

Statistics for Clinical Trial SAS Programmers 1: paired t-test

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ABSTRACT

This paper is intended for SAS programmers who are interested in understanding common statistical method used in clinical trials. The paper will focus on paired t-test that proves the statistical significance. It will introduce the simple statistical background and the sample SAS codes in SAS/STAT®, and it will also show how to use JMP® Software to perform the paired t-test.

INTRODUCTION OF PROC T-TEST

The TTEST procedure performs t tests for one sample, two samples, and paired observations. The one sample t test compares the mean of the sample to a given number. The two samples t test compares the mean of the first sample minus the mean of the second sample to a given number. The paired observations t test compares the mean of the differences in the observations to a given number.

The paper will cover the paired t test.

INTRODUCTION OF PAIRED T-TEST

The paired t-test is used to compare the means of repeated observations (e.g. pre- and post-study) on the same subjects or those of two different observations (e.g. standing and supine blood pressure) given to the same subjects. This paper will focus on the former.

The underlying assumption of the t test is that the observations are random samples drawn from normally distributed populations. This assumption can be checked using the UNIVARIATE procedure, which will not be covered in this paper.

LOGICS

A number of samples are randomly selected from a normal distributed population. The unknown mean of a population, μ is estimated by the sample mean \bar{y} . The sample mean is hypothesized to be some value μ_0 . The greater difference between \bar{y} and μ_0 , the greater the evidence that the hypothesis is not true. Thus, the great difference, which this paper intends to show with the paired t test, will be sufficient evidence that there is a difference in means across the paired observations.

ASSUMPTION

The paired t-test assumes that the differences between paired observations are normally distributed. According to the central limit theorem, the distribution of sample means is approximately normal, regardless of the distribution's shape, if the sample size is large enough - usually about 30 observations.

If the differences are not normally distributed, the mean might not represent the best measure of central tendency. In such cases, a non-parametric rank test, such as Wilcoxon signed-rank test, might be more appropriate.

HYPOTHESIS TEST

The paired t-test is used to test that the mean difference between paired observations is 0, which indicates 'no clinical response'.

Null hypothesis : μ is equal to μ_0

Alternative hypothesis : μ is greater than μ_0

Test statistic : $t = (\bar{y} - \mu_0) / (s / \sqrt{n})$

Decision rule : reject null hypothesis if computed $t > t(0.05, 39)$.

Here, μ is the mean differences from population, μ_0 is zero, \bar{y} and s is the mean and the standard deviation of differences from samples, n is the number of samples, and the alpha is 0.05.

SAMPLE CLINICAL TRAIL

40 subjects are treated with the new drug. Their blood pressures are observed before the treatment and after 12 weeks of treatment. The paper will show the efficacy of the new drug with paired t-test.

THE SAMPLE SAS CODE

```
data bp;
    input subject $ baseline week_12 @@;
    diff = week_12 - baseline;
    datalines;
001 145 160 002 156 170 003 138 160 004 120 152 005 126 164 006 110 156 007 115 157
008 135 157 009 160 145 010 130 160 011 120 160 012 118 146 013 118 160 014 108 145
015 130 155 016 118 120 017 124 136 018 140 145 019 128 120 020 116 136 021 120 144
022 122 152 023 118 136 024 126 120 025 152 145 026 120 155 027 118 130 028 118 136
029 108 155 030 130 130 031 118 130 032 124 145 033 140 152 034 128 136 035 116 155
036 120 120 037 122 144 038 118 145 039 126 130 040 152 167
run;

proc print data=bp;
    title1 "One Sample Paired t-Test";
    title2 "Blood Pressure before treatment and after 12 weeks of treatment";
run;

proc ttest data=bp h0=0;
    var diff;
run;

proc ttest data=bp;
    paired baseline*week_12;
run;
```

We included two proc procedures of proc ttest to indicate that both provide the same result.

