Addendum to
“Gatekeeping tests in dose-response clinical trials based on the Dunnett test”

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Summary
This note serves as an addendum to Dmitrienko et al. (2006). The original paper introduced a parallel gatekeeping procedure based on the Dunnett test and described its applications to the analysis of dose-response clinical trials with multiple endpoints. The note focuses on the topics that were not adequately addressed in the original paper, including a detailed description of the algorithms for computing critical values and multiplicity adjusted $p$-values for this procedure.

1 Introduction
Dmitrienko et al. (2006) developed a parallel gatekeeping procedure based on the Dunnett test (Dunnett, 1955) aimed at addressing multiplicity problems arising in dose-response trials with multiple endpoints. The original paper did not adequately address two important aspects of this procedures:

- Calculation of critical values for individual test statistics (the high-level description given in Appendix A of Dmitrienko et al. (2006) did not provide all details of the algorithm).
- Calculation of adjusted $p$-values (no algorithm was provided in Dmitrienko et al. (2006)).
This note provides a detailed description of the following two algorithms: a general algorithm for computing critical values for the Dunnett-based parallel gatekeeping procedure is discussed in Section 2 and a general algorithm for computing adjusted \( p \)-values is described in Section 3. In addition, Section 4 describes a typographical error in Table II of Dmitrienko et al. (2006).

2 Computation of critical values

This section gives a detailed description of the computation of critical values for the Dunnett-based parallel gatekeeping procedure in the general case of \( s \) endpoints (a brief description of this algorithm can be found in Dmitrienko et al., 2006, Appendix A).

As in Dmitrienko et al. (2006, Section 2), consider a dose-response study designed to compare \( m \) doses of an experimental drug to a control (placebo or an active control). The efficacy of the experimental drug is assessed using a primary endpoint and \( s - 1 \) ordered secondary endpoints. Using the notation introduced in Dmitrienko et al. (2006), let \( \mu_{ij} \) denote the mean response for the \( i \)th endpoint in the \( j \)th dose group \((i = 1, \ldots, s, j = 0, \ldots, m)\). The null hypotheses of interest are given by \( H_{ij} : \mu_{i0} = \mu_{ij} \). The null hypotheses are grouped into \( s \) families to reflect the ordering of the endpoints:

\[
F_i = \{H_{i1}, \ldots, H_{im}\}.
\]

The Dunnett-based parallel gatekeeping procedure is constructed using the principle of closed testing (Marcus et al., 1976). Consider all possible nonempty intersections of the \( ms \) null hypotheses and define a test for each intersection hypothesis. Select an intersection hypothesis \( H \) and let \( \delta_{ij}(H) = 1 \) if \( H \) contains \( H_{ij} \) and 0 otherwise. Let \( t_{ij} \) be the \( t \) statistic for testing \( H_{ij}, i = 1, \ldots, s, j = 1, \ldots, m \). Further, let \( T_{ij}, i = 1, \ldots, s, j = 1, \ldots, m \), denote a set of random variables whose joint distribution is identical to the joint distribution of the \( t_{ij} \)'s under the global null hypothesis. Finally, \( \alpha \) will denote the familywise error rate for the one-sided testing problem, e.g., \( \alpha = 0.025 \).

The decision rule for \( H \) depends, in general, on \( s \) critical values (one critical value for each family of null hypotheses) denoted by \( c_1(H), \ldots, c_s(H) \). The critical values are derived in a sequential manner, i.e., \( c_1(H) \) is computed first, \( c_2(H) \) depends on \( c_1(H) \), \( c_3(H) \) depends on \( c_1(H) \) and \( c_2(H) \), etc. The calculation is performed using the following algorithm.

**Step 1.** Let \( r_1(H) \) denote the number of null hypotheses in Family \( F_1 \) contained in
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\[ H, \text{ i.e.,} \]
\[ r_1(H) = \sum_{j=1}^{m} \delta_{1j}(H). \]

Consider the following two cases:

- If \( r_1(H) = 0 \), set the critical value for the \( t \) statistics associated with \( F_1 \), i.e., \( c_1(H) \), to \( \infty \) (these statistics are excluded from the decision rule for \( H \)) and go to the next step.

