

Analysis of a Questionnaire by Global Statistical Tests

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- Multiplicity, Common Approach in Medical Literature
- Primary and Secondary Outcomes
- Global Statistical Tests (GTS)
 - Hotelling's T^2
 - Generalized Least Square Test (O'Brien)
 - Extended Generalized Least Square Test
- Application on a Questionnaire

- Excessive use of multiple statistical tests in clinical trials can greatly increase the chance of experiment wise false positive findings

Most common approach: Analyze each outcome separately, presenting multiple p-values and an overall conclusion

At best: By an open display of data enabling readers to draw their own conclusions

At worst: Not reporting some nonsignificant outcomes

- Even all outcomes are reported openly, still increased risk of an experiment wise false positive rate.

- **Definition of a single primary outcome**
The p-value for treatment difference represents a formal test of hypothesis. This is also called a confirmatory test. The false positive rate is controlled experiment wise.
- **Secondary outcomes**
The analysis on secondary outcomes is called exploratory, means hypothesis generating. The p-values serve as flag to indicate interesting results.

- The drawback to Bonferroni correction is that it confirms attention to the smallest p-value.
- e.g. 0.01, 0.7, 0.7, 0.7, 0.7
are considered more significant than
- e.g. 0.02, 0.02, 0.02, 0.02, 0.02
the latter appears to contain more convincing evidence of a treatment effect.

E.g. one sample test

- $n > k$
- y_k outcomes, multivariate normally distributed with variance-covariance matrix Σ
- Alternative hypothesis:
At least one outcome is different (from zero)

- $T^2 = n \cdot \bar{y}' \cdot \Sigma^{-1} \cdot \bar{y}$

$$\frac{(n-k)}{(n-1) \cdot k} \cdot T^2 \sim F(k, n-k)$$

$$\bar{y} = (\bar{y}_1, \dots, \bar{y}_k)$$

O'Briens Test Statistic (1984)



E.g. one sample test

- $n > k$ as well as $n < k$
- y_k outcomes, multivariate normally distributed with variance covariance matrix Σ , correlation matrix Θ , respectively
- Alternative hypothesis:
The k standardized treatment differences z_k are all of equal magnitude and in the same direction

- O'Briens test statistic:

$$(n)^{\frac{1}{2}} \cdot \frac{\delta' \cdot \Sigma^{-1} \cdot Y}{(\delta' \cdot \Sigma^{-1} \cdot \delta)^{\frac{1}{2}}} \sim N(0,1)$$
$$\delta' = (\sigma_1, \dots, \sigma_k)$$
$$Y = (\bar{y}_1, \dots, \bar{y}_k)$$

- or alternatively:

$$\frac{J' \cdot \Theta^{-1} \cdot z}{(J' \cdot \Theta^{-1} \cdot J)^{\frac{1}{2}}} \sim N(0,1)$$
$$J' = (1, 1, \dots, 1)$$
$$z = (z_1, z_2, \dots, z_k)$$



O'Briens Examples

Example: All outcomes equally correlated

- $k = 5$
- $\rho = 0$
- $p = 0.379, 0.379, 0.379, 0.379, 0.379$
- O'Brien p-value = 0.0491

$$\begin{pmatrix} 1 & \rho & \rho & \rho & \rho \\ \rho & 1 & \rho & \rho & \rho \\ \rho & \rho & 1 & \rho & \rho \\ \rho & \rho & \rho & 1 & \rho \\ \rho & \rho & \rho & \rho & 1 \end{pmatrix}$$

- $k = 5$
- $\rho = 0.5$
- $p = 0.129, 0.129, 0.129, 0.129, 0.129$
- O'Brien p-value = 0.0497

- Tang et al. “On the Design and Analysis of Randomized Clinical Trials with Multiple Endpoints”, Biometrics 49, 23, (1993)
- Approximate Likelihood Ratio statistic
- “extended” O'Brien test:

$$(n)^{1/2} \cdot \frac{J' \cdot D^{1/2} Y}{\left(J' \cdot D^{1/2} \cdot \Sigma \cdot D^{1/2} \cdot J \right)^{1/2}} \sim N(0,1)$$

$$J' = (1,1,\dots,1)$$

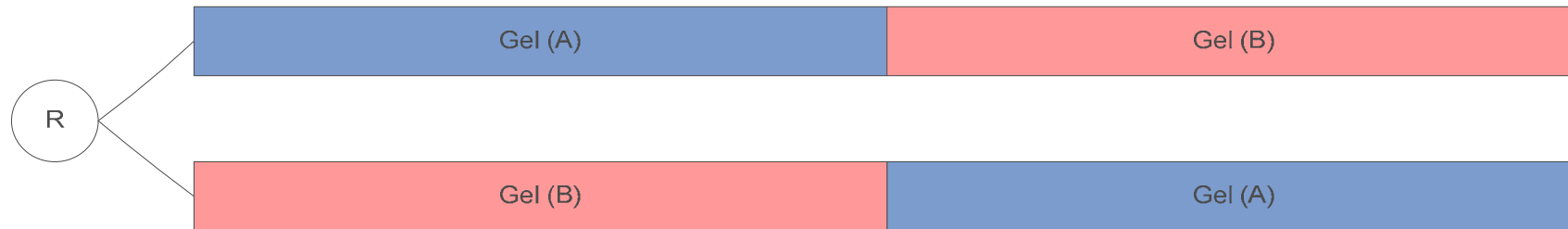
$$Y = (\bar{y}_1, \dots, \bar{y}_k)$$

$$D = \text{diag}(\Sigma^{-1})$$

Flow Chart of the Trial



Design: Blind, randomized, two period, cross-over trial (n=48)



