Abstract

The guideline ICH E14 "The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs" which reached Step 4 on 12-May-2005, contains some statistical challenges. The confidence interval for the endpoint of the "Thorough QT/QTc Study", i.e. a confidence interval for the maximum (over a number of points in time) of the mean (over subjects) difference between the test drug and a placebo control is the most prominent of these problems, since a solution is currently not known. Only by replacing this problem by a multiple test problem is it amenable to well known methods. However, even if treated in this way, the paradoxical situation remains that the power of the test is reduced if measurements are added at additional timepoints. Other points of statistical interest include the choice of a baseline and the selection of a method to correct the QT interval for heart rate. These and other problems need to be investigated if one attempts to optimise the Thorough QT/QTc Study with respect to small sample size without sacrificing power.