

PHASE III DESIGN - SEQUENTIAL METHOD

The study was designed as a double-blind, randomized comparison of single doses of *Test* and *Reference* treatments to conclude on the equivalence or the superiority of one of the treatments as measured by the clinical outcome variable: "*need for repeated intervention*".

CASE STUDY: Objectives - Statistical Considerations

A variable sample-size sequential design was employed in this study which facilitated the simultaneous evaluation of the three hypotheses tested. The selected design (double triangular method developed by Whitehead (1)) requires the enrolment of patients and the evaluation of their responses sequentially, until definitive evidence accumulates to declare the superiority of one treatment to the other or their equivalence. This design also offered the potential benefit of reducing the sample size (as opposed to that of a fixed sample design).

For the purposes of this study, the primary design variable was the incidence of "*repeated intervention*". Based on this parameter, the study was designed to detect the odds of "*repeated intervention*" 3-times higher or lower between the two treatment groups, regardless of the actual values of the incidence rates. The following hypotheses were tested :

H_0 : The incidence of "*repeated intervention*" is equivalent in the two treatment groups.

H_1 : The incidence of "*repeated intervention*" in the Test treatment group is significantly lower than in the Reference treatment group.

H_2 : The incidence of "*repeated intervention*" in the Test treatment group is significantly higher than in the Reference treatment group.

At regular intervals, an interim analysis was performed on accumulated data to determine if any of these hypotheses could be proven. If the evidence supported one of these hypotheses, further enrolment of patients was discontinued and the study was terminated.

METHOD

Interim analyses of the efficacy response were done at regular intervals for the duration of the study to determine if sufficient evidence had accumulated to support any of the hypotheses described above.

The measure of evidence for *treatment difference* is described by the parameter Z . The amount of information available at any point in the trial is measured by the parameter V , where V is proportional to sample size. Based on these parameters, a double triangular region for defining the boundaries for the continuation or termination of the trial is formed as follows (shown in Figure 1):

$$\left. \begin{array}{l} Z = a + \mu V \\ Z = -a + \lambda V \end{array} \right\} \text{for the upper region}$$

$$\left. \begin{array}{l} Z = a - \mu V \\ Z = -a - \lambda V \end{array} \right\} \text{for the lower region}$$

where

$$\lambda = 0.75 \theta_R, \mu = 0.25 \theta_R, a = \frac{2}{\theta_R} \log \left(\frac{1}{2\alpha} \right)$$

θ_R is the reference improvement.

α is the significance level, representing both type I and type II error rates.

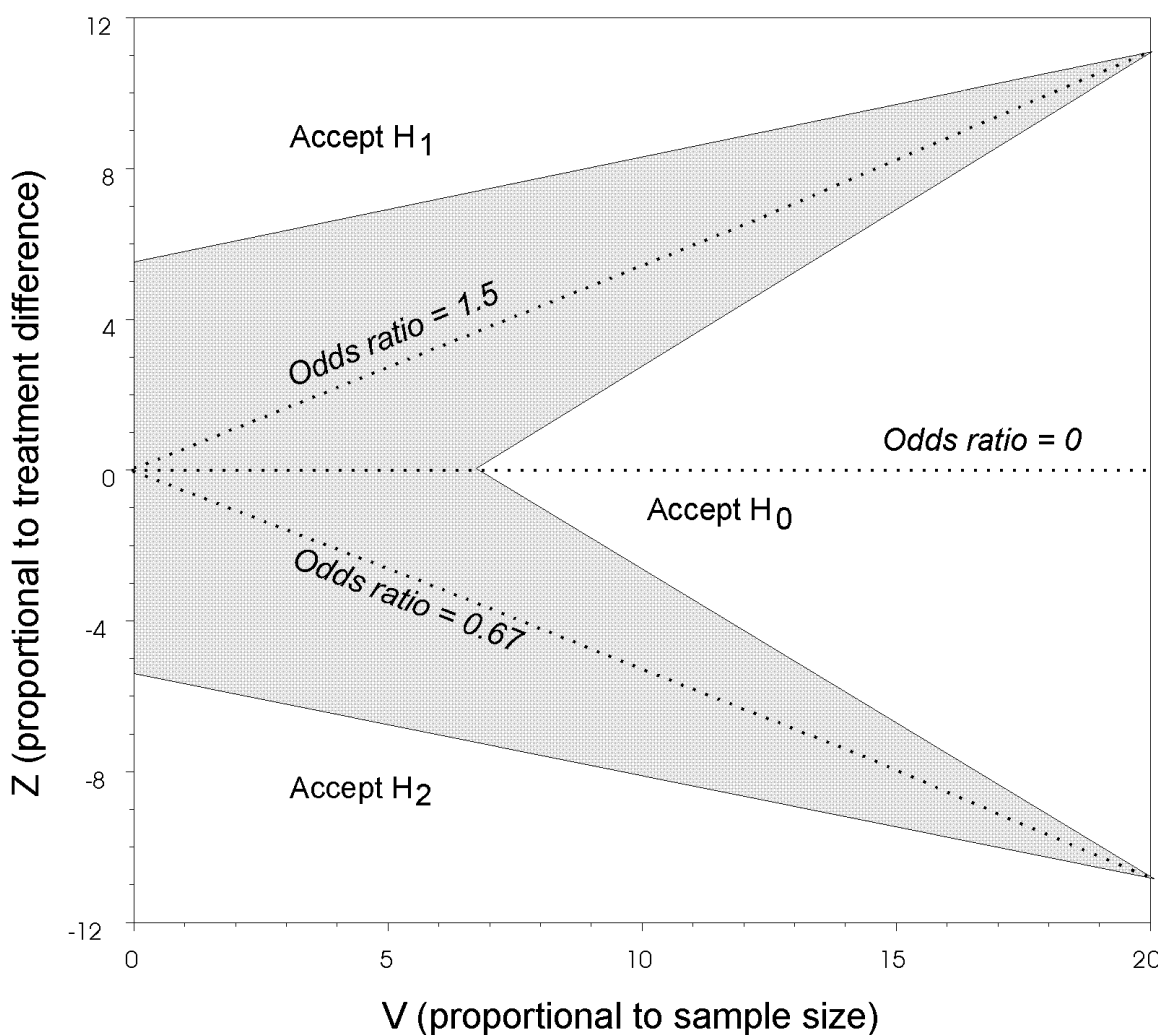
This sequential trial was designed to detect the odds of "repeated intervention" 3-times higher or lower between the two treatment groups.

