BATS 1.0.0 Documentation

Introduction

BATS (Bayesian Adaptive Trial Simulator) is a simulation tool for designing Bayesian Multi-Arm Multi-stage (MAMS) trials.

Requirements

The BATS binary installer runs in Windows 7 or newer. No other dependencies are required.

The BATS Python package requires numpy, pandas, matplotlib, Cython, cython-gsl and PyQt5 packages with Python 3+. In addition, it requires Qt5 and GNU Statistical Library installed.

License

The back-end code of BATS is written in Python and Cython, the Graphic User Interface (GUI) is implemented with Qt 5.6. BATS is freely distributed under the GPLv3 License.

Installation

A binary installer could be downloaded from https://sourceforge.net/projects/bats/

User can also install BATS as a Python package from PyPI, through the following code:

```
$ pip install BATS
```

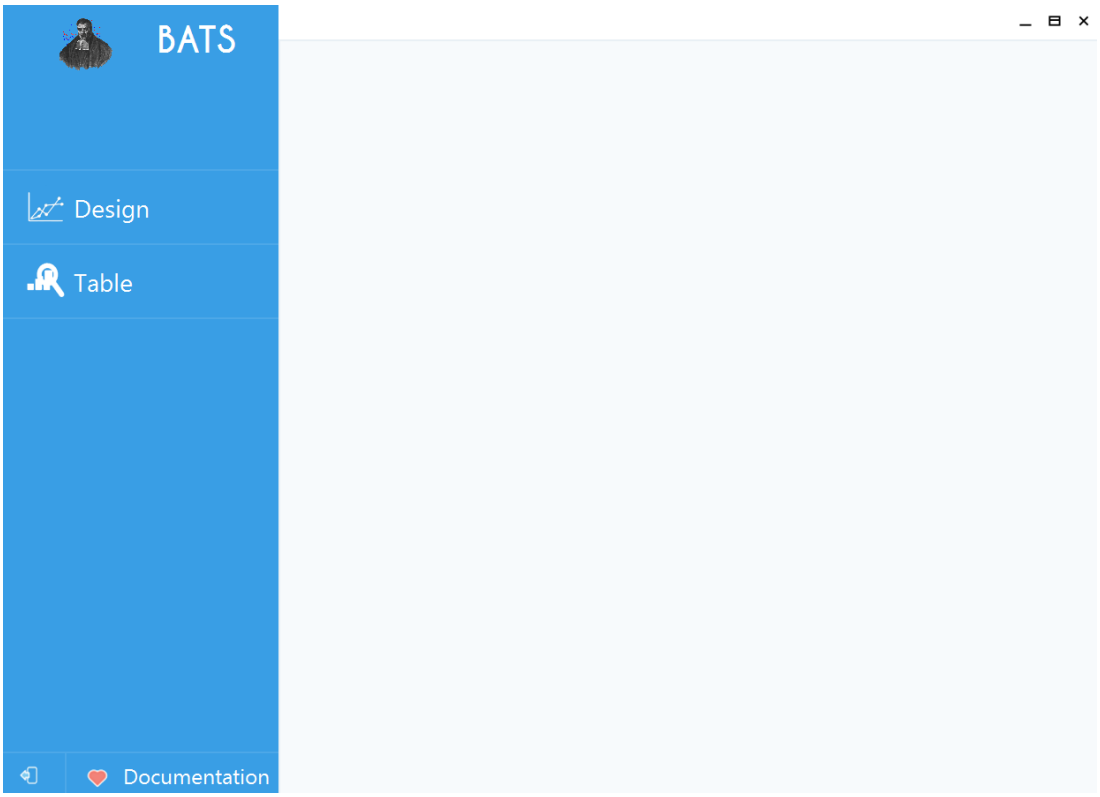
Using BATS

Initialization

To open the tool, double-click on the 'BATS' under the folder or in Python, type in the following code:

```
import BATS

BATS.__init__()
```



The main window is shown as above. It contains a title bar on the top and a menu bar on the left (I need to use number to indicate the area). Users can find two menus in the menu bar:

- **'Design'**, where users can perform a simulation for a specific type of Bayesian trial design

- **‘Table’**, where users can create relevant look-up table that can be used in the simulation to boost up the speed.

