

ANALYSIS OF TWO-PERIOD CROSSOVER TRIALS USING SAS

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OPTIONS LS=76;

PERHAPS ONE OF THE MOST USEFUL OF ALL DESIGNS IN CLINICAL TRIALS IS THE SIMPLE TWO-PERIOD CHANGE-OVER DESIGN. THIS DESIGN IS WIDELY USED IN PHAMACEUTICAL TRIALS INVOLVING THE COMPARISON OF A DRUG TO PLACEBO. EACH SUBJECT ACTS AS HIS OWN CONTROL, THUS REMOVING BIOLOGICAL VARIABILITY OR AMONG SUBJECTS VARIABILITY FROM ERROR ESTIMATES. A LINEAR MODEL IS WRITTEN CONTAINING DIRECT AND RESIDUAL TREATMENT, PERIOD, AND SUBJECT WITHIN SEQUENCE EFFECTS. WHEN THE USUAL NORMALITY AND HOMOGENEITY ASSUMPTIONS ARE MET, THIS ANALYSIS HAS BEEN PRESENTED ACCORDING TO GRIZZLE (1965). KOCH (1972) DESCRIBED THE TWO-PERIOD CHANGE-OVER ANALYSIS WHEN THE USUAL ASSUMPTIONS DO NOT SEEM PLAUSIBLE, WHICH IS OFTEN THE CASE WITH SMALL SAMPLE DRUG-PLACEBO CLINICAL TRIALS. THESE NONPARAMETRIC PROCEDURES EMPLOY REPEATED WILCOXON TESTS ON WITHIN-SUBJECT LINEAR FUNCTIONS CORRESPONDING TO EFFECTS PRESENT IN THE MODEL.

APPROPRIATE HYPOTHESES AND F STATISTICS ARE PRESENTED USING PROC GLM FOR TESTING (A) EQUAL RESIDUAL EFFECTS, (B) TREATMENT EFFECTS IN THE PRESENCE OF RESIDUAL EFFECTS, AND (C) TREATMENT EFFECTS IN THE ABSENCE OF RESIDUAL EFFECTS. THE NONPARAMETRIC COUNTERPART OF THESE TESTS IS ACCOMPLISHED USING PROC NPARIWAY TO TEST (A) RESIDUAL EFFECTS, (B) DIRECT TREATMENT EFFECTS WHEN RESIDUAL EFFECTS ARE ABSENT, (C) PERIOD EFFECTS WHEN RESIDUAL EFFECTS ARE ABSENT, AND (D) DIRECT EFFECTS WHEN RESIDUAL EFFECTS EXIST. FINALLY, IMAN'S SIGN RANK T-TEST FOR DIRECT EFFECTS WHEN RESIDUAL AND PERIOD EFFECTS ARE ABSENT IS DEMONSTRATED.

```
/* *****
 * GRIZZLE PARAMETRIC APPROACH *
 * TO ANALYSIS OF TWO-PERIOD *
 * CHANGE-OVER DESIGN *
 * *
 ***** */
```

DATA IN;

INPUT SEQ SUBJECT \$ Y1 Y2;

CARDS;

```
1 C11 1.75 .55
1 C12 .30 1.05
1 C13 .35 .63
1 C14 .20 1.55
1 C15 .30 0.20
2 C21 7.20 .35
2 C22 7.10 1.55
2 C23 .75 .25
2 C24 2.15 .35
2 C25 3.35 1.50
```

DATA ONE;

SET IN;

```
IF SEQ=1 THEN DO; TRT='G'; RESPONSE=Y1; PERIOD=1; OUTPUT; END;
IF SEQ=1 THEN DO; TRT='H'; RESPONSE=Y2; PERIOD=2; OUTPUT; END;
IF SEQ=2 THEN DO; TRT='H'; RESPONSE=Y1; PERIOD=1; OUTPUT; END;
IF SEQ=2 THEN DO; TRT='G'; RESPONSE=Y2; PERIOD=2; OUTPUT; END;
```

DROP Y1 Y2;

PROC PRINT;

PROC GLM;

```
CLASSES TRT SEQ SUBJECT;
MODEL RESPONSE=TRT SEQ SUBJECT(SEQ);
```

```
TEST H=SEQ E=SUBJECT(SEQ); /* TEST FOR RESIDUAL EFFECTS */
```

```
TITLE GRIZZLE TWO-PERIOD CHANGE-OVER DESIGN;
TITLE2 GRIZZLE, J.E. 1965 BIOMETRICS, 21 PP 467-490;
TITLE3;
TITLE4 TEST FOR RESIDUAL EFFECTS;
```

```

DATA TWO;
SET ONE;

IF PERIOD=1;          /* PERIOD 2 IS DROPPED IF
                      RESIDUAL EFFECTS
                      ARE PRESENT */

PROC GLM;
  CLASSES TRT SUBJECT;
  MODEL RESPONSE=TRT SUBJECT(TRT);
  TEST H=TRT E=SUBJECT(TRT); /* TEST FOR TREATMENT
                              EFFECTS WHEN RESIDUAL
                              EFFECTS ARE PRESENT */

TITLE4 TEST FOR TREATMENT EFFECTS WHEN RESIDUAL EFFECTS ARE PRESENT;

DATA THREE;
SET ONE;

PROC GLM;
  CLASSES SUBJECT PERIOD TRT;
  MODEL RESPONSE=TRT PERIOD SUBJECT; /* F TEST FOR TREATMENT IS
                                      VALID WHEN RESIDUAL
                                      EFFECTS ARE ABSENT */

TITLE4 TEST FOR TREATMENT EFFECTS WHEN RESIDUAL EFFECTS ARE ABSENT;

/* *****
 * KOCH NONPARAMETRIC APPROACH *
 * TO ANALYSIS OF TWO-PERIOD *
 * CHANGE-OVER DESIGN *
 * *
 * ***** */

DATA FOUR;
SET IN;          /* FORMING LINEAR
                  COMBINATIONS OF
                  THE OBSERVATIONS */

SUM = Y1 + Y2;
DIFF= Y1 - Y2;
IF SEQ=1 THEN XDIFF = DIFF;
IF SEQ=2 THEN XDIFF = Y2 - Y1;

ABSXDIFF=ABS(XDIFF);

IF XDIFF < 0 THEN SIGN = -1;
ELSE SIGN = +1;

