Multiplicity for a Group Sequential Trial with Biomarker Subpopulations

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Abstract

Biomarker subpopulations have become increasingly important for drug development in targeted therapies. The use of biomarkers has the potential to facilitate more effective outcomes by guiding patient selection appropriately, thus enhancing the benefit-risk profile and improving trial power. Studying a broad population simultaneously with a more targeted one allows the trial to determine the population for which a treatment is effective and allows a goal of making approved regulatory labeling as inclusive as is appropriate. We examine new methods accounting for the complete correlation structure in group sequential designs with hypotheses in nested subgroups. The designs provide full control of family-wise Type I error rate. This extension of previous methods accounting for either group sequential design or correlation between subgroups improves efficiency (power or sample size) over a typical Bonferroni approach for testing nested populations.

1. Introduction

Conventional design with only one primary study population (an overall population) has recently been challenged [1, 2], particularly when the disease (e.g. cancer) is heterogeneous due to observable clinical or biologic/genomic characteristics. In recent oncology clinical trials, biomarker subpopulations (biomarker +/-) have become increasingly important for drug development in tailored therapies to fulfill regulatory commitments [3]. The use of biomarkers has the potential to facilitate the availability of safer and more effective drug or biotechnology products, to guide dose selection, and to enhance their benefit-risk profile [4]. While the overall population targets the goal of making the approved regulatory labeling as inclusive as possible, evaluating the benefit in a biomarker positive subpopulation can mitigate the risk that biomarker negative patients could dilute the efficacy in the overall population.

In the situation of testing hypotheses in multiple populations, multiplicity needs to be carefully considered to ensure strong control of the family-wise Type I error (or family-wise error rate, FWER) and to maximize the study power. In the setting described above, there is a known correlation structure in the asymptotic distribution for the joint test statistics across interim and final analysis as well as across populations. To-date, people have designed trials accounting for correlation in interim timing [5] or subpopulations [6, 7], respectively, but have not taken advantage of the full correlation structure including both populations and interim analyses, leading to stricter bounds than necessary to control Type I error. Therefore, in this paper, we extend the group sequential design setup with multiple biomarker populations and develop the method and calculations with less conservative bounds, which results in a smaller required sample size or
greater power, while controlling the FWER. This is a realization of the improved weighted parametric test mentioned in Maurer and Bretz [8] for multiple testing in group sequential trials using graphical approaches.

In section 2, we briefly review methods in group sequential design. We introduce the complete correlation structure (CCS) incorporating both interim analyses and populations in Section 3. In the same section, the calculations for adjusted nominal alpha levels, power for hypothesis testing in each population and sample size are also presented. The effect of CCS on clinical trial design is demonstrated in Section 4, and an application of CCS is shown in Section 5. Discussion and extensions of CCS appear in Section 6. Example R program code is included in Appendix C and Appendix D.

2. Background

Group sequential design has played an increasingly important role in modern clinical trials for ethical reasons and economic considerations. In group sequential design, interim analyses are performed during the trial. Further study follow-up may be stopped in accordance with a pre-defined stopping rule as soon as conclusive results are observed. Therefore, a conclusion may be reached at an earlier stage with lower financial and human cost. More importantly, group sequential design offers the possibility to accelerate replacement of an inferior therapy by a superior one compared to fixed sample size study design where a decision only can be made at the end of the trial.

One aspect of group sequential design is to control temporal correlation among interim analyses and the final analysis. Pocock [9, 10] and O’Brien and Fleming [11] initially popularized group sequential test procedures to manage multiplicity. While Pocock suggested having constant adjusted nominal alpha level across stages of the trial, O’Brien and Fleming recommended a more conservative and unequal nominal alpha level at early stages. Both methods require equal stage size and the pre-specified number of the stages. In practice, O’Brien and Fleming’s method is often preferred because of the more conservative early bounds.

Lan and DeMets [12] introduced non-decreasing alpha-spending functions to determine interim efficacy bounds. Their method loosened the rules required by the Pocock and O’Brien and Fleming approaches, allowing flexibility in timing of analysis. They developed spending functions to approximate the Pocock and O’Brien and Fleming designs. Kim and DeMets [13] as well as Hwang, Shih and DeCani [14] also proposed flexible one-parameter families that again can approximate Pocock or O’Brien and Fleming as well as other boundaries. A comprehensive illustration of group sequential design can be found, for example, in Jennison and Turnbull [5], Proschan, Lan, and Wittes [15], and Wassmer and Brannath [16]. More recently, Anderson and Clark [17] suggested 2-parameter spending functions that could be used to further customize bounds in a fit-for-purpose manner.

Above we introduced methods that were applied to a primary endpoint for a single hypothesis. However, it is common to have multiple hypotheses regarding different endpoints and populations with group sequential analysis, increasing the complexity of Type I error control. Here we consider the case of testing treatment effect in both biomarker subpopulation(s) and the overall
population within a single clinical trial. Maurer and Bretz [8] showed the usage of a graphical
approach in group sequential design when multiple hypotheses were tested in a trial. Later in
Maurer, Glimm, and Bretz’s work [18], they extended the algorithm of the test procedure by
implementing group sequential boundaries and suggested its application to a comparison of
multiple endpoints for a subgroup and an overall population. However, they did not provide
detailed instruction on population correlations.

Another useful application of group sequential method is to account for correlation among
subgroups (sub-populations) and the overall population. Spiessens and Debois [6] suggested the
correlation of test statistics between nested subgroup and the overall population can be addressed
using the same method in interim analysis (i.e. group sequential design) because it could improve
the efficiency of clinical trials while controlling the FWER. Holmgren [7] proposed a similar
concept using group sequential design boundaries at early phase (e.g. phase II) in the decision of
choosing a biomarker expression level used in later phase (phase III) trials. However, none of
these papers accounts for the benefit gained when simultaneously accounting for temporal and
population correlation, a situation that arises increasingly in oncology clinical trials.

In this paper, we synthesize the concepts regarding population correlation from Spiessens
and Debois [6] and Holmgren’s [7] and incorporate it with Maurer and Bretz’s work [8] on
multiplicity control for multiple hypotheses in group sequential design. We propose a complete
correlation structure (CCS) for the covariance matrix of test statistics that accounts for both
temporal and population correlations in group sequential design to improve design efficiency.

3. Methods

3.1 Complete Correlation Structure (CCS)

Jennison and Turnbull [5] summarize the asymptotic distribution of test statistics in group
sequential design. We extend this to the above circumstance by the proposed CCS method
accounting for correlations among test statistics at multiple analyses over time (temporal
perspective) as well as of multiple populations. We consider a 2-arm clinical trial comparing the
treatment effect in \( I \) nested biomarker subgroups and the overall population. Each population has
an hypothesis, and these hypotheses are evaluated at \( K \) analyses. We let \( i \) be the index for
increasing nested populations, \( i = 1, 2, ..., I \), while \( k \) represents the index for the stage of interim
analyses and final analysis, \( k = 1, 2, ..., K \).

