interAdapt – An Interactive Tool for Designing and Evaluating Randomized Trials with Adaptive Enrollment Criteria

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Abstract

We consider the problem of designing a randomized trial when there is prior evidence that the experimental treatment may be more effective for certain groups of participants, such as those with a certain biomarker or risk score at baseline. Randomized trial designs have been proposed that dynamically adapt enrollment criteria based on accrued data. Such trial designs aim to learn if the treatment benefits the overall population, only a certain subpopulation, or neither. We introduce the **interAdapt** software tool, which provides a user friendly interface for constructing and evaluating certain adaptive trial designs. These designs are automatically compared to standard (non-adaptive) designs in terms of the following performance criteria: power, sample size, and trial duration. Unlike existing software, **interAdapt** is open-source and cross-platform, and is the first to implement the group sequential, adaptive enrichment designs of (6).

Keywords: Adptive Design, Adaptive Enrollment, Group Sequential Design, Shiny Application.

Introduction

Group sequential, randomized trial designs involve rules for early stopping based on analyses of accrued data. Such early stopping could occur if there is strong evidence early in the trial of benefits or harms of the new treatment being studied. Adaptive enrichment designs include rules for changing enrollment criteria based on data accrued in the ongoing trial. For example, enrollment may be restricted to a certain subpopulation if strong early evidence indicates no benefit for the complementary population. We focus on the class of designs introduced by (6), which combines features of both group sequential and adaptive enrichment designs. For conciseness, we refer to designs in this class as "adaptive designs." These are contrasted with "standard designs," defined to be group sequential designs where the enrollment criteria cannot be changed during the trial (but the trial may be stopped early).

We introduce the **interAdapt** software tool, which provides a user-friendly interface for exploring certain types of adaptive enrichment designs, and for comparing these to standard designs. The software can either be run locally as an R package, or accessed online through a web browser. **interAdapt** is designed to be used by statisticians and clinical investigators to plan

randomized trials. The software provides information that can help users quickly determine if certain adaptive designs offer tangible benefits compared to standard designs, in the context of their specific trial goals and constraints. Calculations typically require less than 1 minute on a standard commercial laptop. Several user inputs are available to allow the user to describe the context of his/her trial. Alternatively, users can upload data from previous studies, and **interAdapt** will automatically compute the relevant parameters for the trial being planned. Once entered, the full set of input parameters can be saved to the user's computer for use in future sessions. Results of the design comparisons can be immediately downloaded in the form of either csv-tables, or printable, html-based reports.

To demonstrate our designs and software, we consider the problem of planning a Phase III trial for a new surgical treatment of stroke, which is considered by (6). The new treatment is called Minimally-Invasive Surgery Plus rt-PA for Intracerebral Hemorrhage (MISTIE), and is described in detail in (5). Previous trials had almost exclusively enrolled participants with little or no intraventricular hemorrhage (IVH) at baseline (referred to as small IVH participants). However, it was conjectured that the treatment may also benefit participants with large IVH volume at baseline. The goal of the Phase III trial being planned was to determine whether MISTIE is effective for the combined population of those with small or large IVH, and, if not, to determine whether MISTIE is effective for the small IVH population (for whom there was greater prior evidence). A standard trial design, e.g., one enrolling the combined population throughout the trial, or one enrolling only small IVH participants throughout the trial, may be inefficient at simultaneously answering these questions. An alternative is to use an adaptive trial design, which would first recruit from the combined population, and then decide whether to restrict enrollment based on results from interim analyses. Though we focus on this stroke trial application throughout, our software tool can be applied in many disease areas.

In Section 1, we formally define the hypothesis testing problem to be addressed by different trial designs. In Section 2, we compare our software to the most similar, currently available commercial software, AptivSolutions ADDPLAN PE (participant Enrichment). In Section 3, we describe how to install **interAdapt** on a personal computer, and how to access it online through a web browser. Section 4 describes the inputs available when using interAdapt, and discusses the interpretation of the application's output. In Section 5, we present an example demonstrating how an adaptive design is created and analyzed with interAdapt.

1. Problem description

We consider the problem of testing whether a new treatment is superior to control. Consider the case where we have two subpopulations, referred to as subpopulation 1 and subpopulation 2. These must be specified before the trial starts, and be defined in terms of participant attributes measured at baseline (e.g., having a high initial severity of disease or a certain biomarker value). We focus on situations where there is suggestive, prior evidence that the treatment may be more likely to benefit subpopulation 1. In the MISTIE trial example, subpopulation 1 refers to small IVH participants, and subpopulation 2 refers to large IVH participants. Let π_1 and π_2 denote the proportion of participants in subpopulations 1 and 2, respectively.