Intake of 4 gels during a 16 k run
after the run, complete gastrointestinal complains questionnaire



Gastro Intestinal Complaints Questionnaire



First section (upper abdominal problems)
out of 3 sections of the questionnaire



1. Which of the following have you experienced **during this run**

	no problem at all	very minor problems	Minor problems	moderate problems	serious problems	severe	very severe	very very severe	the worst it has ever been
Reflux	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Heartburn	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Bloating	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Upper abdominal cramp	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Vomiting	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Nausea	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>



Gastro Intestinal Complaints Questionnaire

Section	Question
upper abdominal problems	Reflux
	Heartburn
	Bloating
	Upper abdominal cramps
	vomiting
	nausea
lower abdominal problems	intestinal cramps
	flatulence
	urge to defecate
	left abdominal pain
	right abdominal pain
	loose stool
	diarrhea
systemic problems	dizziness
	headache
	muscle cramp
	urge to urinate



Raw Data



id	A11	A12	A13	A14	A15	A16	A21	A22	A23	A24	A25	A26	A27	A31	A32	A33	A34	B11	B12	B13	B14	B15	B16	B21	B22	B23	B24	B25	B26	B27	B31	B32	B33	B34			
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51																																					
52																																					
53																																					
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55																																					

Summary Statistics

Section	Question	Gel (A)					Gel (B)				
		n	mean	sd	min	max	n	mean	sd	min	max
upper abdominal problems	Reflux	48	1.58	1.23	1	5	48	2.04	1.57	1	6
	Heartburn	48	1.35	1.14	1	6	47	1.32	0.84	1	5
	Bloating	48	1.94	1.42	1	6	48	2.17	1.75	1	8
	Upper abdominal cramps	48	2.23	1.78	1	7	48	2.27	1.78	1	7
	vomiting	48	1.27	0.87	1	6	48	1.23	0.72	1	4
	nausea	48	2.21	1.66	1	7	48	2.06	1.79	1	8
lower abdominal problems	intestinal cramps	48	1.67	1.10	1	5	48	2.08	1.50	1	6
	flatulence	48	1.38	0.94	1	5	48	1.54	1.20	1	7
	urge to defecate	48	1.48	1.20	1	5	48	1.69	1.78	1	9
	left abdominal pain	48	2.13	1.88	1	8	48	2.15	1.68	1	7
	right abdominal pain	48	1.92	1.75	1	9	48	1.92	1.65	1	7
	loose stool	48	1.00	0.00	1	1	48	1.38	1.36	1	9
systemic problems	diarrhea	48	1.00	0.00	1	1	48	1.13	0.73	1	6
	dizziness	48	1.38	0.91	1	5	48	1.23	0.95	1	6
	headache	48	1.19	0.67	1	4	48	1.23	0.88	1	6
	muscle cramp	48	1.85	1.60	1	9	48	1.60	1.22	1	6
	urge to urinate	47	1.79	1.28	1	5	48	1.56	1.32	1	7

Lower Abdominal Problems

- Exact Wilcoxon tests

$$z = (-2.08, -0.82, -0.91, -0.14, 0, -1.91, -0.68)$$

- Correlation matrix according to Kendall

$$\Theta = \begin{pmatrix} 1 & 0.12 & 0.19 & 0.26 & 0.16 & 0.28 & 0.31 \\ 0.12 & 1 & 0.29 & 0.11 & -0.04 & 0.41 & 0.33 \\ 0.19 & 0.29 & 1 & 0.23 & 0.26 & 0.39 & 0.22 \\ 0.26 & 0.11 & 0.23 & 1 & 0.39 & 0.08 & 0.02 \\ 0.16 & -0.04 & 0.26 & 0.39 & 1 & 0.12 & 0.01 \\ 0.28 & 0.41 & 0.39 & 0.08 & 0.12 & 1 & 0.62 \\ 0.31 & 0.33 & 0.22 & 0.02 & 0.01 & 0.62 & 1 \end{pmatrix}$$

$$\text{weights} = J' \cdot \Theta^{-1} = (0.46, 0.64, 0.31, 0.46, 0.67, 0.04, 0.53)$$

$$\text{O'Brien statistic} = -1.28$$

$$p = 0.20$$

$$\frac{J' \cdot \Theta^{-1} \cdot z}{(J' \cdot \Theta^{-1} \cdot J)^{\frac{1}{2}}} \sim N(0,1)$$

