

Trimmed Mean Analysis Is Not Rocket Science

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Agenda

1. Introduction
2. Practical example of Trimmed Mean Analysis
3. Step-by-step algorithm
4. Generation of permuted samples
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Introduction

- ✓ Intercurrent events, or “failure”
- ✓ Trimmed mean approach was first proposed by Permutt and Li in 2017
- ✓ Interpretation provided by authors:
“Some patients did badly on treatment. Either they completed with bad outcomes, or they dropped out. For some medical conditions, it will not matter much whether they dropped out or completed with bad outcomes, nor how bad the bad outcomes were. The trimmed mean is the average outcome for other patients, those who did best in each group.”



Practical example of Trimmed Mean Analysis

Assuming we have the following statement in Statistical Analysis Plan (SAP):

“The trimmed mean analysis (Permutt and Li 2017) will be performed using ANCOVA model with adjustment for covariates. The dependent variable in the ANCOVA model is the average of non-missing values of Weeks 48, 52, and 56 assessments in change from baseline in BCVA score, categorical covariates of treatment group, baseline BCVA (continuous), as well as randomization stratification factors will be used as fixed effects. Patients will be considered to have the worst outcomes and will be trimmed from analysis if any of the following events occur:

- They have an intercurrent event prior to Week 48*
- They have an intercurrent event at a missed visit between Week 48 and Week 52”*

Such patients will be considered as "must be trimmed patients".

NOTE: Definition of intercurrent event is study-specific information (refer to Protocol/SAP).

Practical example of Trimmed Mean Analysis

Additional notes:

- The inferential statistics for the trimmed mean will be based on the permutation test (~30,000 random samples will be generated with permuted treatment assignments).
- When the proportion of the "must be trimmed patients" in either treatment group in the permuted data exceeds the planned trimmed fraction (approximately 10%), the trimming fraction will be chosen adaptively as the greater of the proportions of the "must be trimmed patients" in the two treatment groups.

Practical example of Trimmed Mean Analysis - Template

Change from Baseline in <Parameter> at <specific time point> (Trimmed Mean Method with ANCOVA),
 Intent-to-Treat Patients
 Protocol: XXXXXX

	Treatment A (N=xx)	Treatment B (N=xx)	Treatment C (N=xx)
Number of Patients Included in ANCOVA Analysis after 10% Trimming	XX	XX	XX
Change in <Parameter at specific time point>			
Adjusted Trimmed Mean (SE)	XX.XX (XX.XXX)	XX.XX (XX.XXX)	XX.XX (XX.XXX)
Difference in Adjusted Trimmed Means (SD)	XX.XX (XX.XXX)	XX.XX (XX.XXX)	
95% CI for Difference in Adjusted Means	(XX.XX, XX.XX)	(XX.XX, XX.XX)	
p-value	X.XXXX	X.XXXX	

NOTE: Standard deviation (SD), 95% CI for difference in adjusted means and corresponding p-value should be obtained as aggregated estimates from all permuted samples.

Step-by-step algorithm

Step 1: Data Selection

- Input data:
 - ADSL (Subject Level Analysis Dataset)
 - Analysis Dataset, e.g. ADOE (Ophthalmic Examinations Analysis Dataset) to get BCVA data (Best Corrected Visual Acuity) at specific visit (where [ADOE.PARAMCD] = "SBCVA" and [ADOE.AVISITN] = 9952).
- Stratification factors defined in Protocol: <strata 1>, <strata 2> and <strata-3>. These ADSL variables will be included into ANCOVA models.

Step-by-step algorithm

Step 2: Find estimates based on trimmed original data

- a) Identify trimming population (excluding "must be trimmed patients" and "missing at random")
- b) Apply ANCOVA model

```
ods output ParameterEstimates = _Est;  
proc glm data = <data selected at point (a)>;  
  class      &trt. <strata factor variables>;  
  model &dep. = &trt. <strata factor variables>  
                base / p solution;  
quit;
```

Macro references:

&trt. –Planned treatment group (TRT01P);

&dep. – Dependent variable (e.g. change from baseline CHG variable);

Step-by-step algorithm

Step 2: Find estimates based on trimmed original data

c) Ranking received results

```
ods output ParameterEstimates = _Est;  
proc glm data = <data selected at point (a)>;  
  class      &trt. <strata factor variables>;  
  model &dep. = &trt. <strata factor variables>  
             base / p solution;  
quit;
```