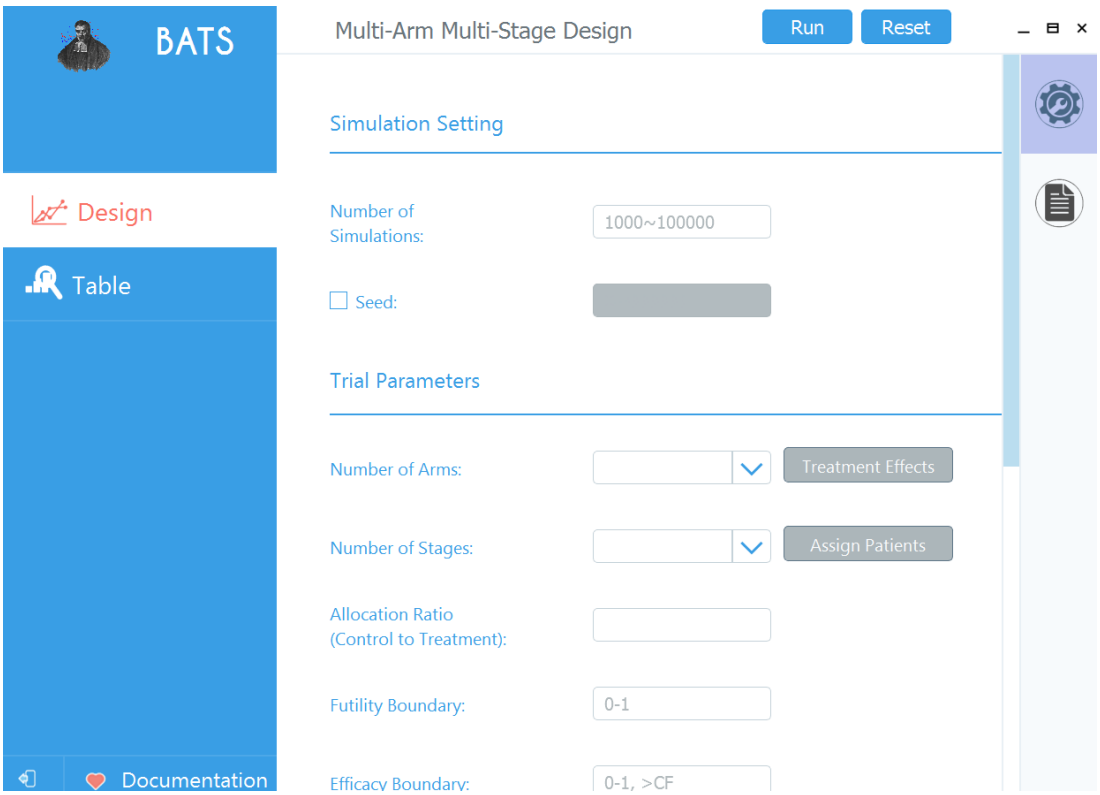
Current supported functions are shown in the following table.

Menu	Supported Functions
Design	Multi-Arm Multi-Stage (MAMS) Design
Table	Create critical value look up table

Open Documentation

The users can open the documentation by clicking on the **‘Documentation’** button on the bottom of the menu bar

Select a Task



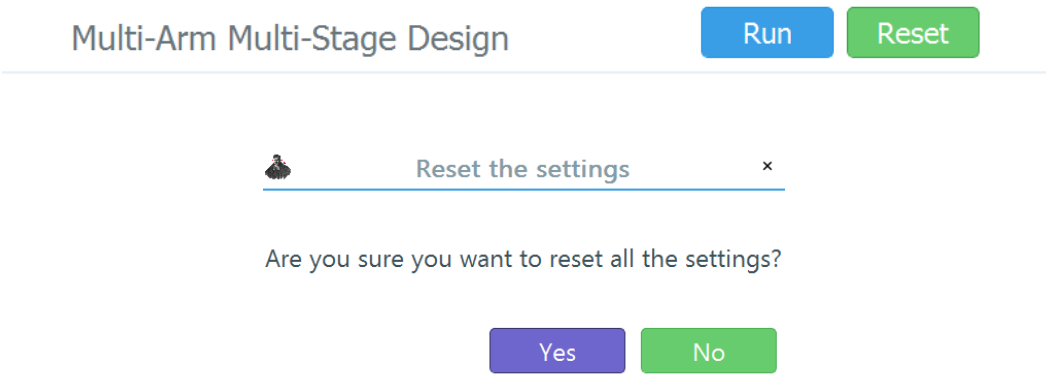
The users can start a task by selecting one of the menus, the corresponding interface for the task directly shows up in the right area of the main window.

