



QUINTILES



Analysing Binary Outcome Data from a Crossover Design Study Using the SAS® System

Anna Pictor, Quintiles Ltd.

DO THINGS BETTER ↔ DO BETTER THINGS™



> www.quintiles.com



Introduction

- ◆ Overview of Crossover Trials.
- ◆ Binary Outcome Data.
- ◆ McNemar, Mainland-Gart and Prescott.
- ◆ McNemar and Mainland-Gart in SAS.
- ◆ Performing Prescott's test in SAS.
- ◆ Worked Example of Prescott's test.
- ◆ Summary.





Overview of Crossover Trials

- ◆ Each patient receives more than one treatment or dosing regimen.
- ◆ Each patient acts as their own control.
- ◆ Can only be used if condition is chronic
- no good if patient cured after first period.
- ◆ Basic 2x2 design - one sequence group receive A then B, the other B then A.



QUINTILES



Binary Outcome Data

- ◆ Could be a question with a binary response:
 - ◆ “Which treatment do you prefer - Drug A or Drug B?”
- ◆ Or a continuous response dichotomised:
 - ◆ “Did patient experience a 10% or greater reduction in blood pressure – yes or no?”



QUINTILES



Binary Outcome Data

- ◆ If response is measured at end of each period could have the following cases:
- ◆ Response on Drug A but not on Drug B would mean patient “preferred” Drug A.
- ◆ Response on Drug B but not on Drug A would mean patient “preferred” Drug B.
- ◆ A response on both or no response on either drug would be “no preference”.



QUINTILES



McNemar's Test

- ◆ Looks at number who prefer Drug A against number who prefer Drug B.
- ◆ Ignores order drugs received in and those patients with “no preference”.
- ◆ Conditions on number of patients who preferred A and calculates probability of this many or more preferences under null hypothesis of equality of treatment effect.



QUINTILES



Mainland-Gart Test

- ◆ Takes period into account but still ignores the “no preference” group.
- ◆ Calculates number who prefer A and prefer B for each sequence group.
- ◆ Looks for an association between period in which preferred drug was taken and sequence.



QUINTILES



Prescott's Test

- ◆ Takes into account period and those who do not express a preference.
- ◆ If a period effect is suspected best to use Mainland-Gart or Prescott rather than McNemar.
- ◆ If it is suspected many patients will not express a preference then Prescott should be used over Mainland-Gart.



QUINTILES



Code for McNemar's Test

- ◆ Example data from 2x2 design trial:

Drug A Drug B	Response	No Response
Response	4	1
No Response	15	4



QUINTILES



Code for McNemar's Test

- ◆ Does not consider the eight patients with same result under both drugs.

```
PROC FREQ DATA=indata;  
    TABLES druga*drugb / AGREE;  
RUN;
```



Code for Mainland-Gart Test

- ◆ Still ignores the “no preference” data but does consider period:

Sequence	Prefers 1 st Period	Prefers 2 nd Period	Total
AB	9	0	9
BA	1	6	7
Total	10	6	16



QUINTILES



Code for Mainland-Gart Test

- ◆ Testing association between period and sequence using Fisher's Exact Test or Chi-Square Test.

```
PROC FREQ DATA=indata;  
  TABLES seqgrp*period /  
    CHISQ MEASURES EXACT;  
  EXACT OR;  
RUN;
```





Code for Prescott's Test

- ◆ Cannot be performed in a SAS procedure.
- ◆ No existing code to edit.
- ◆ So where to look next?
- ◆ Search the internet for Prescott's Test?



Code for Prescott's Test



“John Prescott’s transport policy
fails the test”





Theory for Prescott's Test

- ◆ Time to write a macro!
- ◆ Prescott's Test considers the "no preference" data.
- ◆ Treatment effect can be defined in terms of a difference in period effect between the sequences.
- ◆ Similar to testing continuous data with a Wilcoxon Rank Sum Test.