Let \( n_{ik} \) be the number of observations (or number of events for time-to-event endpoints)
collected cumulatively through stage \( k \) in population \( i \). The information fraction at stage \( k \) for
population \( i \) is \( n_{ik}/n_{iK} \).

Let \( \theta \) represent the underlying effect size for a test statistic. \( H_0: \theta = 0 \) represents no effect
on the treatment arm; \( H_{a}: \theta > 0 \) represents an advantage for the experimental arm treatment. Let
\( Z_{ik} \) be the standardized test statistics for nested population \( i \) at stage \( k \). These standardized test
statistics asymptotically are assumed to follow a multivariate normal distribution

\[
Z_{ik} \sim MVN(\theta, \Sigma)
\]
with a known covariance structure for each pair \((Z_{ik}, Z_{i'k'})\). \(\theta\) is a vector with length of \(I \times K\) for the means of the test statistics \(Z_{ik}\). \(E(Z_{ik}) = 0\) when \(H_0\) is true. The covariance matrix \(\Sigma\) can be calculated by

\[
COV(Z_{ik}, Z_{i'k'}) = \frac{n_{i,i'k}kkk'}{\sqrt{n_{i,k}n_{i'k'}}}
\]  

(2)

where the operator \(\wedge\) represents the minimum. In the numerator for this covariance for a time-to-event outcome, we have the number of events included in both (intersection) test statistics for which we are computing the covariance. The denominator has the geometric mean of the events consider in each statistic separately. For a normal or binary outcome, we would count observations rather than events. For \(k = k'\), this is the result from Spiessens and DeBois [6] and Holmgren [7]. For \(i = i'\), this is a standard group sequential design result. Combining these two results (e.g., independent increment in population and then an increment or decrement in time) yields the general result above. With the entire correlation structure, we can calculate adjusted nominal alpha levels, population power, and sample size that produce a more efficient design than one that does not account for the entire correlation structure. A detailed derivation is provided in Appendix A.

### 3.2 Weighted Parametric Test in Group Sequential Trials

Following Bretz 2011 [19], the weighting scheme of the \(I\) hypotheses can be defined by the weights \(w_i(I), i \in I\), for the global null hypothesis \(H_I\) and the transition matrix \(G = (g_{ij})\) for all \(i, j \in I\). For an intersection hypothesis \(H_J, J \subseteq I\), the weights \(w_i(J), i \in J\), are determined by Algorithm 1 in Bretz 2011 [19]. Since consonance may not hold for weighted parametric testing in group sequential trials with more than two populations as stated in Maurer and Bretz [8], the closed testing procedure should be used. That is, at each analysis (interim or final), we apply the weighted parametric test in which the correlation matrix is defined in Section 3.1 to each intersection hypothesis \(H_J, J \subseteq I\).

The steps to conduct weighted parametric test in group sequential trials are:

1. **Specify the alpha spending function** \(f_i\) for each hypothesis \(H_I, i \in I\). That is, each population hypothesis can have its own alpha spending function. However, in practice, usually the same alpha spending function \(f\) is used unless there is justification otherwise.

2. **At each analysis**, for each intersection hypothesis \(J\), determine the efficacy boundaries \(c_{ik}(J)\) for each component \(i\) in the intersection hypothesis. There are several ways to determine the efficacy boundary. One approach is described below. Additional alternative approaches are described in Appendix B.

   (1) **Interim Analysis 1**, find \(\alpha^*_1(J)\) such that
1 − Pr \left( \bigcap_{i \in J, k \in K} Z_{ik} < c_{ik}(w_i(J)\alpha^*_{1}(J)) \bigg| H_0 \right) = \alpha

Where

- \( Z_{ik} \) follows a multivariate normal distribution \((IK \times 1)\) with mean of 0 and covariance matrix as the CCS by (2) in Section 3.1. In (2), \( n_{i1}(i \in J) \) are the actual sample size (number of events for time-to-event analyses) at Interim Analysis 1, and \( n_{ik} \) (for \( i \in J, k = 2, ..., K \)) are the expected sample size at future analyses.
- For each \( i \), the \( c_{ik} \) is the boundaries from the pre-specified alpha spending function \( f_i \) when the total alpha is \( w_i(J)\alpha^*_{1}(J) \) and analysis timings are \( t_{ik} \), in which \( t_{i1} \) are the actual information fraction for population \( i \) at Interim Analysis 1, and \( t_{ik} \) (for \( i \in J, k = 2, ..., K \)) are the planned timing of future analyses.
- \( \alpha \) is the overall alpha level for the whole trial, e.g. 0.025 (one-sided).

Once \( \alpha^*_{1}(J) \) is found, the efficacy boundaries for each component in \( J \) at Interim Analysis 1 are \( c_{i1}(w_i(J)\alpha^*_{1}(J)) \).

(2) At analysis \( k \) \((k = 2, ..., K)\), find \( \alpha^*_{k}(J) \) such that

\[
1 - \Pr \left( \bigcap_{i \in J, j < k} Z_{ij} < c_{ij} \bigg| \bigcap_{i \in J, j \geq k} Z_{ij} < c_{ij}(w_i(J)\alpha^*_{k}(J)) \right) = \alpha
\]

Where \( c_{ij} \) \((j < k)\) are determined sequentially from the first interim analysis and so on. For example, for the second interim analysis, find \( \alpha^*_{2}(J) \) such that

\[
1 - \Pr \left( \bigcap_{i \in J} Z_{i1} < c_{i1} \bigg| \bigcap_{i \in J, j \geq 2} Z_{ij} < c_{ij}(w_i(J)\alpha^*_{2}(J)) \right) = \alpha
\]

Where \( c_{i1} \) are determined from step (1). Once \( \alpha^*_{2}(J) \) is found, the efficacy boundaries for each component in \( J \) at Interim Analysis 2 are \( c_{i2}(w_i(J)\alpha^*_{2}(J)) \).
3. At analysis $k$, starting from the global null hypothesis, compare the test statistics of each population with the corresponding efficacy boundaries $c_{ik}$. If at least one test statistic is greater than the corresponding boundary, that intersection hypothesis can be rejected. After going through all the intersection hypothesis tests, the individual hypotheses which can be rejected by the closed testing procedure can be claimed successful and can be removed from the weighting graph. The hypotheses left in the updated graph form the new set for the next analysis. This procedure continues until all individual hypotheses are rejected or the final analysis is complete, whichever comes first.