```

```

TITLE NONPARAMETRIC ANALYSIS OF TWO-PERIOD CHANGE-OVER DESIGN;
TITLE2 KOCH, GARY G., BIOMETRICS, JUNE 1972, PP 577-584;
TITLE3;
TITLE4;

PROC PRINT;

PROC SORT;
  BY ABSXDIFF;

DATA FIVE;
SET FOUR;

SRANK = SIGN * _N_;

PROC NPARIWAY WILCOXON;
  VAR SUM;
  CLASS SEQ;          /* WILCOXON TEST FOR EQUAL
                      RESIDUAL EFFECTS */

PROC NPARIWAY WILCOXON;
  VAR DIFF;
  CLASS SEQ;

PROC NPARIWAY WILCOXON;
  VAR XDIFF;
  CLASS SEQ;          /* WILCOXON TEST FOR EQUAL
                      DIRECT EFFECTS WHEN
                      RESIDUAL EFFECTS
                      ARE ABSENT */

PROC NPARIWAY WILCOXON;
  VAR Y1;
  CLASS SEQ;          /* WILCOXON TEST FOR EQUAL
                      PERIOD EFFECTS WHEN
                      RESIDUAL EFFECTS
                      ARE ABSENT */

PROC MEANS T PRT;
  VAR SRANK;          /* IMANS SIGN RANK T-TEST
                      FOR DIRECT EFFECTS WHEN
                      RESIDUAL AND PERIOD
                      EFFECTS ARE ABSENT */

TITLE IMANS SIGN RANK T-TEST FOR DIRECT EFFECTS WHEN RESIDUAL;
TITLE2 AND PERIOD EFFECTS ARE ABSENT;

```

```
DATA;
SET FOUR;          /* SETTING UP DATA FOR REPORTING
                    PURPOSES */
```

```
DUMMY=1;
IF SEQ=1 THEN SEQN='G:H';
IF SEQ=2 THEN SEQN='H:G';
```

```
PROC SORTT;
  BY SEQ SUBJECT;
```

```
PROC RANK OUT=NEW;
  VAR SUM DIFF XDIFF;
  RANKS RSUM RDIFF RXDIFF;
```

```
PROC SORTT;
  BY SEQ;
```

```
PROC MEANS SUM NOPRINT;
  VAR RSUM RDIFF RXDIFF;
  BY SEQ;
  OUTPUT OUT=NEW2 SUM=S1 S2 S3 N=N1;
```

```
PROC SORTT;
  BY N1;
```

```
DATA SIX;
SET NEW2;
```

```
DUMMY=1;
```

```
IF _N_=1;
KEEP S1 S2 S3 DUMMY;
```

```
DATA SEVEN;
MERGE NEW SIX;
  BY DUMMY;
```

```
DATA EIGHT;
SET SEVEN END=EOF;
  BY SEQ;
```

```
OPTIONS NODATE LS=132;
```

```
TITLE;
TITLE2;
```

```
FILE PRINT HEADER=H;
```

```
IF FIRST.SEQ THEN DO; PUT /; END;
PUT @3 SEQN @ 013 SUBJECT @ 020 Y1 5.2 @28 Y2 5.2 @36 SUM 5.2
@45 RSUM 4.1 @50 DIFF 5.2 @59 RDIFF 4.1 @66 XDIFF 5.2
@75 RXDIFF 4.1;
```

```
IF EOF THEN DO;
  PUT // @20 'RANK SUM STATISTIC' @44 S1 5.1 @58 S2 5.1 @74
  S3 5.1/;
  PUT @20 'SIGNIFICANCE LEVEL';
  PUT @50
  'NONPARAMETRIC ANALYSIS OF TWO-PERIOD CHANGE-OVER DESIGN';
  PUT 'KOCH, GARY G., BIOMETRICS, JUNE 1972, PP 577-584';
  END;
```

```
RETURN;
```

```
H:
PUT @1 @39 'TABLE I';
PUT @3 @37 'DATA DISPLAY'/;
PUT @25 'RANKS FOR TWO-PERIOD CROSSOVER ANALYSIS';
PUT @12
  @45 'CROSSOVER'/@1 'SEQUENCE SUBJECT DAY 1 DAY 2 SUM'
@43 ' RANK DIFF RANK DIFF RANK';
```