The interface has a control panel at the top, a sub menu at the rightmost. Users can switch between settings interface and log interface by clicking on the tabs of sub menu

Run a Task

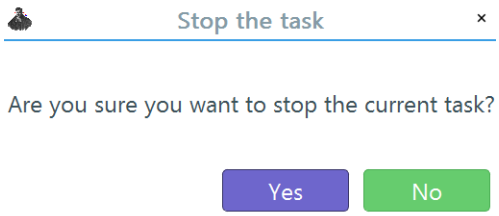
After selecting the specific task to perform and finishing the setting, users can start to run the task by clicking on the **'Run'** button on the top.

Reset a Task



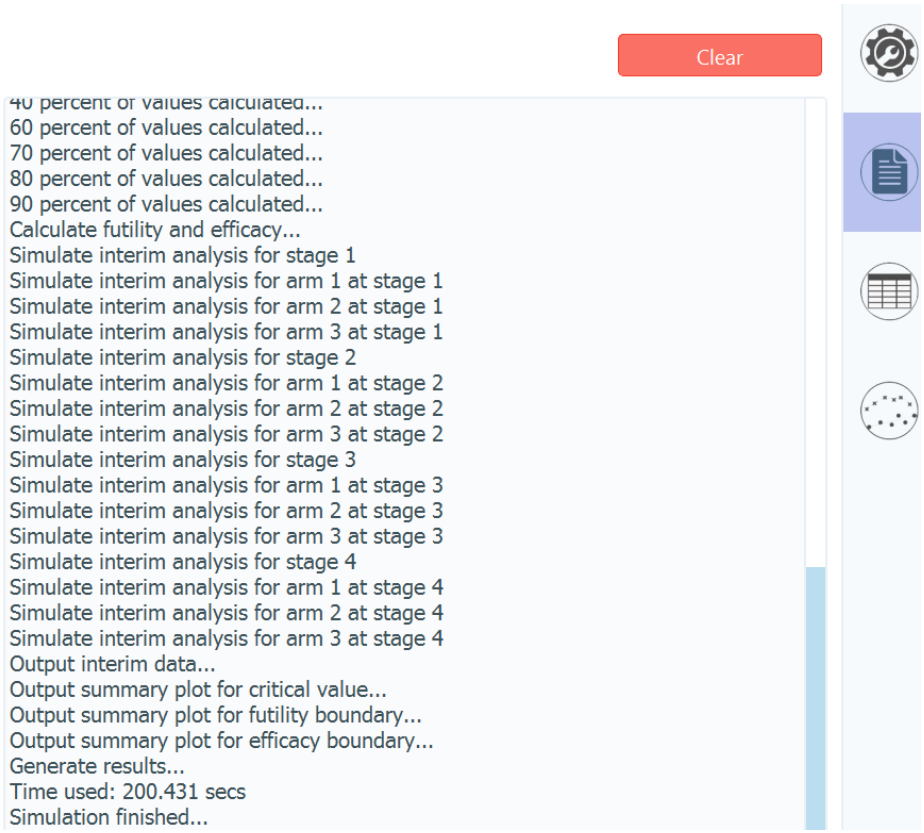
When setting up parameters of the design, users can clear all inputs by clicking on the **'Reset'** button and answering **'Yes'** to the dialog popped up. The input will not be cleared if users response **'No'** or close the dialog.

Stop a Task



The task could also be stopped by clicking on the **'Stop'** button and response **'Yes'** during running. The task would not be stopped if users response **'No'** or close the dialog. During the task progress, users cannot click on the **'Run'** button or change any input in the setting tab.