Both the adaptive and standard designs discussed here involve enrollment over time, and include predetermined rules for stopping the trial early based on interim analyses. Each trial consists of K stages. In stages when both subpopulations are enrolled, we assume that the proportion of newly recruited participants in each subpopulation $s \in \{1, 2\}$ is equal to the corresponding population proportion π_s.

Let $Y_{i,k}$ be the a binary outcome variable for the ith participant recruited in stage k, where $Y_{i,k} = 1$ indicates a successful outcome. Let $T_{i,k}$ be an indicator of the ith participant recruited in stage k being assigned to the treatment. We assume there is an equal probability of being

assigned to treatment or control.

For subpopulation 1, denote the probability of a successful outcome under treatment as p_{1t}, and the probability of a successful outcome under control as p_{1c}. Similarly for population 2, let p_{2t} denote the probability of a success under treatment, and p_{2c} denote the probability of a success under control. We assume each of $p_{1c}, p_{1t}, p_{2c}, p_{2t}$ is in the interval $(0, 1)$. We define the true average treatment effect for a given population to be the difference in the probability of a successful outcome comparing treatment versus control.

In the remainder of this section we give an overview of the relevant concepts needed to understand and use interAdapt. A more detailed discussion of the theoretical context, and of the parameter calculation procedure, is provided by (6).

1.1. Hypotheses

We focus on testing the null hypothesis that on average, the treatment is no better than control for subpopulation 1, and the analogous null hypothesis for the combined population. These two null hypotheses are defined, respectively, as

- H_{01}: $p_{1t} - p_{1c} \leq 0$;

- H_{0C}: $\pi_1(p_{1t} - p_{1c}) + \pi_2(p_{2t} - p_{2c}) \leq 0$.

interAdapt compares different designs for testing these null hypotheses. An adaptive design testing both null hypotheses is compared to a standard design testing only H_{0C}, and to a standard design testing only H_{01}. We refer to the adaptive design as AD, and refer to these two standard designs as SC and SS, respectively. All three trials contain K stages, and the decision to entirely stop the trial early can be made at the end of any stage. The trials differ in that SC and SS never change their enrollment criteria, while AD may switch to enroll only participants from subpopulation 1.

Note that the standard designs discussed here are not the same as those discussed in section 6.1 of (6), which test both hypothesis simultaneously. Implementing standard designs such as those discussed in (6) into the software is an area of future research.

1.2. Test statistics

Three z-statistics are computed at the end of each stage k. The first is based on all enrolled participants in the combined population, the second is based on all enrolled participants in subpopulation 1, and the third is based on all enrolled participants in subpopulation 2. Each z-statistic is a standardized difference in sample means comparing treatment versus control arms. Let $Z_{C,k}$ denote the z-statistic for the combined population, which takes the following form:

$$Z_{C,k} = \left[\frac{\sum_{k'=1}^{k} \sum_{i=1}^{n_{k'}} Y_{i,k'} T_{i,k'}}{\sum_{k'=1}^{k} \sum_{i=1}^{n_{k'}} T_{i,k'}} - \frac{\sum_{k'=1}^{k} \sum_{i=1}^{n_{k'}} Y_{i,k'}(1 - T_{i,k'})}{\sum_{k'=1}^{k} \sum_{i=1}^{n_{k'}}(1 - T_{i,k'})} \right]$$
$$\times \left\{ \left(\frac{2}{\sum_{k'=1}^{k} n_{k'}} \right) \left(\sum_{s \in \{1,2\}} \pi_s [p_{sc}(1 - p_{sc}) + p_{st}(1 - p_{st})] \right) \right\}^{-1/2}$$

The term in square brackets is the difference in sample means between the treatment and control groups. The term in curly braces is the variance of this difference in sample means.

Let $Z_{1,k}$ and $Z_{2,k}$ denote analogous z-statistics restricted to participants in subpopulation 1 and 2, respectively. The z-statistic for subpopulation 1 can be written as follows, where $A_{i,k}$ is the

indicator that the ith subject recruited in stage k is in subpopulation 1:

$$Z_{1,k} = \left[\frac{\sum_{k'=1}^{k} \sum_{i=1}^{n_{k'}} Y_{i,k'} T_{i,k'} A_{i,k'}}{\sum_{k'=1}^{k} \sum_{i=1}^{n_{k'}} T_{i,k'} A_{i,k'}} - \frac{\sum_{k'=1}^{k} \sum_{i=1}^{n_{k'}} Y_{i,k'} (1 - T_{i,k'}) A_{i,k'}}{\sum_{k'=1}^{k} \sum_{i=1}^{n_{k'}} (1 - T_{i,k'}) A_{i,k'}} \right]$$
$$\times \left\{ \left(\frac{2}{\sum_{k'=1}^{k} \sum_{i=1}^{n_{k'}} A_{i,k'}} \right) (\pi_1 [p_{1c}(1 - p_{1c}) + p_{1t}(1 - p_{1t})]) \right\}^{-1/2}$$

The z-statsistic $Z_{2,k}$ is similar to the above, except replacing each occurrence of $A_{i,k'}$ by $(1 - A_{i,k'})$.