$$J' = (1, 1, \dots, 1)$$

$$z = (z_1, z_2, \dots, z_k)$$

Inferential Statistics

A-B > 0 then beneficial: less complains

Section	Question	A-B			Wilcoxon p values	O'Brien p values	
		n	mean	se			
upper abdominal problems	Reflux	48	-0.46	0.23	0.024	0.27	0.52
	Heartburn	47	0.04	0.19	0.959		
	Bloating	48	-0.23	0.25	0.495		
	Upper abdominal cramps	48	-0.04	0.29	0.830		
	vomiting	48	0.04	0.15	0.943		
	nausea	48	0.15	0.29	0.505		
lower abdominal problems	intestinal cramps	48	-0.42	0.20	0.041	0.20	
	flatulence	48	-0.17	0.16	0.385		
	urge to defecate	48	-0.21	0.27	0.339		
	left abdominal pain	48	-0.02	0.31	0.871		
	right abdominal pain	48	0.00	0.31	0.930		
	loose stool	48	-0.38	0.20	0.043		
	diarrhea	48	-0.13	0.11	0.180		
systemic problems	dizziness	48	0.15	0.14	0.277	0.11	
	headache	48	-0.04	0.13	0.915		
	muscle cramp	48	0.25	0.20	0.316		
	urge to urinate	47	0.21	0.21	0.271		

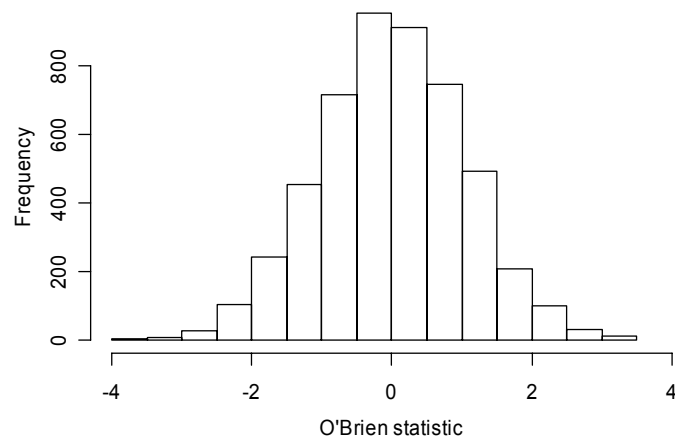
Extended O'Brien and Bootstrapping



Values $\neq 0$ in D

- u. abd. problems 35%
- l. abd problems 30%
- systemic problems 26%

	Hotteling		np. O'Brien		ext. O'Brien		ext. O'Brien bootstrapped	
u. abd. problems	0.39	0.38	0.27	0.52	0.56	0.40	0.56	0.40
l. abd. problems	0.59		0.20		0.089		0.087	
systemic problems	0.30		0.11		0.14		0.16	



D21	D22	D23	D24	D25	D26	D27
-2	-1	0	2	3	-3	-1
1	0	0	2	2	0	0
0	0	-5	0	0	0	0
1	0	0	0	0	0	0
1	0	0	4	-2	0	0
-2	1	2	1	-2	0	0
0	1	0	3	0	0	0
0	0	0	0	0	0	0
0	0	0	-4	-2	0	0
0	-1	0	0	0	0	0
0	2	4	3	1	0	0
0	-1	0	0	0	0	0
-2	-3	0	0	3	0	0
-2	0	1	-3	6	0	0
0	-4	1	0	0	0	0
-3	0	0	0	-6	0	0
0	-3	-4	-2	0	-2	0
3	2	4	1	1	0	0
0	-1	0	6	0	0	0
0	0	0	-4	-6	0	0
0	0	0	0	0	0	0
0	-1	0	0	0	-1	0
-1	2	0	-2	-1	0	0
0	0	0	0	0	0	0
-3	0	-4	0	-3	-8	0
2	0	1	0	0	0	0
0	1	0	0	0	0	0
0	0	0	0	0	0	0
0	0	0	0	0	0	0
-1	0	0	1	1	0	0
-3	0	0	0	0	0	0
-4	-2	-5	-3	-3	-4	-5
0	0	0	-1	-3	0	0
0	0	0	4	4	0	0
0	0	0	0	0	0	0
-1	0	-4	-3	0	0	0
0	0	0	0	0	0	0
0	0	0	0	0	0	0
0	0	0	-4	0	0	0
-2	0	-4	-2	-2	0	0
-1	0	0	0	3	0	0
0	0	0	0	0	0	0
0	0	0	-2	0	0	0
2	0	0	4	4	0	0
0	0	0	-3	0	0	0
-3	0	3	-1	0	0	0
0	0	0	2	2	0	0



- This analysis was performed with R 2.5.1
- The code was validated along an example described in Tang et al. “On the Design and Analysis of Randomized Clinical Trials with Multiple Endpoints”, Biometrics 49, 23, (1993) and can be obtained on demand by **Dominik.Grathwohl@RDLS.Nestle.com**