ANALYSIS OF TWO-PERIOD CROSSOVER TRIALS USING SAS

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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 pharmaceutical 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 NPAR1WAY 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.

OPTIONS LS=76;

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

DATA IN;

INPUT SEQ SUBJ & Y1 Y2;

CARDS;
1 C11 1.75 .35
1 C12 1.30 1.65
1 C13 .85 .63
1 C14 .25 1.55
1 C15 .30 .20
2 C21 7.20 .35
2 C22 7.10 1.25
2 C23 .75 .25
2 C24 2.15 .35
2 C25 3.35 1.50

DATA ONE;

SET IN;

IF SEQ=1 THEN TRT='C', RESPONSE=Y1, PERIOD=1, OUTPUT=NO;
IF SEQ=1 THEN TRT='H', RESPONSE=Y2, PERIOD=2, OUTPUT=NO;
IF SEQ=2 THEN TRT='H', RESPONSE=Y1, PERIOD=1, OUTPUT=NO;
IF SEQ=2 THEN TRT='C', RESPONSE=Y2, PERIOD=2, OUTPUT=NO;
DROP Y1 Y2;

PROC PRINT;

PROC GLM;

CLASS TRT SEQ SUBJ;
MODEL RESPONSE=TRT SEQ SUBJ(SEQ);
TEST H=TRT E=SUBJECT(SEQ); /* TEST FOR RESIDUAL EFFECTS */

TITLE GRIZZLE TWO-PERIOD CHANGE-OVER DESIGN;
TITLE2 GRIZZLE, J.E. 1965 BIOMETRICS, 21 FP 447-496;
TITLE1;
TITLE4 TEST FOR RESIDUAL EFFECTS;

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DATA TWO;
  SET ONE;
  IF PERIOD=1; /* PERIOD 2 IS DROPPED IF RESIDUAL EFFECTS ARE PRESENT */
  PROC GLM;
    CLASS TRT SUBJECT;
    MODEL RESPONSE=TRT SUBJECT TRT*SUBJECT;
    TEST H-TRT E-SUBJECT; /* TEST FOR TREATMENT EFFECTS WHEN RESIDUAL EFFECTS ARE PRESENT */
  TITLE1 TEST FOR TREATMENT EFFECTS WHEN RESIDUAL EFFECTS ARE PRESENT;
  DATA THREE;
  SET ONE;
  PROC GLM;
    CLASS SUBJECT PERIOD TRT;
    MODEL RESPONSE=TRT PERIOD SUBJECT; /* TEST FOR TREATMENT IS VALID WHEN RESIDUAL EFFECTS ARE ABSENT */
  TITLE2 TEST FOR TREATMENT EFFECTS WHEN RESIDUAL EFFECTS ARE ABSENT;
  DATA FOUR;
  SET ONE;
  PROC GLM;
    CLASS SUBJECT PERIOD TRT;
    MODEL RESPONSE=TRT PERIOD SUBJECT; /* TEST FOR TREATMENT IS VALID WHEN RESIDUAL EFFECTS ARE ABSENT */
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  DATA FOUR;
  SET ONE;
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    MODEL RESPONSE=TRT PERIOD SUBJECT; /* TEST FOR TREATMENT IS VALID WHEN RESIDUAL EFFECTS ARE ABSENT */
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  DATA FOUR;
  SET ONE;
  DATA THREE;
  SET ONE;
  PROC GLM;
    CLASS SUBJECT PERIOD TRT;
    MODEL RESPONSE=TRT PERIOD SUBJECT; /* TEST FOR TREATMENT IS VALID WHEN RESIDUAL EFFECTS ARE ABSENT */
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}
DATA;
SET FOUR;                 /* SETTING UP DATA FOR REPORTING 
                          PURPOSES */
DUMMY=1;
IF SET=1 THEN SEGM='C-H';
IF SET=2 THEN SEGM='H-C';
PROC SORT;
   BY SEGM SUBJECT;
PROC RANK OUT=NEW;
   VAR SUN DIFF XDIFF;
   RANKS XDIFF RDIFF XDIFF;
PROC SORT;
   BY SEGM;
PROC MEANS SUM MEAN;
   VAR XDIFF RDIFF XDIFF;
   BY SEGM;
   OUTPUT OUT=NEW2 SUM=S1  S2  S3  H=H1;
PROC SORT;
   BY H1;
DATA SIX;
SET NEW2;
DUMMY=1;
IF  H1='1',
   KEEP S1  S2  S3  DUMMY;
DATA SEVEN;
   MEAN NEW SIX;
   BY DUMMY;
DATA EIGHT;
   SET SEVEN END=DEL;
   BY SEGM;
OPTIONS NOTATE LS=132;
TITLE;
TITLE2;
FILE PRINT HEADER=H;
IF FIRST=1 THEN DO; PUT /;
   PUT 83 SEGM $ 815 SUBJECT $ 820 Y1 5.2 Y2 5.2 X1M 5.2
       X2M 4.1 XSM 4.1 XDIFF 5.2 XDIFF 4.1 ADDR 4.1 ADDR 4.1;
IF ELSE THEN DO;
   PUT 820 'RANK SUM STATISTIC' 844 S1 5.1 S2 5.1 S3 3.1;
   PUT 820 'SIGNIFICANCE LEVEL';
   PUT 850 
      'NONPARAMETRIC ANALYSIS OF TWO-PERIOD CHANGE-OVER DESIGN';
   PUT 'Koch, Gary G., Biometrics, June 1972, PP 577-584';
   END;
RETURN;
N:
   PUT 875 'TABLE I';
   PUT 875 'DATA DISPLAY';
   PUT 875 'RANKS FOR TWO-PERIOD Crossover Analysis';
   PUT 812 
      'Crossover/Ph Sequence Subject Day 1 Day 2 Sum' 
      '043 Rank Diff Rank Diff Rank';
RETURN;