ODS can be used to save output as SAS data set as indicated below.

```
proc ttest data=bp;
    paired baseline*week_12;
    ods output ttests=bp_ttest;
run;
proc print data=bp_ttest;run;
```

Obs	Variable1	Variable2	Difference	tValue	DF	Probt
1	baseline	week_12	baseline - week_12	-7.71	39	<.0001

THE SAS OUTPUT

One Sample Paired t-Test
Blood Pressure before treatment and after 12 weeks of treatment

Obs	subject	baseline	week_12	diff
1	001	145	160	15
2	002	156	170	14
3	003	138	160	22
4	004	120	152	32
5	005	126	164	38
6	006	110	156	46
7	007	115	157	42
8	008	135	157	22

9	009	160	145	-15
10	010	130	160	30
11	011	120	160	40
12	012	118	146	28
13	013	118	160	42
14	014	108	145	37
15	015	130	155	25
16	016	118	120	2
17	017	124	136	12
18	018	140	145	5
19	019	128	120	-8
20	020	116	136	20
21	021	120	144	24
22	022	122	152	30
23	023	118	136	18
24	024	126	120	-6
25	025	152	145	-7
26	026	120	155	35
27	027	118	130	12
28	028	118	136	18
29	029	108	155	47
30	030	130	130	0
31	031	118	130	12
32	032	124	145	21
33	033	140	152	12
34	034	128	136	8
35	035	116	155	39
36	036	120	120	0
37	037	122	144	22
38	038	118	145	27
39	039	126	130	4
40	040	152	167	15

One Sample Paired t-Test
Blood Pressure before treatment and after 12 weeks of treatment

The TTEST Procedure

Statistics

Difference	N	Lower CL Mean	Mean	Upper CL Mean	Lower CL Std Dev	Upper CL Std Dev	Upper CL Std Dev	Std Err	Minimum
baseline - week_12	40	-24.62	-19.5	-14.38	13.108	16.002	20.547	2.5301	-47

Maximum

15

T-Tests

Difference	DF	t Value	Pr > t
baseline - week_12	39	-7.71	<.0001

One Sample Paired t-Test
Blood Pressure before treatment and after 12 weeks of treatment

The TTEST Procedure

Statistics

Variable	N	Lower CL Mean	Mean	Upper CL Mean	Lower CL Std Dev	Std Dev	Upper CL Std Dev	Std Err	Minimum
diff	40	14.382	19.5	24.618	13.108	16.002	20.547	2.5301	-15

Maximum

47

T-Tests

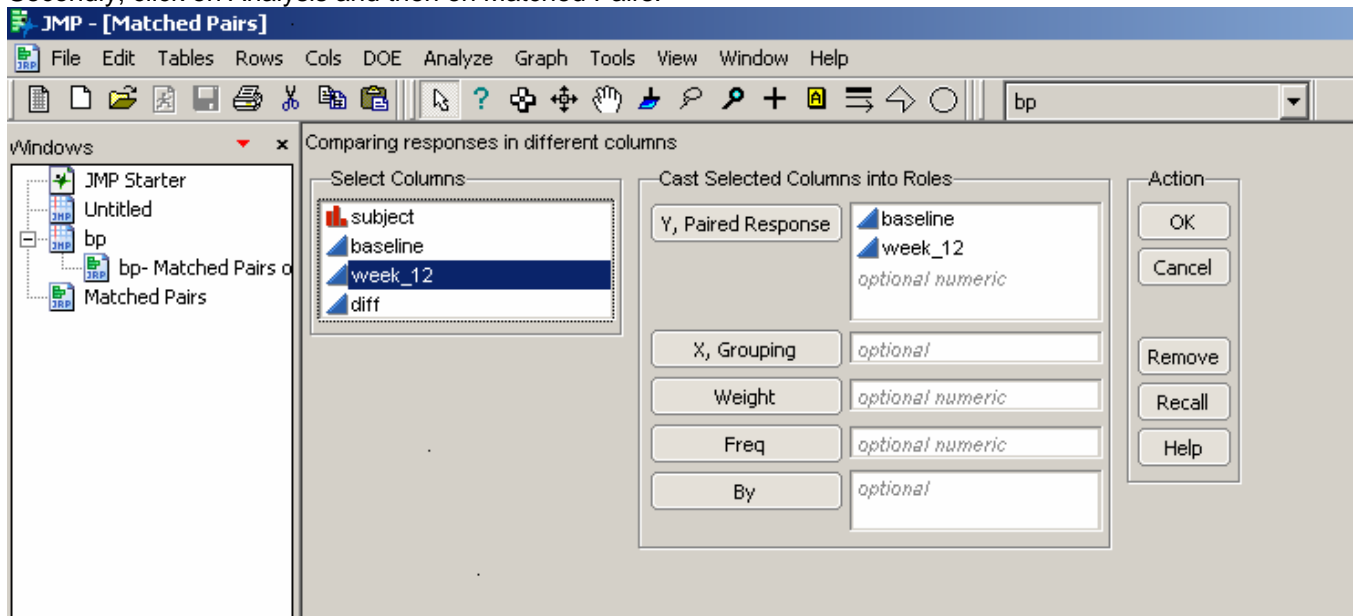
Variable	DF	t Value	Pr > t
diff	39	7.71	<.0001