- If \( r_1(H) > 0 \), one needs to compute a critical value for the \( t \) statistics associated with \( F_1 \). The critical value \( c_1(H) \) is obtained from
  \[ P(R_1 > c_1(H)) = \alpha, \]
  where \( R_1 = \max(T_{11}, \ldots, T_{1m}) \). It is worth noting that, unlike the other critical values, \( c_1(H) \) does not actually depend on \( H \). If \( r_1(H) < m \), go to the next step and stop otherwise. If the algorithm stops at this point, the critical values for the \( t \) statistics corresponding to the null hypotheses in Families \( F_2, \ldots, F_s \) are set to \( \infty \) (in other words, the remaining \( t \) statistics are not included in the decision rule for \( H \)).

**Step 2.** Let \( r_2(H) \) denote the number of testable null hypotheses in Family \( F_2 \) contained in \( H \), i.e., null hypotheses in \( F_2 \) that meet the logical restrictions defined in Section 1 (a secondary dose-control comparison is performed only if the corresponding primary dose-control comparison is significant). Using mathematical notation,
\[ r_2(H) = \sum_{j=1}^{m} \delta_{2j}(H)(1 - \delta_{1j}(H)). \]

Consider the following two cases:

- If \( r_2(H) = 0 \), set the critical value for the \( t \) statistics associated with \( F_2 \) to \( \infty \) and go to the next step.

- If \( r_2(H) > 0 \), compute a critical value for the \( t \) statistics associated with the testable null hypotheses in \( F_2 \) contained in \( H \). The critical value \( c_2(H) \) is found from
  \[ P(R_1^* > c_1(H) \text{ or } R_2^* > c_2(H)) = \alpha, \]
  where
  \[ R_1^* = \max(T_{11}\delta_{11}(H), \ldots, T_{1m}\delta_{1m}(H)), \]
  \[ R_2^* = \max(T_{21}(1 - \delta_{11}(H))\delta_{21}(H), \ldots, T_{2m}(1 - \delta_{1m}(H))\delta_{2m}(H)). \]
Note first that $R_1^*$ depends only on the $t$ statistics associated with the null hypotheses in $\mathcal{F}_1$ that are contained in $H$. Since not all null hypotheses in $\mathcal{F}_1$ are contained in $H$ ($r_1(H) < m$), one can carry over the remaining fraction of the Type I error rate to $\mathcal{F}_2$. In mathematical terms, this means that the probability of $R_1^* > c_1(H)$ is less than $\alpha$ and thus Equation (1) has a positive solution. Secondly, in order to account for the logical restrictions in Family $\mathcal{F}_2$, the definition of $R_2^*$ includes the indicators $\delta_{11}(H), \ldots, \delta_{1m}(H)$. If $H$ contains the primary null hypothesis for the $j$th dose ($H_{1j}$) and secondary null hypothesis for the same dose ($H_{2j}$), then $H_{2j}$ will be given a zero weight to ensure that it cannot be rejected unless $H_{1j}$ is rejected. As before, go to the next step if $r_2(H) < m$ and stop otherwise.

**Steps** $k = 3, \ldots, s - 1$. The same principle is applied to define a critical value for the $t$ statistics associated with $\mathcal{F}_k$. Let $r_k(H)$ denote the number of testable null hypotheses in Family $\mathcal{F}_k$ contained in $H$, i.e.,

$$r_k(H) = \sum_{j=1}^{m} \delta_{kj}(H)(1 - \delta_{1j}(H)),$$

and consider the following two cases:

- If $r_k(H) = 0$, let $c_k(H) = \infty$ and go to the next step.
- If $r_k(H) > 0$, the critical value is found from

$$P(R_1^* > c_1(H) \text{ or } R_2^* > c_2(H) \text{ or } \ldots \text{ or } R_k^* > c_k(H)) = \alpha,$$

where

$$R_k^* = \max(T_{k1}(1 - \delta_{11}(H))\delta_{k1}(H), \ldots, T_{km}(1 - \delta_{1m}(H))\delta_{km}(H)).$$

Go to the next step if $r_k(H) < m$ and stop otherwise.