The decision rules defined later on in this section involve boundaries for $(Z_{C,1}, Z_{C,2}, ... Z_{C,K})$, $(Z_{1,1}, Z_{1,2}, ... Z_{1,K})$, and $(Z_{2,1}, Z_{2,2}, ... Z_{2,K})$. To calculate the familywise Type I error of any given set of decision rules, we make use of the multivariate distribution of $(Z_{C,1}, Z_{C,2}, ... Z_{C,K}, Z_{1,1}, Z_{1,2}, ... Z_{1,K})$, which under the assumptions in (6) is asymptotically normal with a known covariance matrix (4).

1.3. Type I error control

The familywise Type I error rate is the probability of rejecting one or more true null hypotheses. For a given design, we say that the familywise Type I error rate is strongly controlled at level α if the probability of rejecting at least one true null hypothesis (among H_{0C}, H_{01}) is at most α, regardless of the true values of $p_{1c}, p_{1t}, p_{2c}, p_{2t}$. For all three designs, AD, SC, and SS, we require the familywise Type I error rate to be strongly controlled at level α. Since the two standard designs SS and SC each only test a single null hypothesis, the familywise Type I error rate for each is equal to the corresponding Type I error rate.

1.4. Decision rules for early stopping and for modifying enrollment criteria

The decision rules for the standard design SC consist of efficacy and futility boundaries for H_{0C}. At the end of each stage k, the test statistic $Z_{C,k}$ is calculated. If $Z_{C,k}$ is above the efficacy boundary for stage k, we reject H_{0C} and end the trial. If $Z_{C,k}$ is between the efficacy and futility boundaries for stage k, we continue the trial. If $Z_{C,k}$ is below the futility boundary for stage k, we end the trial with the conclusion that we have failed to reject H_{0C}. **interAdapt** makes the simplification that the number of participants enrolled in each stage of SC is constant (n_{SC}), and allows the user to input this per-stage sample size.

The efficacy boundaries for SC are set to be proportional to those described by Wang and Tsiatis (1987). This means that the efficacy boundary for the kth stage is set to $e_{SC}\{(\sum_{k'=1}^{K} n_{k'})/n_k\}^{-\delta}$, where K is the total number of stages, δ is a constant in the range $[-.5, .5]$, and e_{SC} is the constant calibrated to ensure the desired familywise Type I error rate. In order to calculate e_{SC}, we make use of the fact that the random vector of test statistics $(Z_{C,1}, Z_{C,2}, \ldots Z_{C,K})$ follows a multivariate normal distribution with a known covariance structure (4).Using the "mvtnorm" package (2) in R to evaluate the multivariate normal distribution function, we find the proportionality constant e_{SC} such that the null probability of $Z_{C,k}$ exceeding $e_{SC}\{(\sum_{k'=1}^{K} n_{k'})/n_k\}^{-\delta}$ at any stage k is less than or equal to α.

In SC, as well as in SS and AD, we make use of non-binding futility constants. All three designs are calibrated such that familywise Type I error rate is controlled at level α regardless of whether the futility boundaries are ignored. In calculating power however, we do assume that the futility boundaries are adhered to.

Futility boundaries for the first $K - 1$ stages of SC are proportional to $\{(\sum_{k'=1}^{K} n_{k'})/n_k\}^{-\delta}$, but with a different proportionality constant, f_{SC}. The constant f_{SC} is negative by default, though this is not required. In the Kth stage of the trial, **interAdapt** sets the futility bound to be equal

to the efficacy bound. This ensures that $Z_{C,K}$ eventually crosses either the efficacy bound or less futility bound.

The decision boundaries for $Z_{1,k}$ in the SS design are defined by exactly the same form. The efficacy boundary for the kth stage is set equal to $e_{SS}\{(\sum_{k'=1}^{K} n_{k'})/n_k\}^{-\delta}$, where e_{SS} is the constant that ensures the appropriate Type I error rate. The first $K-1$ futility boundaries for H_{01} are set equal to $f_{SS}\{(\sum_{k'=1}^{K} n_{k'})/n_k\}^{-\delta}$, where f_{SS} is a constant that can be set by the user. The futility boundary in stage K is set equal to the final efficacy boundary in stage K. The user can specify the number of participants to enroll in each stage (n_{SS}). This per-stage enrollment rate is set to be constant across stages.

