

Multivariate Extensions of McNemar's Test for Drug Safety Evaluations

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SUMMARY. The analysis of adverse events from clinical trials is one of the most important stages in the development of pharmaceutical products, but neglected in terms of the use of formal statistical methods. This article considers global tests of differences between paired vectors of binomial probabilities, based on safety data from two dependent multivariate binary samples. Such data commonly arises from cross-over or longitudinal studies, in which a multivariate binary response (e.g., several adverse events) is measured at several occasions. A difference between treatments is defined as either an inhomogeneity in the marginal distributions or asymmetry in the joint distribution of the multivariate response. For detecting the first type of difference, we propose a multivariate extension of McNemar's test and show that it is a generalized score test under a GEE approach. Univariate features such as the relationship between the Wald and score test and the dropout of pairs with the same response carry over to the multivariate case and the test does not depend on the working correlation assumption among the components of the multivariate response. We apply the test to a safety trial for a drug, in which two doses of a drug are evaluated by comparing multiple responses by the same subject to each of them. For sparse data, such as occurs when the number of variables is large or the proportions are close to zero, the test is best implemented using a permutation distribution.

Key words: Adverse events; Drug safety; Generalized score test, Marginal homogeneity; Matched pairs; Multiple binary data; Toxicity; Quality of life.