**Step s.** Let $r_s(H)$ denote the number of testable null hypotheses in Family $\mathcal{F}_s$ contained in $H$, i.e.,

$$r_s(H) = \sum_{j=1}^{m} \delta_{sj}(H)(1 - \delta_{1j}(H)),$$

and consider the following two cases:

- If $r_s(H) = 0$, let $c_s(H) = \infty$. 

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• If \( r_s(H) > 0 \), the critical value is found from

\[ P(R^*_1 > c_1 \text{ or } R^*_2 > c_2(H) \text{ or } \ldots \text{ or } R^*_s > c_s(H)) = \alpha, \]

where

\[ R^*_s = \max(T_{s1}(1 - \delta_{11}(H)), \ldots, T_{sm}(1 - \delta_{1m}(H))). \]

An important difference between \( R^*_s \) and the statistics defined at Steps 1 through \( s-1 \) is that \( R^*_s \) does not depend on the indicators \( \delta_{s1}(H), \ldots, \delta_{sm}(H) \). These indicators were included in the definition of \( R^*_1, \ldots, R^*_{s-1} \) to “save” a certain fraction of the Type I error rate for the next family. Since \( F_s \) is the last family, all of the remaining Type I error rate can be “spent” at Step \( s \). The underlying idea is conceptually very similar to the algorithm used in the Bonferroni-based parallel gatekeeping procedure (Dmitrienko et al., 2005, Section 2.7.3).

As mentioned in Dmitrienko et al. (2006), the computation of the critical values in this algorithm can be performed using the method for computing multivariate \( t \) probabilities (Genz and Bretz, 2002).

Now that the critical values for all \( t \) statistics associated with the null hypotheses contained in \( H \) are defined, the intersection hypothesis \( H \) is rejected if at least one of the following conditions is met

- \( \max(t_{11}\delta_{11}(H), \ldots, t_{1m}\delta_{1m}(H)) > c_1(H) \) or
- \( \max(t_{k1}(1 - \delta_{11}(H))\delta_{k1}(H), \ldots, t_{km}(1 - \delta_{1m}(H))\delta_{km}(H)) > c_k(H) \)

for any \( k = 2, \ldots, s \).

Otherwise, \( H \) is accepted. The Dunnett-based gatekeeping procedure rejects the null hypothesis \( H_{ij} \) if all intersection hypotheses containing this null hypothesis are rejected.

### 3 Computation of adjusted \( p \)-values

This section describes the derivation of adjusted \( p \)-values for the null hypotheses in Families \( F_2, \ldots, F_s \) (note that the hypothesis testing problem is formulated as a one-sided problem and all \( p \)-values discussed in this section are one-sided). Using the general definition of adjusted \( p \)-values given in Westfall and Young (1993), the adjusted \( p \)-value for the null hypothesis \( H_{ij} \) is the smallest significance level for which one would reject the null hypothesis using the Dunnett-based gatekeeping procedure. Since this procedure is in fact a closed testing procedure, the following simplified
definition can be used: The adjusted \( p \)-value for the null hypothesis \( H_{ij} \) equals the maximum over the \( p \)-values associated with the intersection hypotheses containing \( H_{ij} \). The null hypothesis \( H_{ij} \) is rejected if the adjusted \( p \)-value is no greater than \( \alpha \).

