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Short Note

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The Use of Sequential Analysis to Improve the Efficiency of Co-twin Control Studies

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The co-twin control model using paired-comparison analysis provides an extremely powerful and cost-effective experimental design for clinical research. This paper suggests the possibility of using sequential analysis to further increase the efficiency and specificity of cotwin control studies.

Key words: *Co-twin control studies, Sequential analysis, Experimental design, Paired comparisons, Methodology, Efficiency*

The costs and risks of human experimentation often severely limit the number of experimental subjects that it is possible to study. The co-twin control model using paired-comparison analysis has been shown to be an extremely efficient design often requiring a small fraction of the number of unrelated experimental subjects needed for a completely randomized design [2]. It is possible to increase the average efficiency of cotwin control studies through the use of sequential analysis.

The method of sequential analysis was developed in the early 1940s by the late Dr. A. Wald of Columbia University [5]. The potential of this experimental method was deemed so great for quality control in defense-related industries that it was classified as a military secret during World War II.

In sequential analysis, data are collected in discrete units (eg, a twin pair randomly assigned to two treatments) and the data are analyzed after each unit is collected. This method allows termination of the experiment after one treatment is shown to be significantly superior or when there is little possibility of rejecting the null hypothesis that there is no difference between the treatments. This allows an increased economy without loss of precision and is extremely valuable not only to minimize the cost of experiments, but also to minimize exposure of subjects to experimental risks.

There are numerous publications reviewing sequential analysis in detail, perhaps the most complete for human applications being "Sequential Medical Trials" by P. Armitage [1]. Therefore, only a single example situation will be given.

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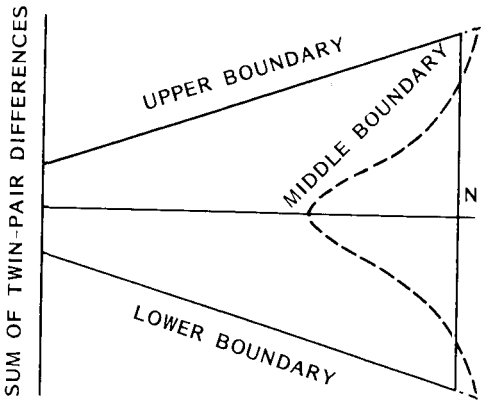

Figure. A sequential analysis model for twin studies using a two-tailed test where an estimate of within-twin-pair variability is available.

N= estimated maximum number of twin pairs needed for the chosen alternative hypothesis.

To use sequential analysis, the investigator should estimate the maximum number (N) of twin pairs needed for an experiment [2] and then choose the most appropriate sequential analysis plan. The investigator first estimates the number of twin pairs needed to detect a chosen difference between the two treatments with, say, 90% certainty at the specified significance level. The Figure, after Schneiderman and Armitage [3], graphically displays a sequential analysis model to be used when an estimate of within-twin pair variability is available for a two-tailed test where neither treatment is prejudged to result in a higher mean. For situations where an estimate of variability is unknown or a one-tailed test is appropriate, see Armitage [1].

The investigator is now ready to begin data collection and plots the cumulative sum of the twin-pair differences (twin on treatment A minus twin on treatment B). The upper and lower boundaries are drawn to correspond to a desired alpha level (generally 0.05 or 0.01) of the test.

If the cumulative sum of twin differences crosses the upper boundary, then the experiment rejects the null hypothesis and finds that treatment A causes a significantly higher mean value for the trait being studied than treatment B. The reverse is true if the cumulative sum crosses the lower boundary.

Inclusion of a middle boundary makes the design a "closed sequential test." The middle wedge-shaped boundary used here is after Schneiderman and Armitage [3, 4] and gives a very conservative basis for the statement that when the middle boundary is crossed, the chances of ultimately rejecting the null hypothesis if the experiment were continued is extremely small. The chance of crossing the upper or lower boundaries after the wedge has been reached is 0.01 times alpha.

We have begun using the sequential analysis procedure in twin studies of heart disease risk factors but are not aware of any previous twin studies using this experimental design. We would appreciate correspondence from other twin researchers who have had experience with sequential analysis and would like to draw it to the attention of those doing, or planning to do, cotwin control studies.

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