3.3 Population Power and Sample Size

When a study is designed, the CCS can be calculated by prevalence of biomarker populations and the design interim analysis timing if the information accumulates at the same rate for different populations under the null and alternative hypothesis. For example, for a study with 2 populations (biomarker subgroup and all comb population) and 3 analyses (two interim analyses and one final analysis). If the prevalence of the biomarker subgroup is $p$, and the design interim analysis timing is $t_1$ and $t_2$ information fraction. According to (2), the upper half of the correlation matrix for $(Z_{11}, Z_{21}, Z_{12}, Z_{22}, Z_{13}, Z_{23})$ is

$$
\begin{bmatrix}
1 & \sqrt{p} & \sqrt{t_1/t_2} & \sqrt{pt_1/t_2} & \sqrt{t_1} & \sqrt{pt_1} \\
\sqrt{p} & 1 & \sqrt{t_1/t_2} & \sqrt{pt_1/t_2} & \sqrt{t_1} & \sqrt{pt_1} \\
\sqrt{t_1/t_2} & \sqrt{t_1/t_2} & 1 & \sqrt{t_2} & \sqrt{pt_2} & \sqrt{t_1} \\
\sqrt{pt_1/t_2} & \sqrt{pt_1/t_2} & \sqrt{t_2} & 1 & \sqrt{t_2} & \sqrt{pt_2} \\
\sqrt{t_1} & \sqrt{pt_1} & \sqrt{t_2} & \sqrt{pt_2} & 1 & \sqrt{pt_2} \\
\sqrt{pt_1} & \sqrt{pt_1} & \sqrt{t_1} & \sqrt{pt_2} & \sqrt{t_2} & 1
\end{bmatrix}
$$

With CCS, find $\alpha^*_K(I)$ such that

$$1 - \Pr\left(\bigcap_{i \in I, k \in K} Z_{ik} < c_{ik}(w_i(I)\alpha^*_K(I)|H_0)\right) = \alpha$$

Where $Z_{ik}$ follows a multivariate normal distribution $(IK \times 1)$ with mean of 0 and covariance matrix as the CCS, and the $c_{ik}$ is the boundaries from the pre-specified alpha spending function $f_t$ when the total alpha is $w_i(I)\alpha_K^*(I)$ and analysis timings are $t_k$. Once $\alpha^*_K(I)$ is found, $c_{ik}$ are known.

When the sample size at each analysis is given, power in each population can be calculated based on the bounds $c_{ik}$. The power in population $i$ is

$$1 - \Pr\left(\bigcap_{k \in K} Z_{ik} < c_{ik} | H_a\right)$$
Where $Z_{ik}$, $k \in K$, follows multivariate normal distribution ($K \times 1$) with mean as the target treatment effect for population $i$, and covariance matrix defined as the in the usual group sequential design (i.e. temporal correlation).

On the other hand, when the desired power for population $i$ is given and the adjusted nominal alpha level $w_i(l)\alpha^*_K(l)$ is known, the sample size for population $i$ can be determined using root-finding with standard group sequential design methods (e.g. gsDesign R package), in which the type I error rate for hypothesis $i$ is $w_i(l)\alpha^*_K(l)$. The sample size for the overall population may need to be adjusted so that each subpopulation has at least the desired power.

4. Effect of Biomarker Prevalence in CCS

In this section, we demonstrate our method in a simple case with only one interim analysis (i.e. $K = 2$) and one subpopulation (i.e. $I = 2$) planned (Example R code is provided in Appendix C). Assuming the FWER is equally split to the subgroup and the overall population (i.e. $w_1 = 0.5, w_2 = 0.5$). We use the Lan and DeMets spending function approximating O’Brien and Fleming bounds. We also assume interim analysis spending time ($t_{i1}$) at 0.5 and adjust subgroup proportion from 0.3 to 0.8 to investigate effect caused by the prevalence of the biomarker subgroup. Define, $p_{ik} = n_{ik}/n_{ik}$, which is the same for $k = 1$ and $k = 2$, if the information accumulates at the same rate for the two populations. Additionally, the effect size for subgroup is set at 0.15. In order to maintain the same power for both populations, we set the effect size for overall population with a proportion of $\sqrt{p}$ the effect size in subgroup (i.e. effect size 0.106 for overall population when the prevalence of biomarker subgroup is $p = 0.5$).

Figures 1-3 showed the effect of biomarker prevalence ($p_{1k}$) to adjusted nominal alpha level ($w_i(l)\alpha^*_K(l)$), population power, and sample size.
In Figure 1, we evaluate the association between the proportion of the subgroup and adjusted nominal alpha level $w_i(I)\alpha_{R}(I)$. When the prevalence of the biomarker subpopulation increases from 0.3 to 0.8, the adjusted nominal alpha level for testing under the complete null hypothesis also increases from 1.37% to 1.73% compared to 1.25% using the Bonferroni method. The larger the proportion in the subgroup, the higher correlation between the subgroup and overall outcomes, resulting in a larger adjusted nominal alpha level.

Figure 2 shows the increase in power compared to a Bonferroni-based sample size for 90% power when the proportion in the subgroup increases; the population power (either power in subgroup or power in overall population) also increases from 91.5% to 92.9% compared to 90.0% with Bonferroni-based testing.

Figure 3 shows the association between the proportion in the subgroup and the percent of sample size saved using the CCS-based group sequential sample size as compared to the Bonferroni-based sample size. The sample size saved increases from 1.9% to 7.0% as the prevalence of the biomarker subpopulation increases. More subjects can be saved as subgroup proportion increases.

Note that there is a drop in Figure 1 and Figure 2 when the prevalence is 0.429. We believe this drop is due to a polyhedral cone selection in numerical integration for multivariate normal distribution when we use `pmvnorm` function with Miwa algorithm in `mvtnorm` package (version 1.0-6) in R 3.4.1. Increasing grid points used in the algorithm does not solve this minor issue. A further evaluation on numerical integration may be useful in the future. We also tested with the default algorithm GenzBretz in `pmvnorm` function that a random seed is specified, but the results are less consistent as compared to Miwa algorithm. In a smaller dimension (less than 20) test condition, the Miwa algorithm may be preferred.