It follows from the definition given above that, in order to derive adjusted \( p \)-values for the null hypotheses in Families \( \mathcal{F}_2, \ldots, \mathcal{F}_s \), one first needs to compute a \( p \)-value for each intersection hypothesis. Consider an arbitrary intersection hypothesis \( H \). It was shown in Section 2 that the decision rule for \( H \) is as follows: Reject \( H \) if

\[
t_1 > c_1(\alpha) \text{ or } t_2 > c_2(\alpha) \text{ or } \ldots \text{ or } t_u > c_u(\alpha)
\]

and accept otherwise. Here \( t_1, \ldots, t_u \) are the test statistics associated with the null hypotheses contained in \( H \) and \( c_1(\alpha), \ldots, c_u(\alpha) \) are the corresponding critical values (note that the critical values and \( u \) depend on the selected intersection hypothesis \( H \)). The critical values are decreasing functions of the familywise error rate \( \alpha \). The \( p \)-value associated with \( H \) is defined as the smallest value of \( \alpha \) for which at least one inequality in (2) holds and can be computed using the algorithm for computing multivariate \( t \) probabilities developed by Genz and Bretz (2002).

**Example**

To illustrate the process of computing multiplicity adjusted \( p \)-values for the Dunnett-based gatekeeping procedure, consider the clinical trial with two doses of an experimental drug tested versus a placebo and two endpoints (Dmitrienko et al., 2006, Section 3). The four null hypotheses arising in this clinical trial are grouped into two families:

- \( \mathcal{F}_1 = \{H_{11}, H_{12}\} \) (low and high doses compared to placebo with respect to the primary endpoint),
- \( \mathcal{F}_2 = \{H_{21}, H_{22}\} \) (low and high doses compared to placebo with respect to the secondary endpoint).

Further, \( t_{11}, t_{12}, t_{21} \) and \( t_{22} \) denote the \( t \) statistics for testing \( H_{11}, H_{12}, H_{21} \) and \( H_{22} \). The decision matrix for the Dunnett-based gatekeeping procedure is displayed in Table 1 (it is identical to Table I in Dmitrienko et al., 2006). The decision matrix defines a decision rule for each of the 15 intersection hypotheses in this multiple testing problem.

Assume, for the sake of simplicity, that the treatment groups in this clinical trial are balanced with \( n \) patients per group and let \( n = 30 \). Also, let \( t_{11} = 2.1, t_{12} = 2.7, t_{21} = 2.9, t_{22} = 2.4 \) and consider the computation of \( p \)-values for individual intersection hypotheses in the following three cases.
Case 1

The process of computing $p$-values for the tests based on a critical value derived from a univariate $t$ distribution (that is, the tests for $H_{0010}^*$ and $H_{0001}^*$) is very straightforward. For example, the $p$-value for $H_{0010}^*$ is

$$p = 1 - F_t(t_{21}),$$

where $F_t(x)$ is the cumulative distribution function of the $t$ distribution with $2(n-1)$ df. Therefore, using the CDF function in SAS,

```sas
p=1-cdf("T",2.9,2*(30-1));
```

and thus the $p$-value for $H_{0010}^*$, denoted by $p_{0010}$, is 0.0026.

Case 2

Now consider the tests in which the critical value is derived from the Dunnett distribution (the tests for $H_{1111}^*$, $H_{1110}^*$, $H_{1101}^*$, $H_{1100}^*$, $H_{1010}^*$, $H_{1001}^*$, $H_{0101}^*$, $H_{0100}^*$, $H_{0011}^*$). The $p$-values for these intersection hypotheses are computed using the Dunnett distribution. Consider, for example, $H_{1111}^*$. The $p$-value for this intersection hypothesis is given by

$$p = 1 - F_D(\max(t_{11}, t_{12})),
$$

where $F_D(x)$ is the cumulative distribution function of the Dunnett distribution with 2 and $3(n-1)$ df. Since $n = 30$, $t_{11} = 2.1$ and $t_{12} = 2.7$, the following SAS code can be used to compute this $p$-value:

```sas
p=1-probmc("DUNNETT1",2.7,.,3*(30-1),2);
```

It is easy to show that $p_{1111} = 0.0079$.

