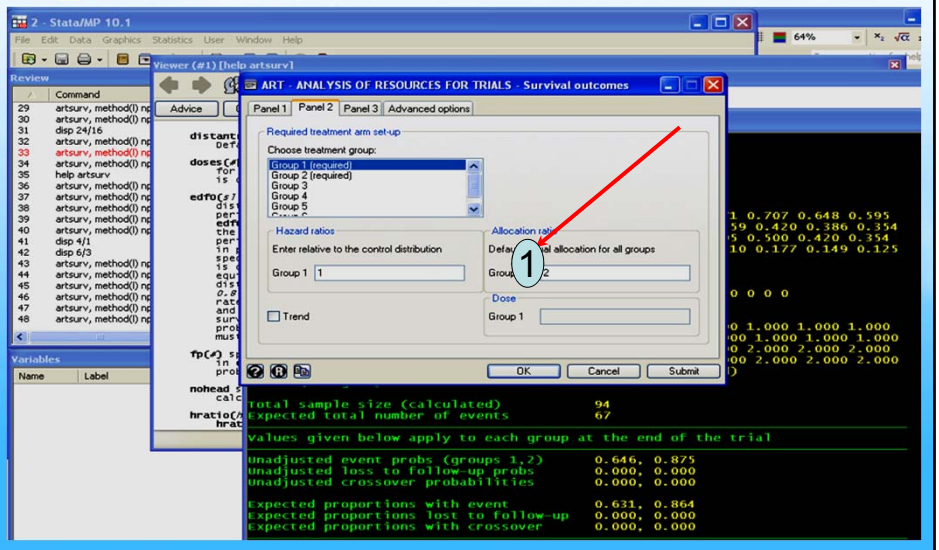
– PS: longer median time will yield larger sample size