5. Example of CCS in Oncology Clinical Trial

In this section, we show the implementation of CCS in a hypothetical oncology clinical trial. Assuming a 2-arm trial with a primary endpoint of overall survival (OS), the OS is assumed to follow an exponential distribution with a median of 17.5 months in both the treatment and control group (randomization ratio 2:1), and the drop-out rate is assumed to be 3% annually. The
FWER of 2.5% (1-sided) is equally distributed to the subgroup and all subjects when the assumed underlying hazard ratio (HR) of OS is 0.65 in the subgroup and HR=0.7 in the overall population. We expect 434 OS events (296 OS events in subjects with biomarker (+)) with 90% power in both populations. The first interim analysis (IA1) is planned at 50% spending time, the second interim analysis (IA2) is planned at 75% spending time, and the final analysis (FA) is conducted when all targeted event counts have been achieved. The prevalence of biomarker (+) subgroup is assumed to be 60%. For detailed R program code, please see Appendix D. The covariance matrix for test statistics \((Z_{11}, Z_{21}, Z_{12}, Z_{22}, Z_{13}, Z_{23})\) is as same as in Section 3.3 and can be calculated as

\[
\begin{bmatrix}
1 & 0.775 & 0.816 & 0.632 & 0.707 & 0.548 \\
0.775 & 1 & 0.632 & 0.816 & 0.548 & 0.707 \\
0.816 & 0.632 & 1 & 0.775 & 0.866 & 0.671 \\
0.632 & 0.816 & 0.775 & 1 & 0.671 & 0.866 \\
0.707 & 0.548 & 0.866 & 0.671 & 1 & 0.775 \\
0.548 & 0.707 & 0.671 & 0.866 & 0.775 & 1 \\
\end{bmatrix}
\]

Table 1 below shows the comparison of Bonferroni-adjusted group sequential design (adjusted with temporal correlations only) and CCS group sequential design (adjusted with both temporal and population correlations) in several elements. The nominal testing level of 1.53% vs. 1.25% using Bonferroni may seem small; however, we note that the sum of the 2 nominal alpha levels for group sequential testing is 1.277% (vs 1.25% which is Bonferroni approach for interim analysis and final analysis without considering temporal correlation) when testing half-way through the trial with overall alpha=1.25% and O’Brien-Fleming-like spending. Thus, the gains from incorporating population correlations here are greater than those correlations over time. This is largely due to the substantial spend on each population whereas there is little spending for this example at interim analysis.

| Elements                  | Bonferroni-adjusted group sequential design | CCS group sequential design |
|---------------------------|---------------------------------------------|------------------------------|
|                           | Subgroup Overall                            | Subgroup Overall             |
| Nominal alpha level       | 1.25 % 1.25 %                               | 1.53 % 1.53 %                |
| Population power*         | 90.00% 90.00%                               | 91.44% 91.36%                |
| Number of events**        | 296 434                                     | 283 415                      |
| Z statistic bound         | 3.35 2.67 2.28                              | 3.24 2.58 2.21               |
| Hazard Ratio Bound        | 0.62 0.73 0.79                              | 0.63 0.64 0.80               |

* With fixed HR(0.65/0.70) and sample size (296/434) in subgroup/overall population.

** With fixed HR (0.65/0.70) and power (90%) in subgroup/overall population.

The nominal alpha level increases from 1.25% to 1.53% when the CCS is adjusted in the group sequential design and FWER is controlled at the same level of 2.5%. The impact of the adjusted nominal alpha level is reflected in Z statistic bounds as well. For example, the bound at
IA1 decreases from 3.35 to 3.24 after adjusting for the CCS. In Table 1, we present the comparison of hazard ratio bounds showing CCS in group sequential design has a minor release and flexible restriction in hypothesis testing. In addition, the gain from CCS group sequential design includes a smaller required number of events with a 4.4%-saving in each population. Lastly, population power increases from 90% to 91.4% with fixed hazard ratio and sample size in both subgroup and overall populations.

The cost of a clinical trial is always an essential concern, and one way to control the budget is recruiting minimum but sufficient patients in the trial. The example above shows a 19-event saving in the overall population after applying CCS in group sequential design. When calculating the number of patients required in this example, a 33-patient (721-688 savings is realized. A recent report in Journal of Clinical Oncology [20] showed the cost of a phase IIIA oncology trial ranged from $75,000 to $125,000 per patient. Assuming the cost per patient in a trial is $100,000, we would save $3.3 million with the application of CCS group sequential design in this example. Alternatively, a 1.36% power increase in Table 1 applied to a trial that could result in a drug approval worth $100 million would have a value of $1.36 million.

6. Extensions

6.1 Extention to more complex Graphical Approach

When multiple endpoints as well as multiple populations are considered in a trial, we suggest applying CCS to the hypotheses with the same endpoint. For instance, Figure 4 shows a hypothetical case using a graphical multiplicity approach similar to Example 2 in Bretz 2011 [19] that includes partial correlation matrix known. There are two endpoints (OS and progression-free survival (PFS)) and two populations. CCS needs to be conducted twice, one time for OS and another time for PFS. For OS, there is a total alpha of 2% available. Splitting this equally, we can test for OS differences initially using the CCS methods shown above. The transfer of nominal alpha once a hypothesis has been rejected is not impacted by CCS; e.g., if H2 were rejected, then H1 may be tested at level alpha=2%. Similarly, if H1 and H2 both are rejected, there is total 2% alpha level that can be transferred to H3 and H4 equally, e.g., 1% alpha level to H3, and 1% alpha level to H4. Since there are only 2 populations, there are still no consonance issues. The gain of nominal alpha level from CCS (e.g. CCS-α 1.1% in H1 and H2 or CCS-α 0.3% in H3 and H4) is only available to the hypothesis testing within the endpoint itself.

Figure 4. Graphical Approach with CCS Adjustment
6.2 Multiple-arm Situation

We focus on 2-arm trials in previous sections, but the weighted parametric closed testing procedure can be easily extended to multiple-arm design with multiple populations. For example, consider a 3-arm, 2-population trial comparing 2 dose arms (e.g., high-dose and low-dose) against a control arm when one interim analysis is planned. Let $Z_{H1i}$ be the test statistics when comparing high-dose with control, and $Z_{L1i}$ be the test statistics for comparing low-dose with control. The CCS correlation matrix is a $8 \times 8$ matrix for the 8 test statistics ($i.e.$ $Z_{H11}, Z_{H12}, Z_{H21}, Z_{H22}, Z_{L11}, Z_{L12}, Z_{L21}, Z_{L22}$). The covariance of any two of these test statistics is the same as explained in Section 3.1. Particularly, the covariance of ($Z_{H1i}, Z_{L1'i}$) is the correlation from the control observations that are included in both high-dose and low-dose test statistics. Once the CCS matrix is known, calculations described in the Section 3 for group sequential monitoring boundaries, power, and sample size can be applied to multiple-arm trials. Note that the computation of high dimensional multivariate normal can be time consuming, Ghosh et al. [21] solved the computational difficulties in boundary calculation in multiple-arm multiple-stage (MAMS) designs and provided a more time-efficient algorithm to compute boundaries.