As shown above, the both proc ttest provide the same results.

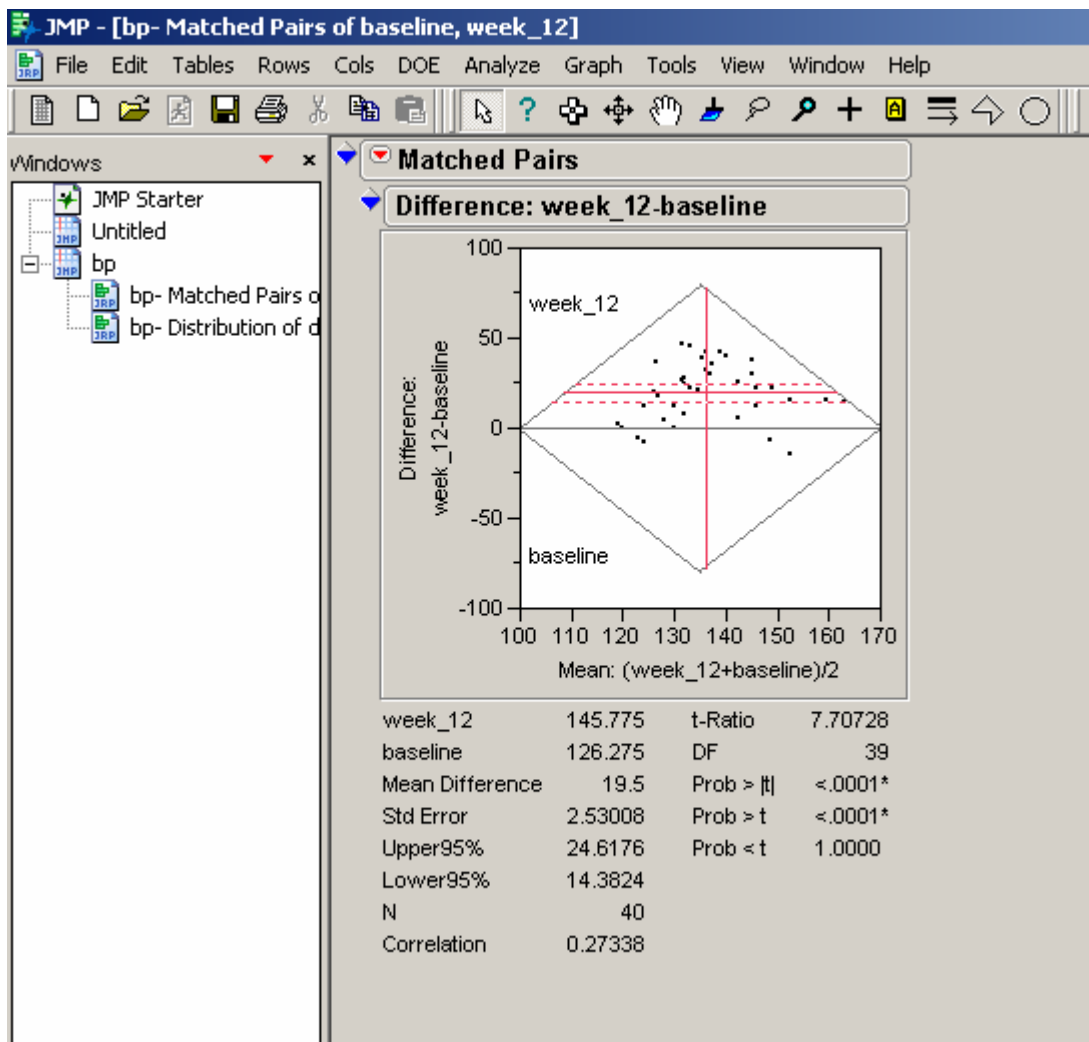
The study wants to find out if the drug is promising. Since SAS automatically compute the two-sided paired p-value, the p-value should be halved to obtain one-tailed result to satisfy the alternative hypothesis. The p-value is still <0.0001. Now, we can reject the null hypothesis and conclude that a significant blood pressure occurs because this p-value is less than the nominal significance level of 0.05, which is the alpha that is defined in the hypothesis.