- Median(Acy) = 3 months
- HR = 6/3 =2

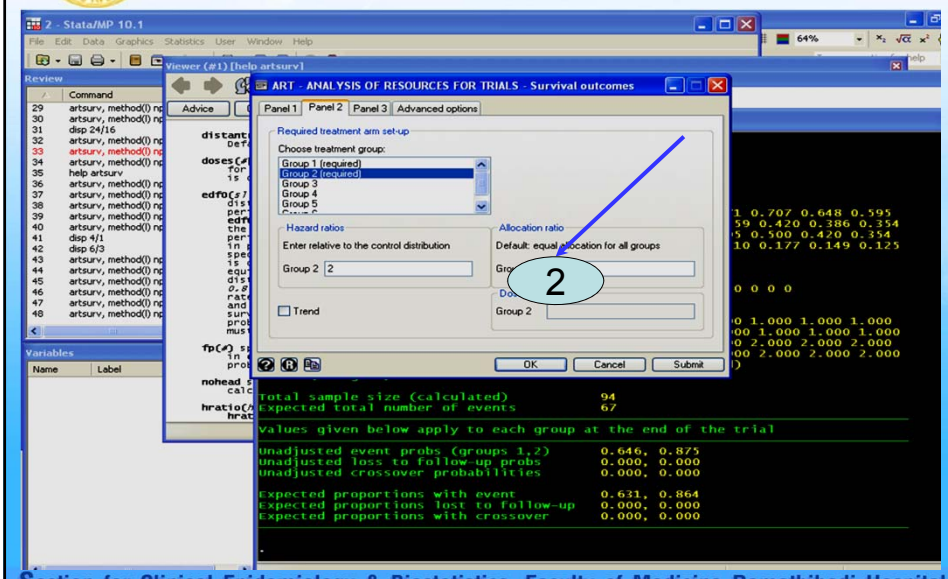
Panel 1



Panel 2 group 1



Panel 2 group 2



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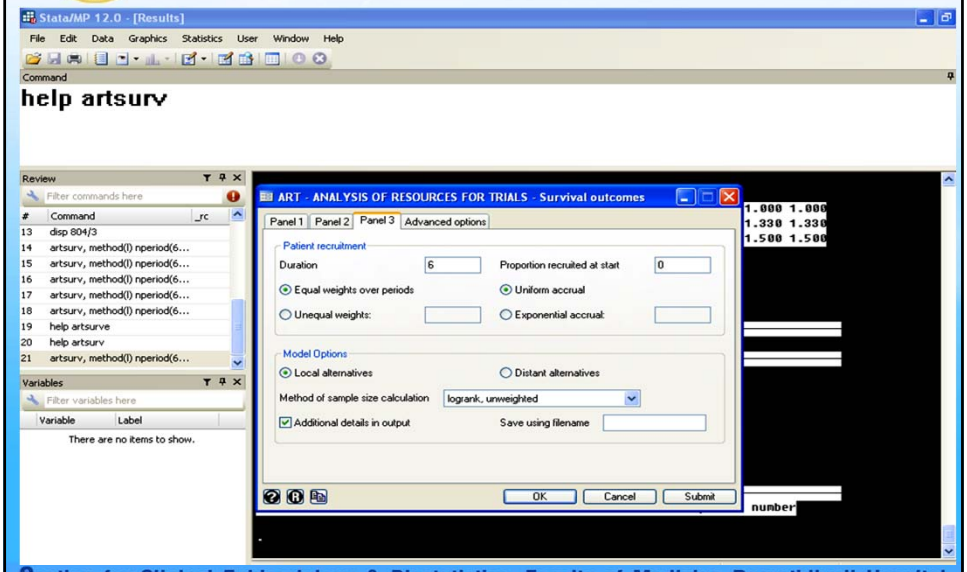
Panel 3



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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                           1.00:2.00

Total number of periods                    12
Length of each period                      One month

Baseline median survival time              6 months
Survival probs per period (group 1)        0.891 0.794 0.707 0.630 0.561 0.500
                                            0.445 0.397 0.354 0.315 0.281 0.250
Survival probs per period (group 2)        0.794 0.630 0.500 0.397 0.315 0.250
                                            0.198 0.157 0.125 0.099 0.079 0.062
Number of recruitment periods              6
Number of follow-up periods                6
Method of accrual                          Uniform
Recruitment period-weights                 1 1 1 1 1 1 0 0 0 0 0 0

Hazard ratios as entered (groups 1,2)      1, 2
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 1.000
Hazard ratios per period (group 2)         2.000 2.000 2.000 2.000 2.000 2.000
                                            2.000 2.000 2.000 2.000 2.000 2.000
Alpha                                      0.050 (two-sided)
Power (designed)                           0.800

Total sample size (calculated)             103
Expected total number of events            82
-------------------------------------------------------------------------------
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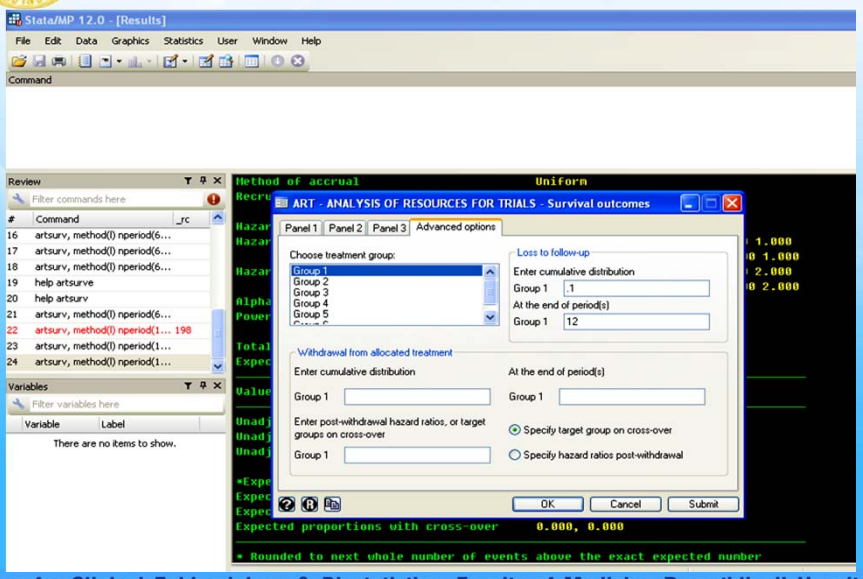
Advance option: lost FU 10% group 1



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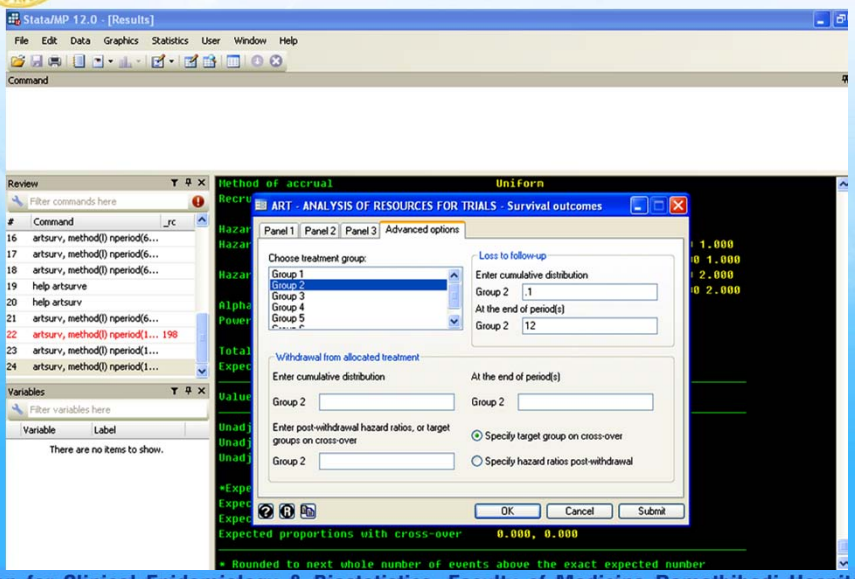
Group 2