7. Discussion

In this paper, we have introduced CCS (complete correlation structure) to manage both temporal and subpopulation correlations among test statistics in group sequential design. To our knowledge, this is the first paper that has accounted for these two aspects simultaneously in a clinical trial design. By synthesizing concepts from the literature, we have built upon the CCS to compute group sequential boundaries, population power, and sample size with weighted parametric closed testing procedure using graphical approach. The advantages of using CCS include more relaxed efficacy boundaries (i.e.greater nominal alpha level), higher population power, or smaller required sample size when FWER is maintained at the same level. The method can be applied to multiple types of outcomes (e.g. normal, binary, and survival type) since it is based on standardized test statistics with the same asymptotic properties for many endpoints.

We have examined the influence of biomarker prevalence on nominal alpha level, population power, and sample size (Figure 1 – Figure 3). The impact of the proportion in the

* CCS-$\alpha$ is the nominal alpha level from using CCS method.
subgroup was more influential than spending time in interim analysis, probably due to the small amount of interim $\alpha$-spending for the temporal analyses. In group sequential design with Bonferroni-style splitting of $\alpha$, we account for the correlation among test statistics at different stages, but the correlation between populations is not incorporated.

When the nominal alpha level is elevated by CCS in group sequential design, the boundary values for hypothesis testing are lowered. In the example at Section 5, the nominal alpha level increases by 0.28% in each population. This improvement increases the chance for a positive efficacy finding. Corresponding HR approximations at bounds are also less stringent when FWER is controlled at the same 2.5% significance level. While these differences may appear minor, narrow misses for statistical significance can be extremely costly in terms of lost opportunity for regulatory approval. Also, the amount the bounds are relaxed are not so different than what can be obtained with group sequential testing accounting for temporal correlations (standard practice) vs. using a Bonferroni adjustment for group sequential testing. The financial savings of $3.3$ million is important and the cost saving would increase if biomarker prevalence is higher than our assumption at 60%. In terms of population power, we have showed CCS in group sequential design had greater power to detect treatment effect while sample size and effect size were fixed, again confirming the cost-effectiveness of this approach.

We have discussed the extension of CCS in Section 6 that CCS is suitable to multiple-arm design and more complex graphical approach with some constraints. These extensions make CCS more feasible to be applied in real-world clinical trials. Such designs are worth further evaluation in future work.

Unfortunately, off-the-shelf software does not provide tools to derive designs or testing for trials incorporating CCS. However, the calculations are not terribly complex using readily available tools in R such as a combination of the “gsDesign” package for group sequential design, the “gMCP” package for graphical hypothesis testing and the mvtnorm package for multivariate normal probability calculations.

8. Conclusion

CCS simultaneously incorporates correlations between populations and interim timing in group sequential design. It has an extensive application to the methods that are widely used in current clinical trials, and it is applicable to designs with multiple arms, multiple stages, and multiple populations. It can also be integrated with the graphical testing approach with the qualification that for more than 2 populations a full closed testing evaluation may be required. The gains in efficiency of CCS in group sequential design as compared to conventional group sequential design includes more relaxed efficacy boundaries (i.e. larger nominal alpha level at each test), greater power or savings in study sample size that are small, but meaningful; in fact, the gains from considering population correlations can be greater than those achieved by incorporating broadly-used temporal correlations.
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Supplemental file.

Appendix A – Derivation of Formula [2] for special case.

In this section, we will show the derivation of Formula [2].

Let $S_{i,k}$ is the logrank score statistic at analysis $k$ for population $i$ which follows the normal distribution asymptotically (Schoenfeld, 1981; Tsiatis, 1982) with

$$E[S_{i,k}] = -\ln(HR) \times n_{i,k} \times r(1 - r)$$

$$Var[S_{i,k}] = n_{i,k} \times r(1 - r)$$

where $r$ is the proportion randomization to the experimental group. Under the null hypothesis, where $HR=1$, we have $-\ln(HR) = 0$. Therefore, $E[S_{i,k}] = 0$ and $Cov[S_{i,k}, S_{i',k'}] = E[S_{i,k}S_{i',k'}]$.

1) For $i = i'$, the Formula [2] is a standard group sequential design result for a single population and a time-to-event endpoint.

2) For $k = k'$, the Formula [2] is the result from Spiessens and DeBois (Spiessens & Debois, 2010) and Holmgren (Holmgren, 2017) since we are adding observations from an independent incremental subgroup and the covariance for the inclusive between the two populations is the variance of the smaller population.

3) For $i < i'$ and $k < k'$, $E[(S_{i',k'} - S_{i,k}) \times S_{i,k}] = E[S_{i',k'} - S_{i,k}] \times E[S_{i,k}] = 0$ using the independent increment property and $E[S_{i,k}S_{i',k'}] = E[S_{i,k}S_{i',k'}] = D_{i,k} \times r(1 - r)$ resulting in

$$Corr(S_{i,k}, S_{i',k'}) = \frac{Cov[S_{i,k}, S_{i',k'}]}{\sqrt{var(S_{i',k'})var(S_{i,k})}} = \frac{n_{i,k}}{\sqrt{n_{i,k}'n_{i,k}}}$$

4) For $i < i'$ and $k > k'$, we have

$$Cov(S_{i,k}, S_{i',k'}) = E[(S_{i,k'} + (S_{i,k} - S_{i,k'}))(S_{i,k'} + (S_{i',k'} - S_{i,k'}))] = Var[S_{i,k'}]$$

since increments are independent in between both nested populations and analyses leading to other terms dropping out. This then leads to

$$Corr(S_{i,k}, S_{i',k'}) = \frac{Cov[S_{i,k}, S_{i',k'}]}{\sqrt{var(S_{i',k'})var(S_{i,k})}} = \frac{n_{i,k'}}{\sqrt{n_{i,k}'n_{i,k}}}$$
Appendix B – Alternative methods to determine efficacy boundary $c_{ik}(J)$

In Section 3.2, we describe the steps to conduct weighted parametric test in group sequential trials. Step 2 of the procedure is at each analysis, for each intersection hypothesis $J$, determine the efficacy boundaries $c_{ik}(J)$ for each component $i$ in the intersection hypothesis. One approach is described in Section 3.2 and alternative approaches are described below.

Define $\alpha_k(J)$ as the cumulative alpha spent at analysis $k$ for an intersection hypothesis $H_J$, $J \subseteq I$

$$\alpha_k(J) = \sum_{i \in J} f(w_i(J)\alpha, t_k)$$

**Alternative approach 1:**

(3) Interim Analysis 1, find $\alpha_1^*(J)$ such that

$$1 - \Pr \left( \bigcap_{i \in J} Z_{i1} < \Phi(1 - w_i(J)\alpha_1^*(J)) | H_0 \right) = \alpha_1(J)$$

Where $Z_{i1}$'s has multivariate normal distribution $(I \times 1)$ with mean of 0 and covariance matrix as defined in Section 3.1, and $\Phi(.)$ is the quantile of the standard normal distribution.