Decision boundaries for AD vary from those of the standard designs two ways. First, because AD simultaneously tests H_{0C} and H_{01} it has two sets of decision boundaries. For the kth stage of AD, let $u_{C,k}$ and $u_{1,k}$ denote the efficacy boundaries for H_{0C} and H_{01} respectively. The boundaries $u_{C,k}$ and $u_{1,k}$ are set equal to $e_{AD,C}\{(\sum_{k'=1}^{K} n_{k'})/n_k\}^{-\delta}$ and $e_{AD,1}\{(\sum_{k'=1}^{K} n_{k'})/n_k\}^{-\delta}$ respectively, where $e_{AD,C}$ and $e_{AD,1}$ are constants set such that the probability of rejecting either hypothesis under the global null hypothesis is zero.

The boundaries for stopping the AD design without rejecting the null hypotheses are denoted as $l_{1,k}$ and $l_{2,k}$. These stopping boundaries are defined relative to the test statistics $Z_{1,k}$ and $Z_{2,k}$. The boundaries are set equal to $f_{AD,C}\{(\sum_{k'=1}^{K} n_{k'})/n_k\}^{-\delta}$ and $f_{AD,S}\{(\sum_{k'=1}^{K} n_{k'})/n_k\}^{-\delta}$ respectively, where $f_{AD,C}$ and $f_{AD,S}$ can be set by the user.

The second way that the decision boundaries of AD differ from those of the standard designs is that we allow more flexibility in the futility boundaries. In each stage k, our adaptive design has the option of stopping enrollment in subpopulation 2, based on the treatment effect estimate $Z_{2,k}$. **interAdapt** also allows the user to specify a final stage for testing an effect in the total population, denoted by stage k^*. Regardless of the results at stage k^*, we always stop enrolling from subpopulation 2 at the end stage k^*, if we have not done so already. The futility boundaries $l_{2,k}$ are not defined for $k > k^*$.

For the AD design, the user can specify two stage specific sample sizes, one for stages when both populations are enrolled ($k \leq k^*$), and one for stages where only participants in subpopulation 1 are enrolled ($k > k^*$). We refer to these two sample sizes as n_1^* and n_k^* respectively.

As described in (6), our decision rules in AD consist of the following steps for each stage k:

1. (Assess Efficacy) If $Z_{C,k} > u_{C,k}$, reject H_{0C}. If $Z_{1,k} > u_{1,k}$, reject H_{01}. If either, or both null hypothesis are rejected, stop all enrollment and end the trial.

2. (Assess Futility of the entire trial) Else, if $Z_{1,k} \leq l_{1,k}$ or if this is the final stage of the trial, stop all enrollment and end the trial for futility, failing to reject either H_{0C} or H_{01}.

3. (Assess Futility for H_{0C}) Else, if $Z_{2,k} \leq l_{2,k}$, or if $k \geq k^*$, stop enrollment from subpopulation 2 in all future stages. In this case, the following steps must then be done:

   3.a If $Z_{1,k} > u_{1,k}$, reject H_{01} and stop all enrollment.

   3.b If $Z_{1,k} \leq l_{1,k}$ or if this is the final stage of the trial, conclude that we've fail to reject either H_{0C} or H_{01}, and stop all enrollment.

   3.c Else, continue to enroll participants from subpopulation 1. If $k < k^*$ then $\pi_1 n_1^*$ participants should be enrolled in the next stage. If $k \geq k^*$, then n_k^* participants should be enrolled in the next stage. For all future stages, ignore steps (1-2), and proceed directly to steps (3.a-3.c).

4. (Continue Enrollment from Combined Population) Else, continue by enrolling $\pi_1 n_1^*$ participants from subpopulation 1 and $\pi_2 n_1^*$ participants from subpopulation 2 for the next stage. Then return to step 1.

The decision rules outputted by **interAdapt** represent the feature that enrollment of subpopulation 2 cannot continue after stage k^* by setting the futility boundary l_{2,k^*} equal infinity. This ensures that $Z_{2,k^*} < l_{2,k^*}$.

To correctly calibrate $e_{AD,C}$ and $e_{AD,1}$, **interAdapt** first chooses $e_{AD,C}$ such the probability of falsely rejecting H_{0C} is $a_c\alpha$, where a_c is a fraction between 0 and 1 that can be specified by the user. Then, conditional on $e_{AD,C}$, **interAdapt** finds the smallest constant $e_{AD,1}$ such that, under the global null of no treatment effect in either subpopulation, we have

$$\mathsf{P}\left(Z_{C,k} > e_{AD,C}\left\{\frac{\sum_{k'=1}^{K} n_{k'}}{n_k}\right\}^{-\delta} \text{ or } Z_{1,k} > e_{AD,1}\left\{\frac{\sum_{k'=1}^{K} n_{k'}}{n_k}\right\}^{-\delta} \text{ for any } k\right) \le \alpha$$

The fact that familywise Type I error rate is controled under the global null implies that it is also strongly controled under all hypotheses (6).