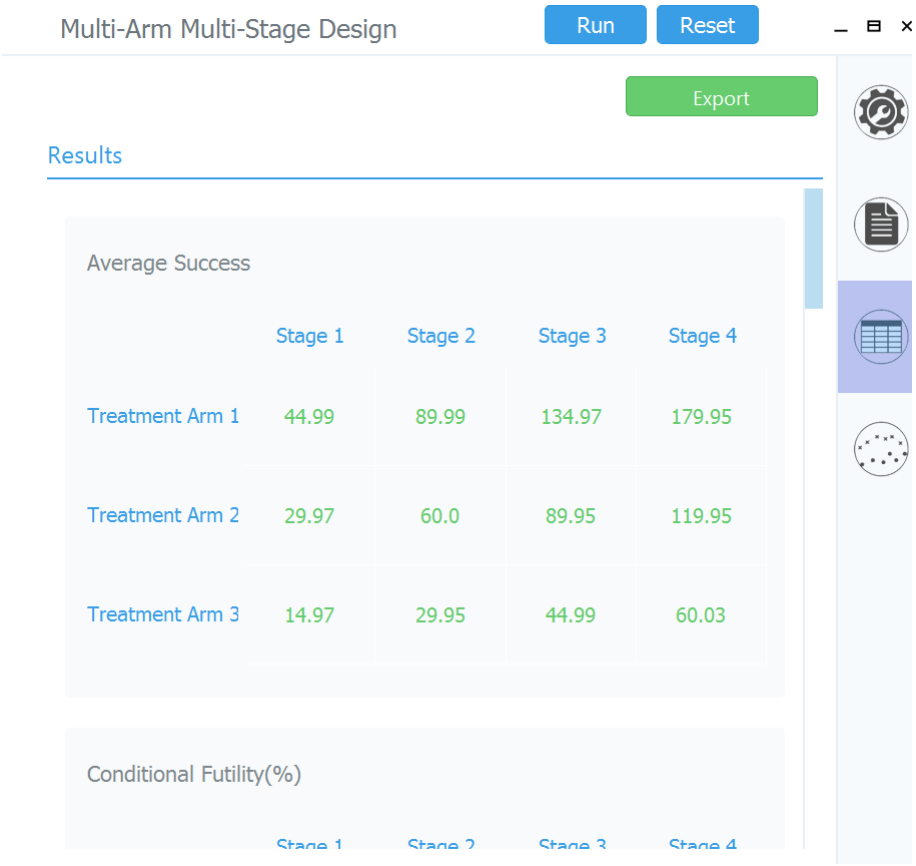
Log System



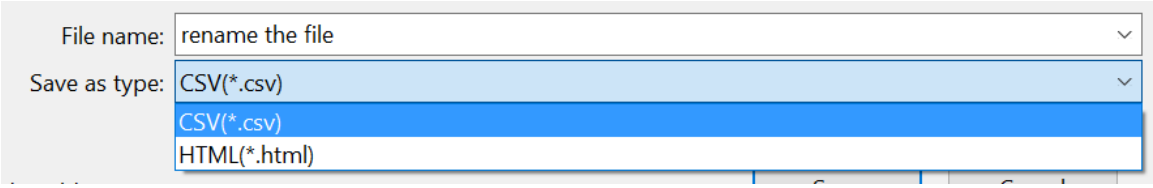
When the task starts, the interface will automatically switch from **'Setting'** tab to **'Log'** tab. The log system will record and show the process of the task. It is useful for users to track the settings for previous tasks. The information for settings will be displayed in red color and the error

information will be displayed in green. Users can clear all the log information by clicking on the **'Clear'** button on the top