Case 3

Lastly, the computation of $p$-values for the remaining intersection hypotheses ($H_{1011}^*$, $H_{1001}^*$, $H_{0111}^*$, $H_{0110}^*$) is more challenging because the associated decision rule involves two critical values. The first critical value ($c_1$) is computed from the Dunnett distribution and the other one ($c_2$) is computed from a bivariate $t$ distribution that depends on the correlation between the two endpoints. In order to find the $p$-values for the four intersection hypotheses, one first needs to compute the values of $c_1$ and $c_2$ as a function of $\alpha$ ($0 \leq \alpha \leq 1$) for an appropriate value of the correlation coefficient $\rho$ (for example, its sample estimate). This calculation relies on the method proposed by Genz and Bretz (2002). The $p$-value for an intersection hypothesis is computed using the critical value functions as the lowest $\alpha$ level at which the hypothesis is rejected.
For example, the $p$-value for $H_{1011}^*$ is defined as the smallest value of $\alpha$ for which $t_{11} > c_1(\alpha)$ or $t_{22} > c_2(\alpha)$. Figure 1 depicts the relationship between the critical values $c_1$ (solid curve) and $c_2$ (dashed curve) and $\alpha$ when $\rho = 0.5$. The test statistics, $t_{11} = 2.1$ and $t_{22} = 2.4$, are represented by the dotted horizontal lines. The $p$-value for the intersection hypothesis is the value of $\alpha$ for which $t_{22} = c_2(\alpha)$ ($p = 0.0190$).

Figure 1. Plot of the critical values, $c_1$ (solid curve) and $c_2$ (dashed curve), as a function of $\alpha$ (correlation coefficient $\rho = 0.5$). The test statistics, $t_{11} = 2.1$ and $t_{22} = 2.4$, are represented by the dotted horizontal lines.

Calculation of adjusted $p$-values for the primary and secondary dose-placebo comparisons

The $p$-values for the 15 intersection hypotheses are displayed in Table 2. These $p$-values were computed for three values of the correlation coefficient ($\rho = 0.3$, 0.4 and 0.5). The calculations were performed using two SAS programs that can be downloaded from the multXpert web site:

Combining the \( p \)-value for the 15 intersection hypotheses shown in Table 2, it is easy to derive the adjusted \( p \)-values for the null hypotheses corresponding to the primary and secondary dose-placebo comparisons using the rule. The adjusted \( p \)-values for three values of the correlation coefficient \((\rho = 0.3, 0.4 \text{ and } 0.5)\) are displayed in Table 3. A null hypothesis is rejected if its adjusted \( p \)-value is less that the pre-specified Type I error rate (one-sided \( \alpha = 0.025 \)). Thus the Dunnett-based parallel gatekeeping procedure rejects one null hypothesis in Family \( \mathcal{F}_1 (H_{12}) \) and one null hypothesis in Family \( \mathcal{F}_2 (H_{22}) \). Note that the test for the other null hypothesis in Family \( \mathcal{F}_2 \) is highly significant \((t_{21} = 2.9)\) but this hypothesis cannot be rejected due to the logical restrictions imposed in this study.

It is worth noting that the adjusted \( p \)-values are virtually independent of the correlation coefficient. The gatekeeping procedure becomes only slightly more conservative (less powerful) with decreasing \( \rho \). If the sample estimate of \( \rho \) is considered unreliable, one can replace it with the lower 95% confidence limit for the correlation coefficient to obtain a more conservative multiplicity adjustment.

4 Typographical error

The critical value \( c_3 \) in Table II in Dmitrienko et al. (2006) was computed from a univariate \( t \) distribution with 87 df and the correct number of degrees of freedom for this critical value is \( 2(n - 1) = 2 \times 29 = 58 \). The correct value of \( c_3 \) is 2.002 (see Table 4).

5 References


Table 1. Decision matrix for a clinical trial with two dose-placebo comparisons and two endpoints ($m = 2$, $s = 2$).