Then the p-value boundaries for each component in $J$ are $w_i(J)\alpha_1^*(J)$. $c_{i1}(J) = \Phi(1 - w_i(J)\alpha_1^*(J))$

(4) At analysis $k$ ($k = 2, ..., K$), find $\alpha_k^*(J)$ such that

$$1 - \Pr \left( \bigcap_{i \in J} \bigcap_{i' < k} Z_{ik'} < c_{ik'}(J) \bigcap_{i \in J} Z_{ik} < \Phi(1 - w_i(J)\alpha_k^*(J)) | H_0 \right) = \alpha_k(J)$$

Where $c_{ik'}(J)$ ($k' < k$) are determined sequentially from the first interim analysis and so on. For example, for the second interim analysis, find $\alpha_2^*(J)$ such that

$$1 - \Pr \left( \bigcap_{i \in J} Z_{i1} < c_{i1}(J) \bigcap_{i \in J} Z_{ik} < \Phi(1 - w_i(J)\alpha_2^*(J)) | H_0 \right) = \alpha_2(J)$$

Where $c_{i1}(J)$ is determined from step (1).

Then the p-value boundaries for each component in $J$ for analysis $k$ are $w_i(J)\alpha_k^*(J)$. $c_{ik}(J) = \Phi(1 - w_i(J)\alpha_k^*(J))$.

**Alternative approach 2:**

For nested populations, in intersection hypothesis $J$, define the index of the largest population as $M$. In this approach, the boundaries for the non-largest populations are kept as the boundaries from the Bonferroni approach without accounting for population correlation, and only to adjust the boundaries for the largest population $M$ when population correlation is incorporated.
(1) Interim Analysis 1, find $c_{M1}(J)$ such that
\[
1 - \Pr\left( \bigcap_{i \in J, i \neq M} Z_{i1} < c_{i1}(J) \cap \bigcap_{i \in J} Z_{M1} < c_{M1}(J) | H_0 \right) = \alpha_1(J)
\]
Where
- $Z_{i1}$’s has multivariate normal distribution ($I \times 1$) with mean of 0 and covariance matrix as defined in Section 3.1.
- $c_{i1}(J)$ for $i \in J, i \neq M$ are the efficacy boundaries from the pre-specified alpha spending function $f_i$ when the total alpha is $w_i(J) \alpha$ and analysis timings are $t_{i1}$.

(2) At analysis $k$ ($k = 2, ..., K$), find $c_{Mk}(J)$ such that
\[
1 - \Pr\left( \bigcap_{i \in J, k' < k} Z_{ik'} < c_{ik'}(J) \cap \bigcap_{i \in J, i \neq M} Z_{ik} < c_{ik}(J) \cap Z_{Mk} < c_{Mk}(J) | H_0 \right) = \alpha_k(J)
\]
Where
- $c_{ik'}(J)$ ($k' < k$) are determined sequentially from the first interim analysis and so on.
- $c_{ik}(J)$ for $i \in J, i \neq M$ are the efficacy boundaries at analysis $k$ from the pre-specified alpha spending function $f_i$ when the total alpha is $w_i(J) \alpha$ and analysis timings are $t_{i1}, ..., t_{ik}$.
Appendix C - R program example in Section 4

Introduction

Below is an example of R program for application of Complete Correlation Structure (CCS) based on the same setting as in the Section 4. We assume i.i.d. observations in a 2-arm trial testing for treatment effect in a subgroup and overall population. Suppose one interim analysis will be performed at 50% pending time of the trial and the prevalence of the subgroup is also 50%. The correlation matrix for the interim test statistics \(Z_{11}, Z_{12}\) and final test statistics \(Z_{21}, Z_{22}\) is

\[
\begin{bmatrix}
1 & \sqrt{0.5} & \sqrt{0.5} & 0.5 \\
\sqrt{0.5} & 1 & 0.5 & \sqrt{0.5} \\
\sqrt{0.5} & 0.5 & 1 & \sqrt{0.5} \\
0.5 & \sqrt{0.5} & \sqrt{0.5} & 1 \\
\end{bmatrix}
\]

Nominal Alpha Allocation

We set up a group sequential design using Lan-DeMets spending function to approximate O'Brien-Fleming bound for both subgroup and the overall population and equally split Type I error of 2.5% (1-sided) into two populations. The boundaries for Z-statistics in interim and final analysis can be calculated as below.

Design setup

```R
# Clean out data
rm(list=ls())

# Loading packages
library(xtable)
library(ggplot2)
library(gsDesign)
library(mvtnorm)

# Regular GS design bounds
z <- gsDesign(test.type=1,k=2,sfu=sfLDOF,alpha=.0125)$upper$bound
round(z,3)
## [1] 3.345 2.246

# Construct correlation matrix
corrmatrix <- matrix(.5^c(0,.5,.5,1, .5, 0, 1,.5, .5, 1, 0,.5, 1,.5, 0),nrow=4)
corrmatrix
## [,1] [,2] [,3] [,4]
## [1,] 1.0000000 0.7071068 0.7071068 0.5000000
## [2,] 0.7071068 1.0000000 0.5000000 0.7071068
```
The overall 1-sided Type I error with above correlation structure can be calculated using `pmvnorm` function.

```r
# Study familywise Type I error and compared to 0.025
tru_stu_alpha <- 1 - pmvnorm(upper = c(z[1], z[1], z[2], z[2]), corr = corrmatrix, algorithm = Miwa())[1]
round(tru_stu_alpha, 4)
## [1] 0.0214
```

As compared to the setting of family-wise error rate 0.025, we only use 0.0214 nominal alpha level in the study.

Next, we build a function to compute the adjusted nominal alpha level.

```r
nomalpha <- function(x, target, corrmatrix) {
  z <- gsDesign(test.type = 1, k = 2, sfu = sfLDOF, alpha = x)$upper$bound
  return(1 - pmvnorm(upper = c(z[1], z[1], z[2], z[2]),
                      corr = corrmatrix, algorithm = Miwa())[1] - target)
}
# adjusted nominal alpha
alphaadj <- uniroot(nomalpha, lower = .0125, upper = .025,
                     target = .025, corrmatrix = corrmatrix)$root
round(alphaadj, 4)
## [1] 0.0147
```

# alternative bounds
```r
altbound <- gsDesign(k = 2, test.type = 1, alpha = alphaadj, sfu = sfLDOF)$upper$bound
round(altbound, 3)
## [1] 3.260 2.184
```

The alternative boundaries are 3.26, 2.184 with respect to adjusted nominal alpha level 0.0147. Compared to regular group sequential design boundaries, 3.345, 2.246, CCS-adjusted group sequential design has ease boundaries.