View Results



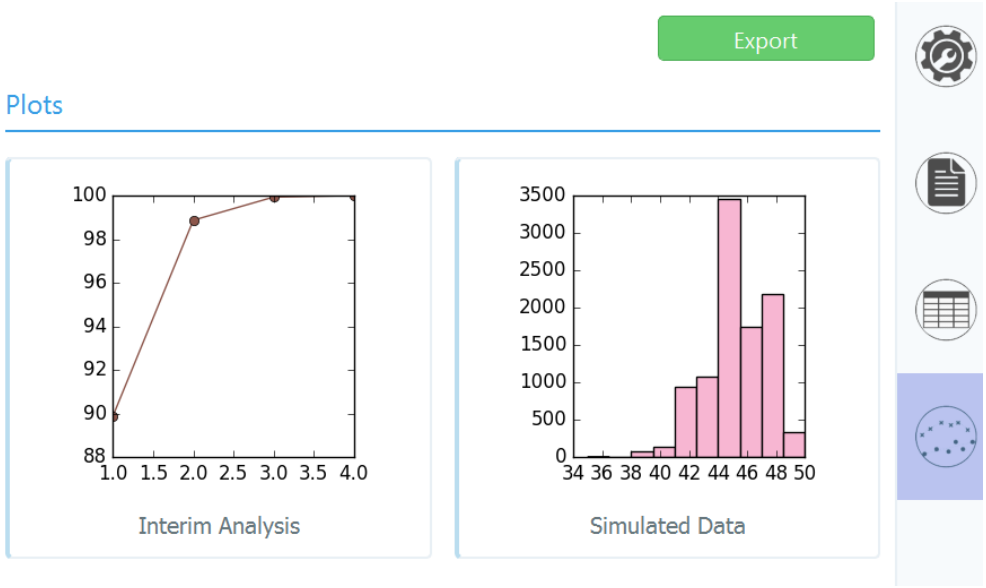
The **'Table'** tab is immediately available when a task is finished and it has summary results to output. Users can view the summary results or export them to the local disk by clicking on the **'Export'** button.



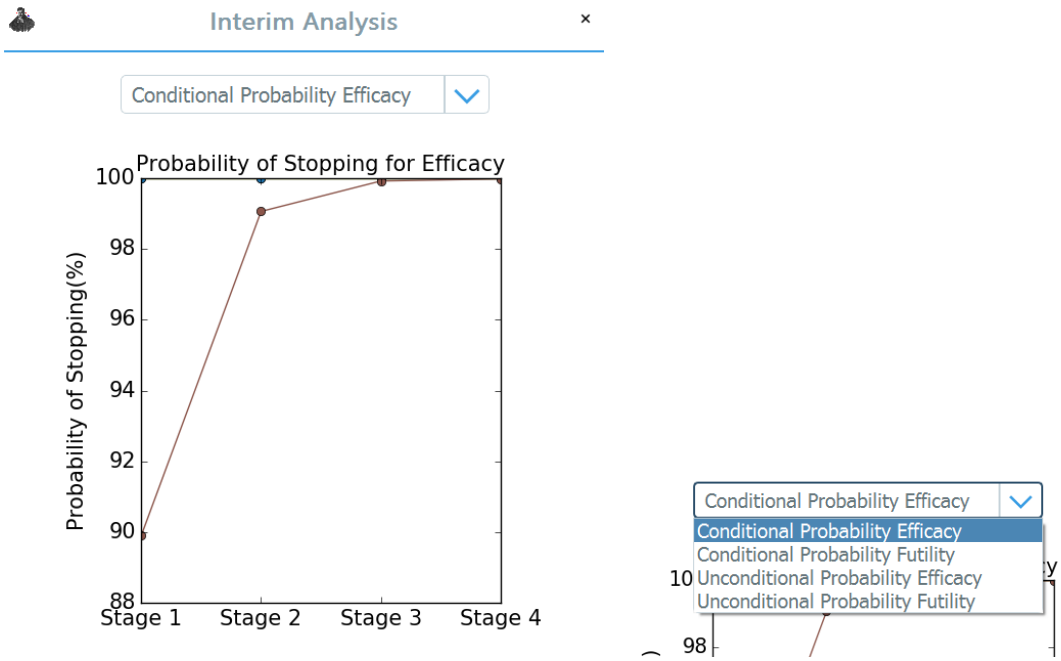
Currently, two file types (.csv and .html) are supported for the exported results and users can specify the output file name in the 'File name:' input.