<table>
<thead>
<tr>
<th>Intersection hypothesis</th>
<th>Rejection rule</th>
</tr>
</thead>
<tbody>
<tr>
<td>$H_{1111}^*$</td>
<td>$t_{11} &gt; c_1$ or $t_{12} &gt; c_1$</td>
</tr>
<tr>
<td>$H_{1110}^*$</td>
<td>$t_{11} &gt; c_1$ or $t_{12} &gt; c_1$</td>
</tr>
<tr>
<td>$H_{1101}^*$</td>
<td>$t_{11} &gt; c_1$ or $t_{12} &gt; c_1$</td>
</tr>
<tr>
<td>$H_{1100}^*$</td>
<td>$t_{11} &gt; c_1$ or $t_{12} &gt; c_1$</td>
</tr>
<tr>
<td>$H_{1011}^*$</td>
<td>$t_{11} &gt; c_1$ or $t_{22} &gt; c_2$</td>
</tr>
<tr>
<td>$H_{1010}^*$</td>
<td>$t_{11} &gt; c_1$</td>
</tr>
<tr>
<td>$H_{1001}^*$</td>
<td>$t_{11} &gt; c_1$ or $t_{22} &gt; c_2$</td>
</tr>
<tr>
<td>$H_{1000}^*$</td>
<td>$t_{11} &gt; c_1$</td>
</tr>
<tr>
<td>$H_{0111}^*$</td>
<td>$t_{12} &gt; c_1$ or $t_{21} &gt; c_2$</td>
</tr>
<tr>
<td>$H_{0110}^*$</td>
<td>$t_{12} &gt; c_1$ or $t_{21} &gt; c_2$</td>
</tr>
<tr>
<td>$H_{0101}^*$</td>
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</tr>
<tr>
<td>$H_{0100}^*$</td>
<td>$t_{12} &gt; c_1$</td>
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<td>$H_{0011}^*$</td>
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<td>$H_{0001}^*$</td>
<td>$t_{22} &gt; c_3$</td>
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</table>
Table 2. *P*-values for the intersection hypotheses in the clinical trial with two dose-placebo comparisons and two endpoints (correlation coefficient, $\rho = 0.3$, 0.4 and 0.5). The test statistics are given by $t_{11} = 2.1$, $t_{12} = 2.7$, $t_{21} = 2.9$ and $t_{22} = 2.4$.

<table>
<thead>
<tr>
<th>Intersection hypothesis</th>
<th>$p$-value</th>
<th>$\rho = 0.3$</th>
<th>$\rho = 0.4$</th>
<th>$\rho = 0.5$</th>
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</thead>
<tbody>
<tr>
<td>$H^*_{1111}$</td>
<td></td>
<td>0.0079</td>
<td>0.0079</td>
<td>0.0079</td>
</tr>
<tr>
<td>$H^*_{1110}$</td>
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<td>0.0079</td>
<td>0.0079</td>
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<tr>
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<tr>
<td>$H^*_{0001}$</td>
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</table>

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Table 3. Adjusted p-values for the null hypotheses in the clinical trial with two dose-placebo comparisons and two endpoints (correlation coefficient, $\rho = 0.3, 0.4$ and 0.5).

<table>
<thead>
<tr>
<th>Family $F$</th>
<th>Null hypothesis $H$</th>
<th>$p$-value $\rho = 0.3$</th>
<th>$p$-value $\rho = 0.4$</th>
<th>$p$-value $\rho = 0.5$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$F_1$</td>
<td>$H_{11}$</td>
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<td>0.0353</td>
<td>0.0353</td>
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<tr>
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<td>$H_{12}$</td>
<td>0.0079</td>
<td>0.0079</td>
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</tr>
<tr>
<td>$F_2$</td>
<td>$H_{21}$</td>
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<td>0.0353</td>
<td>0.0353</td>
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<tr>
<td>$F_2$</td>
<td>$H_{22}$</td>
<td>0.0194</td>
<td>0.0192</td>
<td>0.0190</td>
</tr>
</tbody>
</table>
Table 4. Critical values for individual intersection hypotheses in a clinical trial with two dose-placebo comparisons and two endpoints \((m = 2, s = 2)\). The correlation between the two endpoints \((\rho)\) ranges between 0.01 and 0.99, overall one-sided Type I error probability is 0.025 and sample size per treatment group is 30 patients.

<table>
<thead>
<tr>
<th>Correlation between the endpoints ((\rho))</th>
<th>(c_1)</th>
<th>(c_2)</th>
<th>(c_3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01</td>
<td>2.249</td>
<td>2.309</td>
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