At each interim analysis, estimates of Z and V are computed from accumulated information. These estimates are calculated as follows:

$$Z^* = \frac{n S_m - m T_n}{m + n}$$

$$V^* = \frac{m n (S_m + T_n) \{ (m - S_m) + (n - T_n) \}}{(m + n)^3}$$

The values of m and S_m are the observed number of patients and number of "Repeated interventions" at the current stage of the trial in the Test treatment group, respectively. The values of n and T_n are similarly defined for the Reference treatment group.



The values of Z^* and V^* for each interim analysis are then plotted and overlaid on the double triangular region. A path representing the progress of the study is obtained by connecting the points by a straight line. Graphically, the decision rules for continuing or terminating the study can be defined as follows:

- If the path crosses the upper boundary of the triangular region, terminate the study and declare "*Reference treatment has a lower incidence compared to Test treatment*".
- If the path crosses the lower boundary of the triangular region, terminate the study and declare "*Test treatment has a lower incidence compared to Reference treatment*".
- If the path continues along the horizontal $Z = 0$ line, and crosses beyond the triangular wedge, terminate the study and declare no significant treatment difference.
- If none of the above statements are valid, continue the study.

Assessing Treatment Difference

Once the trial has terminated with acceptance of one of the hypotheses, the *treatment difference* and *associated significance level* are computed. The critical value associated with the significance level is represented by the parameter C and computed as $C = \theta_R^2 V^*$, where V^* is the final estimate of V at study termination. The p-value associated with C is obtained from tables in Whitehead (1). Since the trial was designed as a two-sided alternative, the actual significance level is twice the p-value from the table.

For values of C , the tables provide upper, median and lower values which can be used to estimate the *treatment difference* and produce associated 95% confidence limits.

These values are represented by k_L , k_M and k_U . For the double triangular test, if the study terminates on the upper boundary, then an estimate of the treatment difference is given by the median estimate of $\theta_M = k_U * \theta_R$, with lower and upper 95% confidence limits of $\theta_L = k_L * \theta_R$ and $\theta_U = k_U * \theta_R$, respectively. Alternatively, if the study terminates on the lower boundary, then, due to symmetry, the values from the table are interpreted as negative and the treatment difference with 95% confidence limits are calculated as before.

Adjustments for Overrunning

In situations where the study terminates, but information continues to accumulate, the estimate of *treatment difference* and the *associated significance level* need to be adjusted. This additional information is represented by new estimates of Z and V , denoted by Z^{**} and V^{**} . An adjusted value of V is computed by combining the estimates at study termination with those obtained from overrunning as:

$$V^0 = \frac{-a - R_{obs} V_e}{R_{obs} + \mu}$$

where a and μ were defined previously for the triangular region, $V_e = V^{**} - V^*$ and $R_{obs} = \frac{Z^{**}}{V^{**}}$.

The adjusted value of C is now $C^0 = \theta_R^2 V^0$. This value is then used in the tables to obtain the appropriate significance level.