QUINTILES



Theory for Prescott's Test

- ◆ Notation used in Stephen Senn's Cross-over Trials in Clinical Research:

Sequence	1 st Period	No Pref.	2 nd Period	Total
AB	d	e	f	r_1
BA	g	h	k	r_2
Total	s_1	s_2	s_3	N



QUINTILES



Theory for Prescott's Test

- ◆ The difference between periods for sequence AB is measured by d-f.

Sequence	1 st Period	No Pref.	2 nd Period	Total
AB	d	e	f	r_1
BA	g	h	k	r_2
Total	s_1	s_2	s_3	N



QUINTILES



Theory for Prescott's Test

- ◆ Similarly the difference between periods for sequence BA is measured by $g-k$.

Sequence	1 st Period	No Pref.	2 nd Period	Total
AB	d	e	f	r_1
BA	g	h	k	r_2
Total	s_1	s_2	s_3	N



QUINTILES



Theory for Prescott's Test

- ◆ Then (d-f) - (g-k) measures the preferences for one treatment over the other.
- ◆ But because the marginal totals are fixed the results from Sequence AB can be used to derive the results from Sequence BA.
- ◆ So we only need to consider (d-f).



QUINTILES



Theory for Prescott's Test

- ◆ Consider all possible contingency tables where $(d-f)$ is equal to or more extreme than the observed $(d-f)$.
- ◆ Then the p-value is calculated as the sum of the probabilities of observing these contingency tables.



Code for Prescott's Test

- ◆ How to calculate this in SAS?
- ◆ Set up a data set with 3 variables:
 - ◆ Sequence at two levels (AB and BA)
 - ◆ Preference (prefer first period, no preference or prefer second period)
 - ◆ Count holding the number of patients with each response





Code for Prescott's Test

◆ Form of input dataset:

Sequence	Preference	Response
AB	Prefer 1 st	4 (d)
AB	No Pref.	21 (e)
AB	Prefer 2 nd	1 (f)
BA	Prefer 1 st	6 (g)
BA	No Pref.	20 (h)
BA	Prefer 2 nd	1 (k)



QUINTILES



Code for Prescott's Test

- ◆ Transpose this data to get one row with the counts stored in variables called d, e, f, g, h and k.
- ◆ Calculate the row and column totals r1, r2, s1, s2 and s3.
- ◆ Calculate and retain the observed (d-f) in a separate variable.
- ◆ Output the row to a dataset.



QUINTILES



Code for Prescott's Test

- ◆ Create all possible contingency tables by considering all combinations of d and f and output them as rows to the dataset if they are valid.
- ◆ Lowest possible cell value is zero so start with $d=0$ and $f=0$.
- ◆ Calculate e , g , h and k using the fixed row and column totals derived from the input data.



QUINTILES



Code for Prescott's Test

- ◆ If $(d-f)$ exceeds the observed $(d-f)$ then output row to the dataset.
- ◆ Increment f by 1 and repeat the process.
- ◆ When maximum f is reached reset f to zero and increment d by 1.
- ◆ This is performed using nested DO loops.



QUINTILES



Code for Prescott's Test

- ◆ When all combination of d and f have been considered will have a dataset who's rows represent all the valid contingency tables.
- ◆ Calculate probability of observing each of these contingency tables in order to derive the p-value.



QUINTILES



Code for Prescott's Test

- ◆ Probability of observing a table uses combinations.
- ◆ nC_r equals $n! / r!(n-r)!$
- ◆ In SAS use function COMB(n,r)



Code for Prescott's Test

- ◆ s^1C_d is number of ways of choosing first cell value from first column total.

Sequence	1 st Period	No Pref.	2 nd Period	Total
AB	d	e	f	r_1
BA	g	h	k	r_2
Total	s_1	s_2	s_3	N



QUINTILES



Code for Prescott's Test

- ◆ s^2C_e is number of ways of choosing second cell value from second column total.

