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Two Methods to Collapse Two Treatment Groups into One Group

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ABSTRACT

When studies include different vaccine regimens (eg 1 Dose, 2 Dose) or multiple doses of the same treatment (eg 10 mg, 20 mg), statistics for each regimen or dose are summarized in separate columns in a table.

Sometimes, it is of interest to combine the multiple regimens or doses into 1 group. This presentation will discuss 2 methods to combine multiple columns of a table into 1 column. One way is to collapse the regimens or doses into 1 group and analyze the data as if they were 1 group. Another way is to keep the regimens or doses in separate groups and use the ESTIMATE statement in SAS PROC MIXED to combine them.

These 2 methods will be compared and discussed with an example and a simulation.

INTRODUCTION

This paper discusses 2 methods to combine 2 different vaccine regimens (eg 1 Dose, 2 Dose) or multiple doses of the same treatment (eg 10 mg, 20 mg) into 1 group.

Method 1 is called the “2 Model Pooled Approach”. The 1st model in the “2 Model Pooled Approach” analyzes the data with the original treatment groups. For example, the 1st model will estimate the treatment effect for 1 Dose, 2 Dose, and Placebo. The 2nd model in the “2 Model Pooled Approach” analyzes the data with 2 treatment groups collapsed. For example, the 2nd model will estimate the treatment effect for the combined 1 Dose or 2 Dose (and Placebo). The 2nd model requires a new treatment variable (eg if TRT in (“1 Dose” “2 Dose”) then TRT2 = “1 Dose or 2 Dose”). The 2nd model estimates the treatment effect for the combined 1 Dose or 2 Dose (the treatment effect for Placebo from the 2nd model will not be used).

Method 2 is called the “1 Model Separate Treatment Approach”. The “1 Model Separate Treatment Approach” is identical to the 1st model in the “2 Model Pooled Approach”. However, it will also include the ESTIMATE statement to estimate the treatment effect for the combined 1 Dose or 2 Dose. Two versions of the “1 Model Separate Treatment Approach” will be reviewed, one with equal weights and one with sample size weights.

EXAMPLE

Figure 1 illustrates a vaccine study with 2 vaccine regimens (eg 1 Dose and 2 Dose) and Placebo.

Figure 1: Study Design

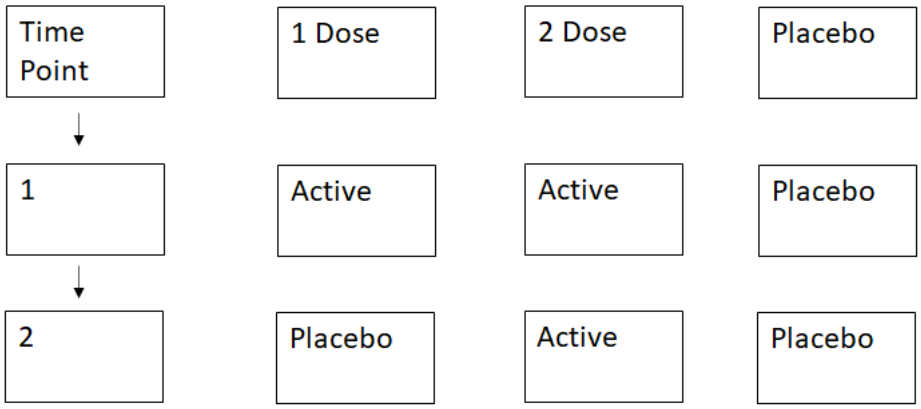

Table 1 provides the results from the "2 Model Pooled Approach".

Table 1: Results from the "2 Model Pooled Approach"

Column 1	Column 2	Column 3	Column 4
1 Dose Estimate [95% CI]	2 Dose Estimate [95% CI]	1 Dose or 2 Dose Estimate [95% CI]	Placebo Estimate [95% CI]
116 [110, 122]	494 [458, 532]	**189** **[179, 199]**	11 [10, 11]

Table 2 provides the results from the "1 Model Separate Treatment Approach" (sample size weights).