**Population power**

We set up the effect size at 0.15 and chose a portion of $1/\sqrt{2}$ to obtain the same power in each population.

```r
# Effect size
delta <- 0.15/(1/sqrt(2))
x1 <- gsDesign(delta = delta[1], k = 2, sfu = sfLDOF, alpha = .0125)
x2 <- gsDesign(delta = delta[2], k = 2, sfu = sfLDOF, alpha = .0125)
```

# Subgroup power
power.sub <- \texttt{sum(gsProbability}(\texttt{theta=delta[1]},\texttt{n.I=ceiling}(x1$n.I), \texttt{k=2, a=(-20,-20), b=altbound}$upper$prob) \\
\texttt{# Overall power}

\texttt{power.ova <- sum(gsProbability}(\texttt{theta=delta[2]},\texttt{n.I=ceiling}(x2$n.I), \texttt{k=2, a=(-20,-20), b=altbound}$upper$prob) \\
\texttt{round(power.sub,3)} \\
\texttt{## [1] 0.919} \\
\texttt{round(power.ova,3)} \\
\texttt{## [1] 0.919}

The population power adjusted with CCS in group sequential design is 0.919. It elevates about 2% from default power setting at 0.9.

\textbf{Sample size}

The sample size in regular group sequential design is calculated as below.

\texttt{N <- ceiling(c(x1$n.I[2],x2$n.I[2]))} \\
\texttt{N} \\
\texttt{## [1] 570 1140}

570 subjects in subgroup and 1140 subjects in overall population.

The CCS-adjusted sample size with fixed power (0.9) and fixed effect size are calculated as below.

\texttt{# Subgroup} \\
\texttt{SS.sub <- ceiling(gsDesign}(\texttt{k=2, sfu=sfLDOF, delta=delta[1], alpha=alphaadj}$Sn.I[2])) \\
\texttt{SS.sub} \\
\texttt{## [1] 551}

\texttt{# Overall} \\
\texttt{SS.ova <- ceiling(gsDesign}(\texttt{k=2, sfu=sfLDOF, delta=delta[2], alpha=alphaadj}$Sn.I[2])) \\
\texttt{SS.ova} \\
\texttt{## [1] 1101}

The required sample sizes are 551 in subgroup and 1101 in the overall population. We save 19 subjects and 39 subjects in the subgroup and overall population respectively.
Appendix D - R program in Section 5

# Clean out data
rm(list=ls())
# loading packages
library(xtable)
library(ggplot2)
library(gsDesign)
library(mvtnorm)

z1 <- gsSurv ( k = 3 , test.type = 4 , alpha = 0.0125 , beta = 0.1,
               timing = c( 0.5,0.75 ) , sfu = sfLDOF , sfupar = c( 0 ) ,
               sfl = sfHSD , sflpar = c(-8 ) , lambdaC = log(2) / 17.5 ,
               hr = 0.65 , hr0 = 1 , eta = 0.0025 , gamma = c( 2.5,5,7.5,10 ) ,
               R = c(1,1,1,8 ) ,S = NULL , T = 37.5 , minfup = 26.5 , ratio = 2)$upper$bound

z2 <- gsSurv ( k = 3 , test.type = 4 , alpha = 0.0125 , beta = 0.1,
               timing = c( 0.5,0.75 ) , sfu = sfLDOF , sfupar = c( 0 ) ,
               sfl = sfHSD , sflpar = c(-8 ) , lambdaC = log(2) / 17.5 ,
               hr = 0.7 , hr0 = 1 , eta = 0.0025 , gamma = c( 2.5,5,7.5,10 ) ,
               R = c(1,1,1,8 ) ,S = NULL , T = 37.5 , minfup = 26.5 , ratio = 2)$upper$bound

round(z1)
## [1] 3.345 2.670 2.281

CCS correlation matrix

corr_6by6 <- function(p_s, t_i1, t_i2){
  # p_s is Proportion of subgroup
  # t_i1 is information time proportion of first IA
  # t_i2 is information time proportion of second IA
  # Covariance formula
  covZ <- function(p1,p2,t1,t2){
    sqrt((min(p1,p2)*min(t1,t2))/(max(p1,p2)*max(t1,t2)))
  }
  cov12 <- covZ(p_s,1,t_i1,t_i1)
  cov13 <- covZ(p_s,p_s,t_i1,t_i2)
  cov14 <- covZ(p_s,1,t_i1,t_i2)
  cov15 <- covZ(p_s,p_s,t_i1,1)
  cov16 <- covZ(p_s,1,t_i1,1)
  cov23 <- covZ(1,p_s,t_i1,t_i2)
  cov24 <- covZ(1,1,t_i1,t_i2)
  cov25 <- covZ(1,p_s,t_i1,1)
  cov26 <- covZ(1,1,t_i1,1)
  cov34 <- covZ(p_s,1,t_i2,t_i2)
  cov35 <- covZ(p_s,p_s,t_i2,1)
  cov36 <- covZ(p_s,1,t_i2,1)
}

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cov45 <- covZ(1,p_s,t_i2,1)
cov46 <- covZ(1,1,t_i2,1)
cov56 <- covZ(1,p_s,1,1)

# build up corr matrix
corrmatrix <- matrix(c(1, cov12, cov13, cov14, cov15, cov16, cov12, 1, cov23, cov24, cov25, cov26, cov13, cov23, 1, cov34, cov35, cov36, cov14, cov24, cov34, 1, cov45, cov46, cov15, cov25, cov35, cov45, 1, cov56, cov16, cov26, cov36, cov46, cov56, 1), nrow=6)
corrmatrix
}
corrmatrix <- corr_6by6(p_s=0.6, t_i1=0.5, t_i2=0.75)