View Plots

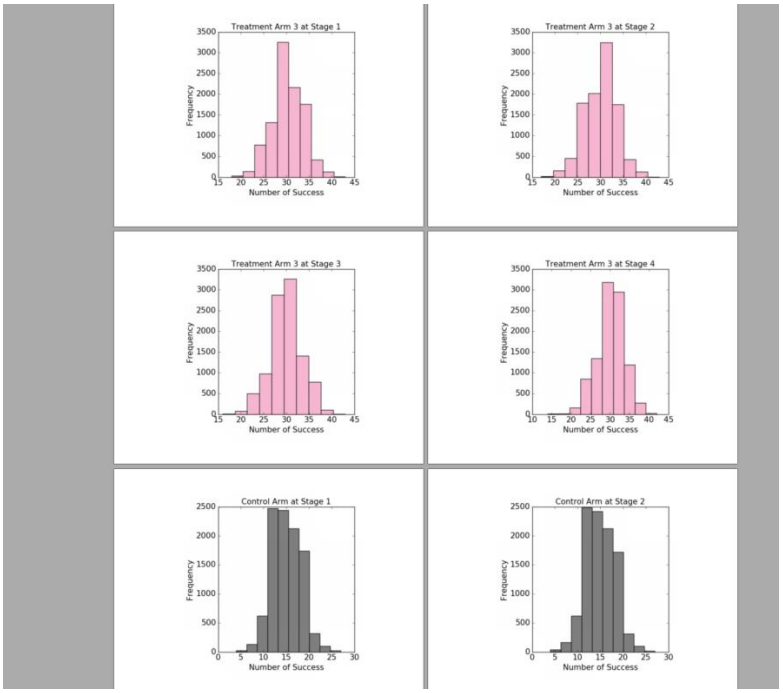
If the results include plots, the **'Plot'** tab will also be available once the task is finished.



The **'Plot'** tab will display modules that corresponding specific type of plots. For example, the tab above contains plots related to interim analysis and the simulated outcomes.



Users can click on each module to open a graph viewer and select a plot to look at through the drop-down box. The graph viewer could be closed by clicking on the close button or press on place outside the viewer. Similar to the tables, the plots can be exported by clicking on the **'Export'** button, in a single pdf file. Each page of the file will contain one plot.



MAMS Design

Introduction

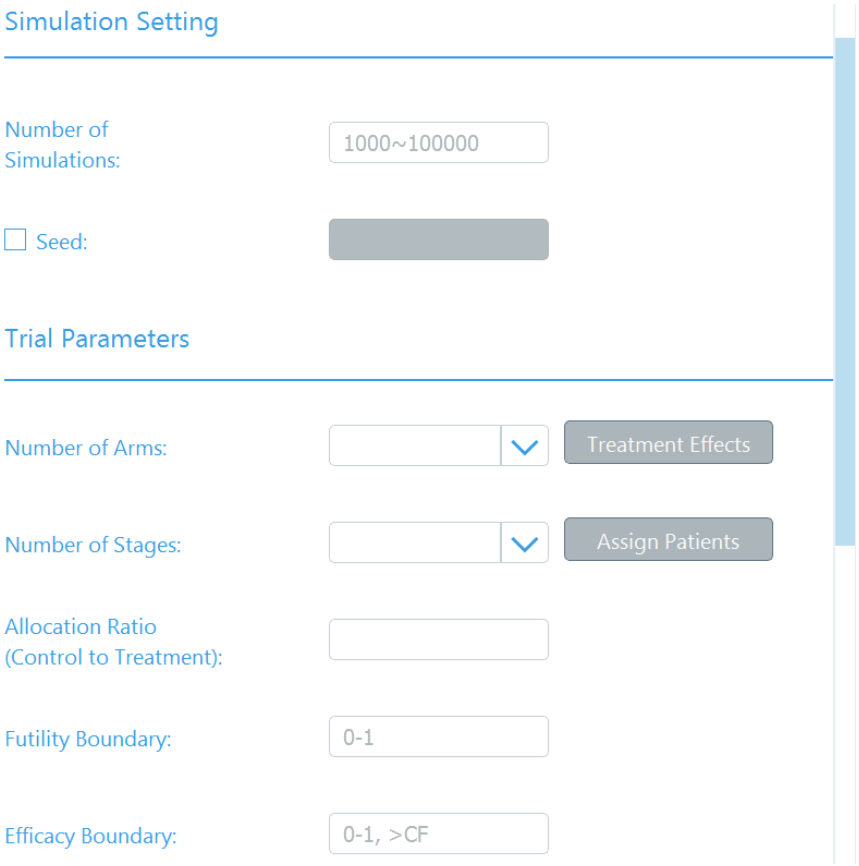
The multi-arm multi-stage (MAMS) design was proposed as a novel adaptive Phase II/III clinical trial design (Royston et al, 2011) in which multiple therapeutic treatments are simultaneously compared to a pooled control. Similar, to a two-arm group sequential design, the trial can be stopped early for overwhelming efficacy, or one or more treatment arms can be stopped early for futility. By simultaneously investigating multiple candidate agents, the design can potentially reduce the cost and time of drug development, particularly in cases where there are a large number of candidate treatments in the pipeline. In addition, this design requires significantly fewer patients compared to separately testing each agent against individual control groups.