Table 2: Results from the "1 Model Separate Treatment Approach" (sample size weights)

Column 1	Column 2	Column 3	Column 4
1 Dose Estimate [95% CI]	2 Dose Estimate [95% CI]	1 Dose or 2 Dose Estimate [95% CI]	Placebo Estimate [95% CI]
116 [110, 122]	494 [458, 532]	**189** **[180, 197]**	11 [10, 11]

Table 3 provides the results from the "1 Model Separate Treatment Approach" (equal weights).

Table 3: Results from the "1 Model Separate Treatment Approach" (equal weights)

Column 1	Column 2	Column 3	Column 4
1 Dose Estimate [95% CI]	2 Dose Estimate [95% CI]	1 Dose or 2 Dose Estimate [95% CI]	Placebo Estimate [95% CI]
116 [110, 122]	494 [458, 532]	**239** **[229, 251]**	11 [10, 11]

Notice the differences in the combined 1 Dose or 2 Dose estimate (Column 3) in bold. In Table 3, the "1 Model Separate Treatment Approach" (equal weights) yields a larger estimate than in Table 1 and Table 2. This is because the "2 Model Pooled Approach" (Table 1) and the "1 Model Separate Treatment Approach" (sample size weights) (Table 2) calculate a weighted average. However, the "1 Model Separate Treatment Approach" (equal weights) (Table 3) does not calculate a weighted average. Since the treatment effects and sample sizes for 1 Dose and 2 Dose are unequal, the "1 Model Separate Treatment Approach" (equal weights) does not provide the "correct" estimate for the combined 1 Dose or 2 Dose effect.

SAS CODE

Below is SAS code for the "2 Model Pooled Approach". It creates a new treatment variable (TRT2) and runs 2 models: the first model uses TRT and the second model uses TRT2:

```
data temp; set temp;
  format trt2 $3.;
  if trt in ('1 Dose' '2 Dose') then trt2='1 Dose or 2 Dose';
  if trt='Placebo'              then trt2='Placebo';
run;

* Column 1 2 4;
ods output Lsmeans=Lsmeans124;
proc mixed data=temp;
  class trt;
  model y = trt;
  lsmeans trt / cl alpha=0.05;
run;

* Column 3;
ods output Lsmeans=Lsmeans3;
proc mixed data=temp;
  class trt2;
  model y = trt2;
  lsmeans trt2 / cl alpha=0.05;
run;
```

Below is SAS code for the "1 Model Separate Treatment Approach". It creates 2 output datasets, LSMEANS and ESTIMATES and includes the ESTIMATE statement. The first ESTIMATE statement uses equal weights and the second ESTIMATE statement uses sample size weights. The sample size weights can be obtained from PROC FREQ:

```
* Column 1 2 4;
ods output Lsmeans=Lsmeans;
```

```
* Column 3;
ods output Estimates=Estimates;
proc mixed data=adimm;
  class trt;
  model y = trt;
  lsmeans trt / cl alpha=0.05;
  estimate 'EW 1 Dose or 2 Dose' intercept 1 trt 0 0.5 0.5;
  estimate 'SW 1 Dose or 2 Dose' intercept 1 trt 0 0.6651 0.3349;
run;
```

SIMULATION AND RESULTS

A simulation was conducted to compare the "2 Model Pooled Approach" and the "1 Model Separate Treatment Approach" (equal weights and sample size weights) on the estimate of the combined 1 Dose or 2 Dose regimen effect.

Data were simulated to follow the vaccine study design illustrated in Figure 1. Data were simulated for 1 Dose, 2 Dose, and Placebo. Although the Placebo group was included in the simulations, it is not of interest.

In the first set of simulations (scenarios S1-S3), the treatment effect for 1 Dose = 2 Dose = 10. In the second set of simulations (scenarios S4-S6), the treatment effect for 1 Dose = 10 and the treatment effect for 2 Dose = 20. Within each set of simulations, sample sizes are equal or different. 10,000 simulations were performed using Gaussian distributed data with a variance of 1. Table 4 outlines the simulation scenarios S1-S6.

Table 4: Simulation Scenarios

Scenario	Statistic	1 Dose	2 Dose	Placebo
	Mean	10	10	0
S1	N	100	100	100
S2	N	100	200	100
S3	N	200	100	100
	Mean	10	20	0
S4	N	100	100	100
S5	N	100	200	100
S6	N	200	100	100

The results of the simulation are included in Table 5.