2. Related software

The most comparable available software is AptivSolutions ADDPLAN PE (participant Enrichment), an impressive, commercial software that implements certain types of adaptive enrichment designs. It has many features that our software does not have. Conversely, there are features of our software that ADDPLAN PE does not have. First, ADDPLAN PE does not implement the class of designs from (6). Second, in ADDPLAN PE, the user must a priori designate a particular stage (e.g., stage 2) at which a change to enrollment may be made, even though there may be large a priori uncertainty as to when sufficient information will have accrued to make such a decision. In contrast, our software is more flexible, in that one can select designs (by setting k^* to the maximum number of stages) in which the decision to change enrollment criteria can be made at any stage.

interAdapt also has the benefits of being cross-platform and open-source, while ADDPLAN PE is commercial software that is only compatible with the Windows OS.

3. Running interAdapt

interAdapt is an interactive application built on the **shiny** package (**?**) for the R programming language (http://www.r-project.org/). The user interface is shown in the user's default web browser, while the back-end calculations are all done in R. Users can run **interAdapt** either by installing R and the **interAdapt** R package locally on their computer, or by simply using a web browser view **interAdapt** online. Both options are free and quick to set up. However, because online application will slow down noticeably when accessed by multiple users, we encourage heavy users to install **interAdapt** locally.

3.1. Running interAdapt over the web

interAdapt is currently hosted on the RStudio webserver, and can be accessed simply visiting the link below. http://spark.rstudio.com/mrosenblum/interAdapt

3.2. Running interAdapt locally

To run **interAdapt** locally, one must first install the R programming language. R runs on both Windows & MacOS, with the most current versions available for download at (http://www.r-project.org/). After downloading and installing R, activating the R application will

open an "R Console" window where typed commands are executed by R. interAdapt is available as a package for R, and can be installed by typing the lines below into the R Console, while connected to the Internet. The return key must be pressed after each line of code. The first and third lines will cause R to give feedback on the installation progress, which we do not show here.

```
install.packages('devtools')
library('devtools')
install_github(username='aaronjfisher',repo='interAdapt',subdir='r_package')
```

Once interAdapt has been installed, the application can be run without an internet connection by the opening the R Console and typing.

```
library('interAdapt')
runInterAdapt()
```

4. User interface

Inputs to **interAdapt** can be entered in the side panel on the left, with outputs are shown in the main panel on the right. The parameters in the input panel let the user describe known or assumed characteristics of their populations of interest, as well as their trial design parameters. Input parameters include the proportion of participants in each subpopulation, the participant recruitment rate in each subpopulation, and the desired familywise Type I error rate. The output section displays the decision boundaries and trial designs that will satisfy the requirements specified by the user. It also compares the performance of the three designs, AD, SC and SS. Performance is compared in terms of power, expected sample size, and expected trial duration.

All tables generated by **interAdapt** can be downloaded as csv files by clicking on the download button beneath the table. Users can also download an automated report of the results by clicking the "Generate Report" button at the bottom of the output panel. This report is generated with the **knitr** package for R ([7]). Citations in the report are created using the **knitcitations** package ([1]).

4.1. Inputs

Parameters in the input panel are organized into two sections, basic parameters and advanced parameters. To view the different sets of parameters, click the drop down menu titled "Show basic parameters."

Basic parameters can be entered using either "Batch mode" or "Interactive mode". In Batch mode, **interAdapt** will not analyze the entered parameters until the "Apply" button is pressed. This allows for several parameters to be changed at once without waiting for **interAdapt** to recalculate the results after each individual change. In Interactive mode, **interAdapt** will automatically recalculate the results after each change, allowing the user to quickly see the effect of changing one specific input parameter. Switching between Batch mode and Interactive mode can be done using the dropdown menu at the top of the Basic Parameters section. Interactive mode is not available when entering advanced parameters.

To save the current set of inputs, select the dropdown menu titled "Show basic parameters" and select "Show All Parameters and Save/Load Option". From here, you can save the current parameters as a csv file, or load a previously saved csv file of inputs. Regardless of whether **interAdapt** is being run online or locally, these saved csv files are always stored on the user's computer. You may also load a 3-column dataset into **interAdapt** in the form of a csv, where each row contains information about a participant in the trial. The first column must contain binary indicators of subpopulation, where 1 denotes subpopulation 1, and 2 denotes subpopulation 2. The second column must contain an indicator of the treatment arm (T_i), and the third column must contain the binary outcome measurement (Y_i). The first row of this dataset file is expected to be a header row of labels, rather than values for the first individual. From this dataset, **interAdapt** will calculate π_1, p_{1c}, p_{1t}, p_{2c}, and p_{2t}, and adjust the input sliders accordingly.