Sequence	1 st Period	No Pref.	2 nd Period	Total
AB	d	e	f	r_1
BA	g	h	k	r_2
Total	s_1	s_2	s_3	N



QUINTILES



Code for Prescott's Test

- ◆ Similarly for the third column:

Sequence	1 st Period	No Pref.	2 nd Period	Total
AB	d	e	f	r_1
BA	g	h	k	r_2
Total	s_1	s_2	s_3	N



QUINTILES



Code for Prescott's Test

- ◆ Probability of observing this table is the product of these combinations:

$$\text{COMB}(s_1, d) * \text{COMB}(s_2, e) * \text{COMB}(s_3, f)$$

- ◆ Sum the probabilities for each table, divide total by $\text{COMB}(N, r_1)$ to get one-sided p-value.
- ◆ Multiply by 2 to get two-sided p-value.



QUINTILES



Worked Example

- ◆ 2x2 design crossover study.
- ◆ Reduction in Migraine Attacks.
- ◆ 50% or greater reduction from baseline in number of migraine attacks experienced over treatment period.
- ◆ Active versus Placebo.



Worked Example

◆ Observed results:

Sequence	1 st Period	No Pref.	2 nd Period	Total
Act-PI	4	21	1	26
PI-Act	6	20	1	27
Total	10	41	2	53



Worked Example

- ◆ First row of dataset will hold the observed table values:

d	e	f	g	h	k
4	21	1	6	20	1



Worked Example

- ◆ Calculate the row and column totals and the observed (d-f):

d	e	f	g	h	k	r1	r2	s1	s2	s3	N	dminusf
4	21	1	6	20	1	26	27	10	41	2	53	3



Worked Example

- ◆ Consider the first new row with $d=0$ and $f=0$:

d	e	f	g	h	k	r1	r2	s1	s2	s3	N	dminusf
4	21	1	6	20	1	26	27	10	41	2	53	3
0	26	0	10	15	2	26	27	10	41	2	53	3



QUINTILES



Worked Example

- ◆ But d-f here is only zero so does not exceed the observed (d-f) so not a valid contingency table.

d	e	f	g	h	k	r1	r2	s1	s2	s3	N	dminusf
4	21	1	6	20	1	26	27	10	41	2	53	3
0	26	0	10	15	2	26	27	10	41	2	53	3



QUINTILES



Worked Example

- ◆ Increment f by 1 and repeat the process, but again $d-f$ does not exceed the observed.

d	e	f	g	h	k	r1	r2	s1	s2	s3	N	dminusf
4	21	1	6	20	1	26	27	10	41	2	53	3
0	26	0	10	15	2	26	27	10	41	2	53	3
0	25	1	10	16	1	26	27	10	41	2	53	3



QUINTILES



Worked Example

- ◆ First valid table is when $d=3$ and $f=0$.

d	e	f	g	h	k	r1	r2	s1	s2	s3	N	dminusf
4	21	1	6	20	1	26	27	10	41	2	53	3
0	26	0	10	15	2	26	27	10	41	2	53	3
0	25	1	10	16	1	26	27	10	41	2	53	3
.	.	.	.	.	.	.	.	.	.	.	.	.
3	23	0	7	18	2	26	27	10	41	2	53	3



QUINTILES



Worked Example

- ◆ Probability of the first contingency table is calculated as:
 $\text{COMB}(10,4) * \text{COMB}(41,21) * \text{COMB}(2,1)$
- ◆ Repeat for each table.
- ◆ Sum over all tables.
- ◆ Divide total by $\text{COMB}(53,26)$...
- ◆ ...gives one-sided p-value of 0.8048



QUINTILES



Summary

- ◆ Can group any data to show a “preference” for one treatment or the other.
- ◆ Advantage of Prescott’s Test is that it takes order of treatments and “no preference” group into account.
- ◆ No procedure in SAS but can produce contingency tables and calculate p-value by following the algorithm.



QUINTILES



QUINTILES



Any Questions?

DO THINGS BETTER ↔ DO BETTER THINGS™



> www.quintiles.com