Table 5: Simulation Results

Scenario	Dose 1 and Dose 2	Bias	95% CI Width	Coverage
S1	Equal Weights	-0.00014	0.278	0.95
	Sample Size Weights	-0.00014	0.278	0.95
	Pooled	-0.00014	0.278	0.95
S2	Equal Weights	0.00062	0.241	0.95

	Sample Size Weights	0.00044	0.227	0.95
	Pooled	0.00044	0.227	0.95
S3	Equal Weights	0.00118	0.241	0.95
	Sample Size Weights	0.00081	0.227	0.95
	Pooled	0.00081	0.227	0.95
S4	Equal Weights	-0.00129	0.278	0.95
	Sample Size Weights	-0.00129	0.278	0.95
	Pooled	-0.00129	1.173	1
S5	Equal Weights	-1.66722	0.241	0
	Sample Size Weights	-0.00055	0.227	0.95
	Pooled	-0.00055	0.956	1
S6	Equal Weights	1.665773	0.241	0
	Sample Size Weights	-0.00079	0.227	0.95
	Pooled	-0.00079	0.956	1
Equal Weights = “1 Model Separate Treatment Approach” (equal weights) Sample Size Weights = “1 Model Separate Treatment Approach” (sample size weights) Pooled = “2 Model Pooled Approach”				

For scenarios S1-S3, all 3 methods (the “2 Model Pooled Approach” and the “1 Model Separate Treatment Approach” (equal weights and sample size weights) provide comparable results for bias, the 95% confidence interval widths, and coverage. None of the methods have bias for the estimate of the combined 1 Dose or 2 Dose treatment effect. The 95% confidence interval widths are comparable, and the coverages are about 95%. All 3 methods behave similarly because the treatment effect is the same, 1 Dose = 2 Dose = 10, so the weighted average and the equal weights average yield similar results.

For scenario S4, there is no bias for the estimate of the combined 1 Dose or 2 Dose treatment effect. Even though Dose 1 and Dose 2 means are different, the sample sizes are the same so the weighted average is equivalent to the equal weights average. The “2 Model Pooled Approach” has a wide 95% CI width because it estimates the combined 1 Dose or 2 Dose treatment effect by “mixing” 2 groups or subjects with unequal means. The wide 95% CI results in a coverage of 100%. Scenario S4 shows that the “2 Model Pooled Approach” is only appropriate when the Dose 1 and Dose 2 treatment effects are similar. Scenario S4 illustrates the difference between the “2 Model Pooled Approach” and the “1 Model Separate Treatment Approach” (sample size weights). While the “2 Model Pooled Approach” “mixes” 2 groups, the “1 Model Separate Treatment Approach” (sample size weights) estimates the combined 1 Dose or 2 Dose treatment effect by estimating the 1 Dose and the 2 Dose treatment effects separately and then taking a weighted average of these 2 estimates.

For scenario S5, the “1 Model Separate Treatment Approach” (equal weights) has large bias. This is because the Dose 1 and Dose 2 treatment effects and sample sizes are different but the “1 Model Separate Treatment Approach” (equal weights) is using an “incorrect” equal weights average. As a result of the large bias, the coverage is 0%. The “2 Model Pooled Approach” has a wide 95% CI width and the coverage is 100% for the same reason as explained in S4.

For scenario S6, the results are the same as scenario S5 except the bias is positive instead of negative because the sample sizes are flipped.

DISCUSSION AND CONCLUSION

The “2 Model Pooled Approach” and the “1 Model Separate Treatment Approach” (equal weights and sample size weights) are 2 ways to combine 2 different vaccine regimens or multiple doses of the same treatment into 1 group.

The “2 Model Pooled Approach” is “straight forward” (ie create a new treatment variable that collapses the 2 treatment groups together) but should only be used if the Dose 1 and Dose 2 treatment effects are similar. Otherwise, the combined Dose 1 or Dose 2 treatment effect will have an overly wide confidence interval.

The “1 Model Separate Treatment Approach” (sample size weights) can be used even if the Dose 1 and Dose 2 treatment effects and the sample sizes of the 2 groups are unequal. It also performs better than the “1 Model Separate Treatment Approach” (equal weights). However, the “1 Model Separate Treatment Approach” (sample size weights) requires an additional step of calculating sample size weights using PROC FREQ.

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

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