The *adjusted treatment difference* is calculated as:

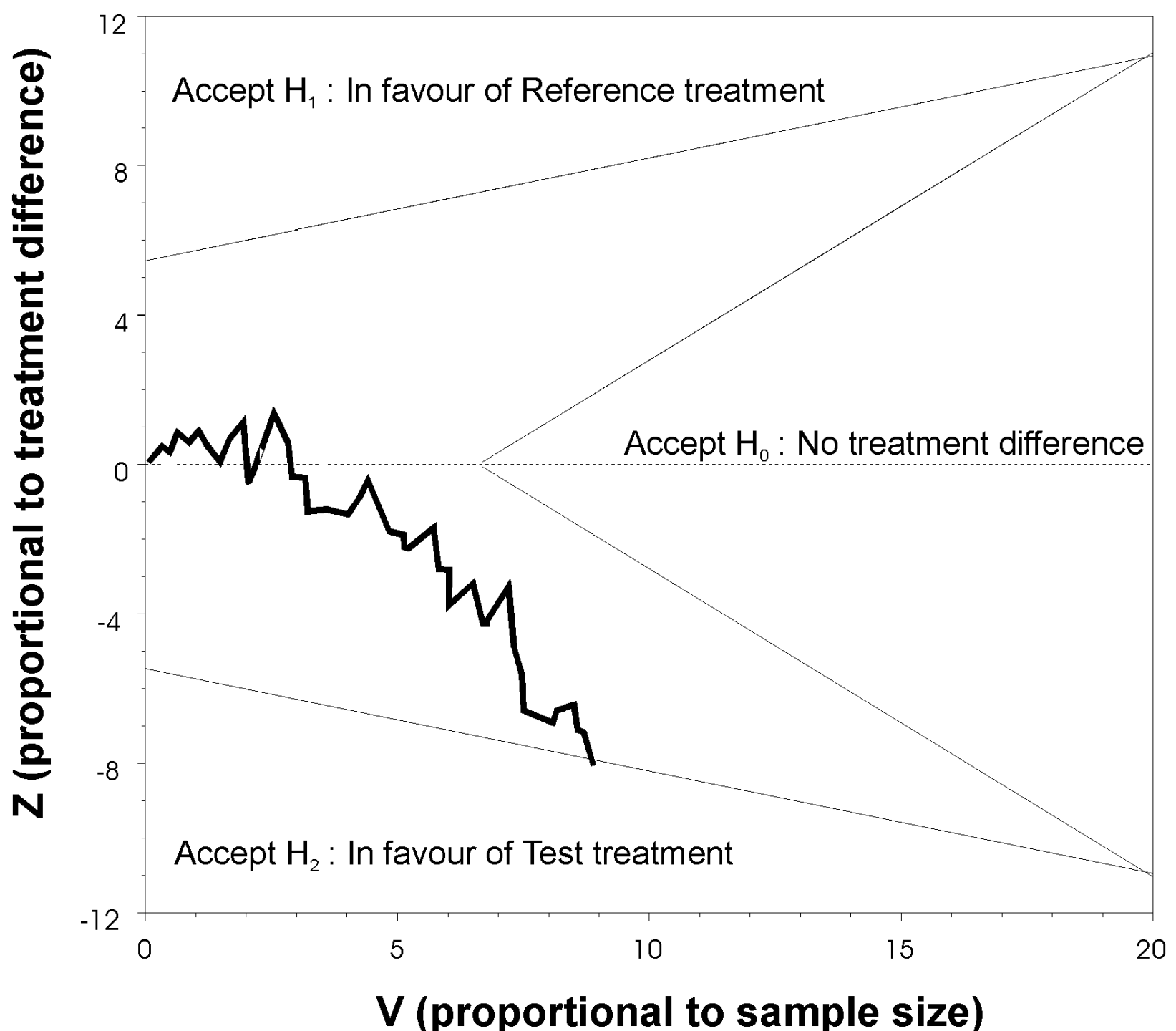
$$\theta_M^0 = \frac{\theta_M V^* + (Z^{**} - Z^*)}{V^{**}}$$

where θ_M is the un-adjusted estimate of *treatment difference* obtained at study termination.

RESULTS

Over the 22-month span of the study, 317 and 318 patients were evaluated for efficacy in the *Test* and *Reference* treatment groups, respectively. Of the 47 patients who required "*repeated intervention*", 15 (5%) were in the *Test treatment* group and 32 patients (10%) were in the *Reference* treatment group.

The figure below describes the progress of the sequential trial for the duration of the study. The path indicates that the trial terminated at the lower boundary of the triangular region with the declaration that "*Test treatment had a significantly lower incidence of repeated intervention compared to Reference treatment*".



The sequential trial detected an incidence of "*repeated intervention*" 2.03 times lower for Test treatment vs Reference treatment, at a significance level of $p = 0.0312$ (the 95% confidence limits of the odds ratio were 1.1 and 2.8).

Adjustment for over-running : Following study termination, information on an additional two "*repeated interventions*" accumulated. The adjusted treatment estimate was $\theta_M^0 = -0.6813$ yielding an adjusted odds ratio of 1.98. The significance level adjusted for this data was $p = 0.030$.

REFERENCES

1. Whitehead, J. The design and analysis of sequential clinical trials. Ellis Horwood Limited. 1983.
2. Whitehead, J. Supplementary analysis at the conclusion of a sequential clinical trial. Biometrics 1986; 42:461-471.