- **C0** : intercept
- **C1**: <strata 1> category, **C2**: <strata 2> category, **C3**: <strata 3> category
- **C4**: baseline

Step-by-step algorithm

Step 2: Find estimates based on trimmed original data

c) Ranking received results

```
_residual = &dep. - (C0 + C1 + C2 + C3 + C4*base)
```

```
_x = rand('UNIFORM', 0, 1);
```

usubjid	...	_residual	_x
XXXX	...	XX.XXXX	XX.XXXX
...	...	...	...
XXXX	...	XX.XXXX	XX.XXXX

Step-by-step algorithm

Step 2: Find estimates based on trimmed original data

d) Perform trimming based on ranked data

Based on ranked data, 10% of patients will be excluded from each treatment group by considering “worst” results.

usubjid	...	_residual	_x
XXXX	...	XX.XXXX	XX.XXXX
...	...	...	...
XXXX	...	XX.XXXX	XX.XXXX

Step-by-step algorithm

Step 2: Find estimates based on trimmed original data

e) Apply ANCOVA model based on trimmed data

```
proc glm data = <data trimmed at point (d)>;  
  class      &trt. (ref = "&ref.") <strata factor variables>;  
  model &dep. = &trt.              <strata factor variables>  
                        base / p solution;  
  lsmeans    &trt. / pdiff stderr cl;  
  ods output lsmeans = <ds_lsmeans> lsmeandiffcl = <ds_lsmeandiffcl>;  
run;
```

Macro references:

&trt. –Planned treatment group (TRT01P);

&dep. – Dependent variable (e.g. change from baseline CHG variable);

&ref. – Reference treatment for comparison.

Step-by-step algorithm

Step 3: Find estimates for each of 30,000 permuted samples

1. Treatment permutation within each unique “**strata combination block**”.
2. Estimates derivation of the difference in trimmed means for an applied permutation.

Strata combination: <1st level of strata 1>, <2nd level of strata 2> and <1st level of strata-3>.

To find out “**strata combination blocks**”, the following steps can be followed:

- a) Order all patients by “strata combination”, RADDT & RFSTDTC and create “blocks” including certain number of patients (“**block size**”).
- b) “**block size**” needs to be discussed with Biostats.
- c) Each “block” should be present only in one “**strata combination**”.

Generation of permuted samples

Step 3: Find estimates for each of 30,000 permuted samples

For particular “**strata combination block**”, the permutation of treatments can be performed as follows:

```
proc iml;
  reset print;

  use trt;
    read all var{&trt.} into TRT;
  close;

  P      = ranperm(TRT); /* perform permutation */
  P_tr = P`;             /* transpose row P to column P_tr */

  create tmp from P_tr[colname = "&trt."];
    append from P_tr;
  close;
quit;
```

- Difference in trimmed mean estimates is calculated by following (a) to (e) points from Step 2.
- One summary dataset with all differences in trimmed means from Step 2 (e) in **<ds_lsmeandiffcl>** dataset.

Step-by-step algorithm

Step 4: Find aggregated estimates from all the permuted samples

- standard deviation (SD)
- 95% CI for the difference in the adjusted means
- p-value

```
proc univariate noprint data = <summary dataset at Step 3>;  
  by &trt.;  
  var difference;  
  output out = diff_stats  
    stddev = _stddev  
    pctlpts = 2.5 97.5  
    pctlpre = P;  
run;
```

P2_5 – 2.5 percentile

P97_5 – 97.5 percentile

Step-by-step algorithm

Step 4: Find aggregated estimates from all the permuted samples

The one-sided p-value for the difference in the adjusted means:

$$((\# \text{ of cases where difference in trimmed means for permuted sample} > \text{DIFF_ORIG}) + 1) / (\# \text{ of permutations} + 1)$$

where **DIFF_ORIG** is estimated difference in trimmed means, was obtained at Step 2 (e).

Summary

- Identification of ICE (Protocol / SAP)
- Rank the “must-be-trimmed” patients with the worst order.
- Trim the worst $p\%$ of the observations in each treatment arm.
- Calculate required estimates using trimmed data.
- Repeat the above steps for each permuted sample to create an observed distribution for the estimated difference in trimmed means.

THANK YOU

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