USING JMP SOFTWARE

First, open the file and select the pre-prepared data set bp that SAS codes created. Secondly, click on Analysis and then on Matched Pairs.



Move baseline and week_12 as shown in the diagram and click on OK.



The JMP software, shown above, provides the same p-value that SAS software does.

THE ADVANTAGE OF KNOWING STATISTICAL ANALYSES IN CLINICAL TRIALS

The understanding of some of statistical analyses in clinical trials helps the SAS programmers to link the relationship between SAS database and tables, listings and graphs. The main statistical analyses in clinical trials are t-test, ANOVA, Wilcoxon Test, ANCOVA, Chi-Square Test, Fisher's Exact Test, McNemar's Test, Log-Rank Test and so on. Each analysis is used for a different purpose.

It also helps SAS programmers to understand what statisticians try to achieve in the clinical trials. There weren't many statistical analyses on safety data, but there are a lot of statistical analyses on efficacy data. In the normal clinical trials, statisticians state in the protocol or SAP (Statistical Analysis Plan) what kind of statistical analyses to do. If SAS programmers understand the kind of statistical analyses that statisticians try to do in the clinical trials, they will have an easier time to build SAS database, especially the efficacy database.

SAS programmers and statisticians can also work together to automate the process so that statisticians do not need to spend too much time in SAS programming. For example, SAS programmers prepare the efficacy data in the way that statisticians can use it very easily or SAS programmers provide the whole SAS codes to generate the efficacy results. This process will help to save the time and efforts in both sides.

SAS programmers can have better communications and working relationships with statisticians. The understanding of statistical analyses helps SAS programmers to have a better understanding on the statisticians' sides - their issues, problems and even shortcomings.

Therefore, knowing statistical analyses helps SAS programmers to be better. The job descriptions of SAS programmers go beyond programming. SAS programmers interact with other team members. SAS programmers need to understand how the whole study team works. SAS programming is a part of process. Knowing more process makes better SAS programmers.

CONCLUSION

The paired t-test can provide the statistical analyses on the clinical trial of one sample population. By using proc ttest, SAS programmers can derive the clinical statistical significant value, which can indicate whether the drug works for the patients or not.

CONTACT INFORMATION

Your comments and questions are valued and welcomed. Please contact the author at

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REFERENCE

Glenn A. Walker, Common Statistical Methods for Clinical Research

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