A detailed explanation of each input is given below.

Basic parameters

- Subpopulation 1 proportion (π_1): The proportion of the population in subpopulation 1. This is the subpopulation in which we have prior evidence of a stronger treatment effect.

- Probability outcome = 1 under control, subpopulation 1 (p_{1c}): The probability of experiencing a successful outcome for control participants in subpopulation 1. This is used in estimating power and expected sample size of each design.

- Probability outcome = 1 under control, subpopulation 2 (p_{2c}): The probability of experiencing a successful outcome for control participants in subpopulation 2. This is used in estimating power and expected sample size of each design.

- Probability outcome = 1 under treatment for sub-population 1 (p_{1t}): The probability of experiencing a successful outcome for treated participants in subpopulation 1. Note that a specific effect size is not specified for subpopulation 2. Instead, **interAdapt** generates the relevant performance metrics for a range of several possible effect sizes in subpopulation 2. This range can be specified in the Advanced Parameters section.

- Per stage sample size, combined population (n_1^*): The number of participants enrolled in stages 1 through k^* of AD. Per stage enrollment for SC and SS can be entered in the advanced parameters section.

- Per stage sample size for stages where only sub-population 1 is enrolled (n_k^*): The number of participants required for each stage after stage k^*, in the AD design.

- Alpha (FWER) Requirement (α): The familywise Type I error rate for all hypotheses in the trial. In AD, this is the probability of falsely rejecting either H_{0C} or H_{01}. In SC it is the probability of falsely rejecting H_{0C}. In SS it is the probability of falsely rejecting H_{01}.

- Proportion of Alpha allocated to H0C (a_C): To control the familywise Type I error rate in the AD design, the test of H_{0C} is first calibrated to have a Type I error rate equal to $a_C\alpha$. The decision rules for H_{01} are then calibrated so that the overall familywise Type I error rate is equal to α.

Advanced parameters

- Delta (δ): This parameter defines the curvature of the efficacy and futility boundaries, which are all proportional to $\{(\sum_{k'=1}^{K} n_{k'})/n_k\}^{-\delta}$.

- Number of Iterations for simulation: Z-statistics are simulated generate the power, expected sample size, and expected trial duration. Generally, about 10,000 simulations are needed for reliable results. It is our experience that a simulation with 10,000 iterations takes about 15 seconds on a modern personal computer.

- Time limit for simulation, in seconds: If the simulation time exceeds this threshold, calculations will stop and the user will get an error message saying that the application has "reached CPU time limit". To remove the error, either the number of iterations can be reduced, or the time limit for simulation can be extended. **interAdapt** does not allow for this time limit to exceed 90 seconds.

- Total number of stages (K): The total number of stages for all three designs.

- Participants enrolled per year from combined population: The number of participants that can be recruited per year in the combined population. This affects the estimated duration of the trials. The recruitment rates for subpopulations 1 and 2 are equal to the combined population recruitment rate multiplied by π_1 and π_2 respectively.

- Lower bound for treatment effect in sub-population 2: **interAdapt** simulates performance metrics under a range of treatment effect sizes for subpopulation 2. This sets the lower bound for this range.

- Upper bound for treatment effect in sub-population 2: **interAdapt** simulates performance metrics under a range of treatment effect sizes for subpopulation 2. This sets the upper bound for this range.

- Last stage sub-population 1 is enrolled under an adaptive design (k^*): In the adaptive design, we don't enroll any participants from subpopulation 2 after stage k^*.

- Per stage sample size for standard group sequential design enrolling combined pop (n_{SC}): The number of participants enrolled in each stage for SC.

- Per stage sample size for standard group sequential design enrolling only subpop. 1 (n_{SS}): The number of participants enrolled in each stage for SS.

- H_{0C} futility boundary proportionality constant for the adaptive design ($f_{AD,C}$): This is used to calculate the futility boundary for H_{0C} in the adaptive design, which is set to $f_{AD,C}\{(\sum_{k'=1}^{K} n_{k'})/n_k\}^{-\delta}$ in stage k.

- H_{01} futility boundary proportionality constant for the adaptive design ($f_{AD,S}$): This is used to calculate the futility boundary for H_{01} in the adaptive design, which is set to $f_{AD,S}\{(\sum_{k'=1}^{K} n_{k'})/n_k\}^{-\delta}$ in stage k.