Adjusted nominal Alpha Level

nomalpha <- function(x,target,corrmatrix){
z1 <- gsSurv ( k = 3 , test.type = 4 , alpha = x , beta = 0.1,
               timing = c( 0.5,0.75 ) , sfu = sfLDOF , sfupar = c( 0 ) ,
               sfl = sfHSD , sfpar = c( -8 ) , lambdaC = log(2) / 17.5 ,
               hr = 0.65 , hr0 = 1 , eta = 0.0025 , gamma = c( 2.5,5,7.5,10 ) ,
               R = c(1,1,1,8 ) , S = NULL , T = 37.5 , minfup = 26.5 , ratio = 2 )$upper$sbound
z2 <- gsSurv ( k = 3 , test.type = 4 , alpha = x , beta = 0.1,
               timing = c( 0.5,0.75 ) , sfu = sfLDOF , sfupar = c( 0 ) ,
               sfl = sfHSD , sfpar = c( -8 ) , lambdaC = log(2) / 17.5 ,
               hr = 0.7 , hr0 = 1 , eta = 0.0025 , gamma = c( 2.5,5,7.5,10 ) ,
               R = c(1,1,1,8 ) , S = NULL , T = 37.5 , minfup = 26.5 , ratio = 2 )$upper$sbound
return(1-pmvnorm(upper=c(z1[1],z2[1],z1[2],z2[2],z1[3],z2[3])),
corr=corrmatrix, algorithm = Miwa())[1]-target)
alphaadj <- uniroot(nomalpha,lower=.010,upper=.025,
target=.025,corrmatrix=corrmatrix)$root
alphaadj

## [1] 0.01532291

altbound <- gsSurv ( k = 3 , test.type = 4 , alpha = alphaadj , beta = 0.1,
               timing = c( 0.5,0.75 ) , sfu = sfLDOF , sfupar = c( 0 ) ,
               sfl = sfHSD , sfpar = c( -8 ) , lambdaC = log(2) / 17.5 ,
               hr = 0.7 , hr0 = 1 , eta = 0.0025 , gamma = c( 2.5,5,7.5,10 ) ,
               R = c(1,1,1,8 ) , S = NULL , T = 37.5 , minfup = 26.5 , ratio = 2 )$upper$sbound
round(altbound,2)

## [1] 3.24 2.58 2.21
Sample Size using Bonferroni-adjusted GS design

#Subgroup
\[
x_1 \leftarrow \text{gsSurv}(k = 3, \text{test.type} = 4, \alpha = 0.0125, \beta = 0.1, \text{timing} = c(0.5, 0.75), \text{sfu} = \text{sfLDOF}, \text{sfupar} = c(0), \text{sfl} = \text{sfHSD}, \text{sflpar} = c(-8), \lambda C = \log(2)/17.5, \text{hr} = 0.65, \text{hr0} = 1, \text{eta} = 0.0025, \gamma = c(2.5, 5, 7.5, 10), R = c(1, 1, 1, 8), S = \text{NULL}, T = 37.5, \text{minfup} = 26.5, \text{ratio} = 2)
\]

#Overall
\[
x_2 \leftarrow \text{gsSurv}(k = 3, \text{test.type} = 4, \alpha = 0.0125, \beta = 0.1, \text{timing} = c(0.5, 0.75), \text{sfu} = \text{sfLDOF}, \text{sfupar} = c(0), \text{sfl} = \text{sfHSD}, \text{sflpar} = c(-8), \lambda C = \log(2)/17.5, \text{hr} = 0.7, \text{hr0} = 1, \text{eta} = 0.0025, \gamma = c(2.5, 5, 7.5, 10), R = c(1, 1, 1, 8), S = \text{NULL}, T = 37.5, \text{minfup} = 26.5, \text{ratio} = 2)
\]

\[
N_2 \leftarrow \text{ceiling}(x_1[n.I[3], x_2[n.I[3]])
\]

\[
N_2
\]

## [1] 296 434

Sample Size using CCS GS design

\[
N_{\text{sub}} \leftarrow \text{ceiling}(\text{gsSurv}(k = 3, \text{test.type} = 4, \alpha = \text{alphaadj}, \beta = 0.1, \text{timing} = c(0.5, 0.75), \text{sfu} = \text{sfLDOF}, \text{sfupar} = c(0), \text{sfl} = \text{sfHSD}, \text{sflpar} = c(-8), \lambda C = \log(2)/17.5, \text{hr} = 0.65, \text{hr0} = 1, \text{eta} = 0.0025, \gamma = c(2.5, 5, 7.5, 10), R = c(1, 1, 1, 8), S = \text{NULL}, T = 37.5, \text{minfup} = 26.5, \text{ratio} = 2)sn.I[3])
\]

\[
N_{\text{overall}} \leftarrow \text{ceiling}(\text{gsSurv}(k = 3, \text{test.type} = 4, \alpha = \text{alphaadj}, \beta = 0.1, \text{timing} = c(0.5, 0.75), \text{sfu} = \text{sfLDOF}, \text{sfupar} = c(0), \text{sfl} = \text{sfHSD}, \text{sflpar} = c(-8), \lambda C = \log(2)/17.5, \text{hr} = 0.7, \text{hr0} = 1, \text{eta} = 0.0025, \gamma = c(2.5, 5, 7.5, 10), R = c(1, 1, 1, 8), S = \text{NULL}, T = 37.5, \text{minfup} = 26.5, \text{ratio} = 2)sn.I[3])
\]

\[
N_{\text{corr}} \_ \text{adjusted} \leftarrow c(N_{\text{sub}}, N_{\text{overall}})
\]

\[
N_{\text{corr}} \_ \text{adjusted}
\]

## [1] 283 415

Power

\[
\text{power.subgroup} \leftarrow \text{sum(\text{gsProbability}(\theta = x_1$delta, n.I = \text{ceiling}(x_1 sn.I), k = 3, a = c(-20, -20, -20), b = \text{altbound}$upper$s prob))}
\]

\[
\text{power.overall} \leftarrow \text{sum(\text{gsProbability}(\theta = x_2$delta, n.I = \text{ceiling}(x_2 sn.I), k = 3, a = c(-20, -20, -20), b = \text{altbound}$upper$s prob))}
\]

\[
\text{power.subgroup}
\]

## [1] 0.9139928
HR bound using Bonferroni-adjusted GS design

IA1.HR.bound <- \text{exp}(-3.35/\sqrt{217*(1/3)*(2/3)})
IA2.HR.bound <- \text{exp}(-2.67/\sqrt{326*(1/3)*(2/3)})
FA.HR.bound <- \text{exp}(-2.28/\sqrt{434*(1/3)*(2/3)})
a_HR_e <- \text{round}(c(IA1.HR.bound, IA2.HR.bound, FA.HR.bound),2)

a_HR_e
## [1] 0.62 0.73 0.79

HR bound using CCS GS design

IA1.HR.bound_a <- \text{exp}(-3.24/\sqrt{217*(1/3)*(2/3)})
IA2.HR.bound_a <- \text{exp}(-2.58/\sqrt{326*(1/3)*(2/3)})
FA.HR.bound_a <- \text{exp}(-2.21/\sqrt{434*(1/3)*(2/3)})
a_HR_a <- \text{round}(c(IA1.HR.bound_a, IA2.HR.bound_a, FA.HR.bound_a),2)

a_HR_a
## [1] 0.63 0.74 0.80

Reference

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