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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                       1.00:2.00
Total number of periods                12
Length of each period                  One month
Baseline median survival time          6 months
Survival probs per period (group 1)    0.891 0.794 0.707 0.630 0.561 0.500
                                        0.445 0.397 0.354 0.315 0.281 0.250
Survival probs per period (group 2)    0.794 0.630 0.500 0.397 0.315 0.250
                                        0.198 0.157 0.125 0.099 0.079 0.062
Number of recruitment periods          6
Number of follow-up periods            6
Method of accrual                      Uniform
Recruitment period-weights             1 1 1 1 1 1 0 0 0 0 0 0
Hazard ratios as entered (groups 1,2)  1, 2
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 1.000
Hazard ratios per period (group 2)     2.000 2.000 2.000 2.000 2.000 2.000
                                        2.000 2.000 2.000 2.000 2.000 2.000
Alpha                                  0.050 (two-sided)
Power (designed)                       0.800
Total sample size (calculated)         107
Expected total number of events        82
```

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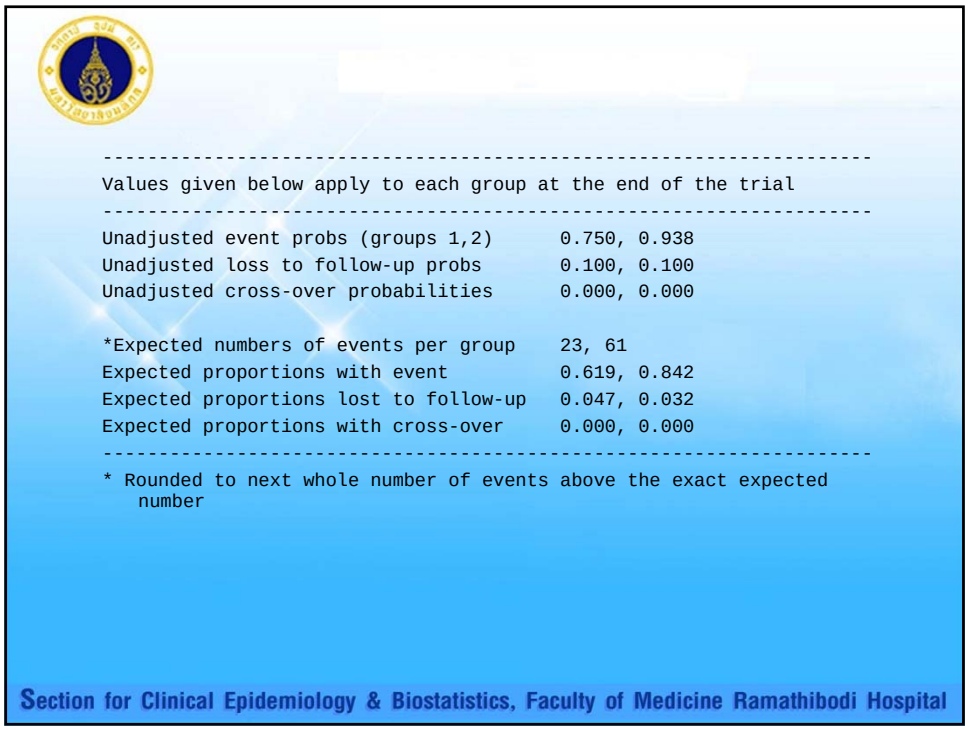

Values given below apply to each group at the end of the trial	
Unadjusted event probs (groups 1,2)	0.750, 0.938
Unadjusted loss to follow-up probs	0.100, 0.100
Unadjusted cross-over probabilities	0.000, 0.000
*Expected numbers of events per group	23, 61
Expected proportions with event	0.619, 0.842
Expected proportions lost to follow-up	0.047, 0.032
Expected proportions with cross-over	0.000, 0.000

* Rounded to next whole number of events above the exact expected number