- H_{0C} futility boundary proportionality constant for the standard design (f_{SC}): This is used to calculate the futility boundary for H_{0C} in SC, which is set to $f_{SC}\{(\sum_{k'=1}^{K} n_{k'})/n_k\}^{-\delta}$ in stage k.

- H_{01} futility boundary proportionality constant for the standard design (f_{SS}): This is used to calculate the futility boundary for H_{01} in SS, which is set to $f_{SS}\{(\sum_{k'=1}^{K} n_{k'})/n_k\}^{-\delta}$ in stage k.

4.2. Outputs

The output panel of the user interface is split into three sections, "About interAdapt", "Designs" output and "Performance" output. The "About interAdapt" section gives a brief introduction to the software, and a link to the full software documentation. The Designs output gives a road plan for how to conduct each of the three trials: FA, AD and SC. This includes the efficacy boundaries; user specified non-binding futility boundaries, and number of participants to recruit by the end of each stage. Performance output compares the three designs in terms of their power, expected sample size, and expected duration. The radio buttons at the top of the output section can be used to switch between these three sections.

Designs output

The designs output gives information on how to conduct each of the three trials. Tabs at the top of the page can be used to navigate between the results for each design. Each of the first three tabs each correspond with one of the designs, and the fourth tab shows all three designs side by side.

In the "Adaptive" tab, the table at the bottom of the page shows the required number of participants that must be recruited by the end of each stage.For each stage k, the table also gives efficacy boundaries for $Z_{1,k}$ and $Z_{C,k}$, and futility boundaries for $Z_{1,k}$ and $Z_{2,k}$. Because we always stop enrolling subpopulation 2 after stage k^*, futility boundaries for $Z_{2,k}$ in stage k^* and later stages are not given. For the same reason, efficacy boundaries for $Z_{C,k}$ are not given for stages $k > k^*$. A plot at the top of the page shows these efficacy and futility boundaries for $Z_{C,k}$, $Z_{1,k}$ and $Z_{2,k}$ over all stages of the trial.

The two tabs for the standard designs have a comprable layout. Note that the efficacy boundaries for SS and SC are identical. This is because the efficacy boundary depends only on the null distribution of z-statistics, which unaffected by the choice of study population. The two standard trials each pull from only one subpopulation, so their efficacy boundaries are the same.

The final tab combines the tables from the first three tabs, and omits plots of the decision boundaries.

Performance output

interAdapt shows performance of each of the three designs in terms of four metrics: power, expected sample size, and expected duration. These metrics all depend, among other things, on the true treatment effect in each subpopulation. A treatment effect for subpopulation 1 can be specified in the Basic Parameters section, and a range of values for the treatment effect in subpopulation 2 can be specified in the Advanced Parameters section. **interAdapt** will calculate performance metrics for the specified range of treatment effects, and generate charts of each metric plotted against the underlying treatment effect in subpopulation 2. These four plots can be accessed via the tabs at the top of the page. The table at bottom of the output section shows all four metrics side by side, with each column of the table denoting a different treatment effect in subpopulation 2.

When the true treatment is very strong, trials will tend to be able to detect the treatment effect more easily, and will be more likely to stop early for efficacy. This translates to an overall increase in power, a decrease in expected sample size, and a decrease in expected trial duration. Conversely, if the true underlying treatment effect is significantly harmful, the trials will be more likely to stop early for futility. This also leads to small expected sample sizes, and shorter expected durations. Trials will tend to last the longest when the treatment effect is positive, but not overwhelmingly strong. These patterns are reflected in the plots shown by interAdapt.

The power plot shows the power of AD to reject H_{0C}, to reject H_{01}, and to reject at least one of H_{0C} or H_{01}. As the standard design SC only tests H_{0C}, **interAdapt** only shows it's power to reject H_{0C}. Likewise, **interAdapt** only shows the power of SS to reject H_{01}. Note that the

power of SC and AD to reject H_{0C} both increase as the treatment effect for subpopulation 2 increases. The power of AD to reject H_{01} decreases as the treatment effect in subpopulation 2 increases, but this is only because AD does not bother to test H_{01} after a treatment effect in the combined population is discovered.

In general, power of a trial can be increased by increasing the per-stage sample size (n_1^*, n_k^*, n_{SS} and n_{SC}), increasing the number of stages (K), lowering the futility boundaries (f_{SC}, f_{SS}, $f_{AD,C}$, or $f_{AD,S}$), or relaxing the required Type I error rate (α).

The power of SS is constant with respect to the true treatment effect in subpopulation 2, as we'd expect since SS does not take any data from subpopulation 2. The expected sample size and expected duration for SS are also constant with respect to the true treatment effect in subpopulation 2.

In the plot of expected sample size for each design, we see that trials tend to need to recruit more participants when the treatment effect is weak. For designs testing for an effect in the combined population, this means that the expected sample size will be highest when the weighted average treatment effect across subpopulations is weak. If the treatment effect is significantly positive in subpopulation 1, the highest possible expected sample size may come at a negative value for the true treatment effect in subpopulation 2. In general, lowering K or k^*, increasing the futility bounds (f_{SC}, f_{SS}, $f_{AD,C}$, or $f_{AD,S}$), or relaxing the required Type I error rate (α), can all decrease the expected sample size.

The plot of expected trial duration for each design shows patterns very similar to those in the plot of expected sample size. A trial's duration is defined as the time until the last participant's outcome is measured. Like expected sample size, the expected duration can be decreased by lowering K or k^*, increasing the futility bounds (f_{SC}, f_{SS}, $f_{AD,C}$, or $f_{AD,S}$), or relaxing α. Increasing the recruitment rate can also shorten the expected duration of a trial.

5. Example of entering input and interpreting output

The default inputs to **interAdapt** come from the motivating example of the MISTIE Phase III trial. This section presents a summary of this trial, and of the design goals of the investigators, as described in (6). The MISTIE trial studied a new surgical treatment for stroke, and measured participant's outcomes by their disability score on the modified Rankin Scale (mRS) 180 days after enrollment. A successful outcome was defined as a mRS score less than or equal to 3.

The Phase II trial for the MISTIE treatment had only enrolled participants with with little or no intraventricular hemorrhage (IVH). More specifically, participants had been categorized as "small IVH" if their IVH volume was less than 10ml, and did not require a catheter for intracranial pressure monitoring. Otherwise, pateints were classified as "large IVH." The Phase II trial only recruited small IVH participants, and yeiled a treatment effect estimate of 12.1% [95% CI: (-2.7%, 26.9%)]. The investigators thought that the treatment could also be effective in large IVH pateints, but no data had yet been collected to test this. Thus, we refer to the subpopulation of small IVH participants as subpopulation 1, as there was more prior evidence of treatment efficacy in this subpopulation.

The study designers were concerned with the calibrating power and alpha level of the Phase III trial under the following three scenarios:

(a) The average treatment effect is 12.5% for both small and large IVH pateints;

(b) The average treatment effect is 12.5% for small IVH participants, and zero large IVH participants;

(c) The treatment effect is zero both subpopulations.

In the context of these scenarios, the study coordinators had three goals:

(i) At least 80% power for testing H_{0C} in scenario (a);

(ii) At least 80% power for testing H_{01} in scenario (b);

(iii) A familywise Type I error rate (α) of .025.

Prior research by (3) indicated that the proportion of participants with small IVH (π_1) was .33, that the probability of a positive outcome under control was .25 for small IVH participants (p_{1c}), and that the probability of a positive outcome under control was .2 for large IVH participants (p_{2c}). If the true treatment effect in subpopulation 1 was 12.5% then the probability of a positive outcome under treatment for participants in subpopulation 1 (p_{1t}) would be approximately 12.5%+25%=37.5%.

Since the adaptive design AD tests H_{0C} as well as H_{01}, it must achieve all three goals (i)-(iii). The standard design SC need only achieve (i) and (iii), and the standard design SS need only achieve (ii) and (iii). Recall that **interAdapt** allows the user to specify a range of treatment values for subpopulation 2, and will display the power of the trial designs across this range. By default, **interAdapt** sets the range of values for the treatment affect in subpopulation 2 to [-.2, .2], letting the user see the power of all three designs under scenarios (a) and (b).

The remaining default input parameters come from the analysis section of (6). Here, the authors first fixed $K = 5$ and $\delta = -.5$, and then searched for values of the remaining parameters that minimize the average expected sample size over scenarios (a)-(c) for the adaptive design, while still achieving goals (i)-(iii). They found a minimum average expected sample size at $k^* = 4$, $n_1^* = 150$, $n_k^* = 311$, and $f_{AD,C} = f_{AD,S} = 0$.

Now we turn to the output of **interAdapt** that results from the default parameters, and show that each of the three designs achieves its relevant goals. In the power plot, we see that AD has 80% power to reject H_{0C} in scenario (a), and 80% power to reject H_{01} in scenario (b). SC has 80% power to reject H_{0C} in scenario (a), and SS has 80% power to reject H_{01} in scenario (b). Although it is not shown, we know that the familywise Type I error rate is less than .025, as this was specified as an input to interAdapt.

Summary

We described the **interAdapt** application for designing and simulating trials with adaptive enrollment criteria. We provided an overview of the theoretical problem the application addresses, and gave an explanation of the application's inputs and outputs.

Current limitations of the software include that the outcome is assumed to be binary.

Acknowledgements

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