Statistical Properties

In the general Bayesian MAMS design, subjects may be randomized to a control treatment $(j=0)$ or one of $j=1,\ldots,J$ experimental treatments and the primary outcome Y_{ij} for subjects, $i=1,\ldots,n_j$ are independently Bernoulli distributed with probability p_j, $0 \le p_j \le 1$. Suppose the trial is partitioned in to k stages $(k=1,\ldots,K)$, each terminating in an interim or final analysis respectively. That is, at stage k, a total of n_{jk} subjects have been randomized to each treatment arm, and $Y_{.jk}=\sum_{i=1}^{n_{jk}} Y_{ijk}$ positive outcomes have been observed, where $Y_{.j1} \le \ldots \le Y_{.jK}$ and $Y_{.jk} \le n_{jk}$. At the end of each stage, it might be of interest to calculate the posterior probability that each active treatment is superior to the control treatment. That is, for each treatment arm we calculate the posterior probability of

treatment success assuming a uniform prior and binomial likelihood yielding: $\left(p_j \mid Y_{.jk}, n_{jk}\right) \sim Beta\left(1+Y_{.jk}, 1+n_{jk}-Y_{.jk}\right)$. At each interim analysis we use the respective posterior distributions to calculate the probability that each treatment is superior to control by a pre-specified margin, δ. That is, to test the null hypothesis $H_0 : p_{jk} - p_{0k} \le \delta$, we define the following quantity of interest $P\left(\hat{p}_{jk} - p_{0k} > \delta\right)$. If the probability exceed boundary for efficacy ($C_{E,jk}$) or futility ($C_{F,jk}$) of continued evaluation, randomization to that active treatment is terminated. Similarly, at the end of the trial, we may want to calculate the posterior probability, or alternatively, we may want to calculate the predictive probability (i.e. the probability that we will reject the null hypothesis given additional patients are randomized to each arm). Here, the probability of observing s_j future successes given an additional m_j subjects is calculated from the pmf of the $Beta - Binomial\left(m_j, 1+Y_{.jK}, 1+n_{jK}-Y_{.jK}\right)$ distribution. The predictive probability of success comparing active arm j to control is then defined as $\sum_{s_0=Y_{0K}}^{s_{0,MAX}} \sum_{s_j=Y_{.jK}}^{m_j} P\left(s_j\right) I\left[P\left(\tilde{p}_{jK} - \tilde{p}_{0K} > \Delta\right) > C_P\right]$, where $\tilde{p}_{jK} \sim Beta\left(1+\left(Y_{.jK}+s_j\right), 1+\left(n_{jK}+m_j\right)-\left(Y_{.jK}+s_j\right)\right)$ and C_P is the threshold to reject the null hypothesis $H_0 : \tilde{p}_{jK} - \tilde{p}_{0K} \le \Delta$.

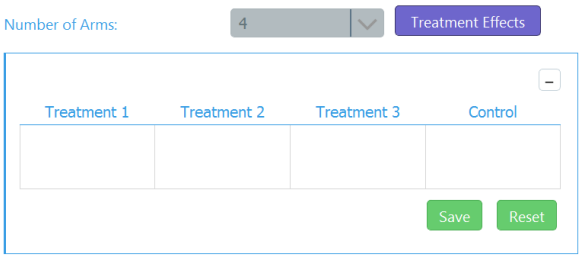
Setting



Number of Simulations: The number of simulations is restricted from 1,000 times to 100,000 times.

Seed: The seed to generate the look-up table. With the same seed the same table will be generated.

Number of Arms: The number of treatment arms in the trial, including one control arm. The minimum number of arms is 3 and the maximum is 10.



Treatment Effects: The true treatment effect of each arm. Users can specify them after selecting the number of arms and clicking on the **'Treatment Effects'** button. Click on **'Save'** to save the treatment effects, click on **'Reset'** to reset all the entries. Once the number of arms is changed, all entered treatment effects will be reset.

Number of Stages: The number of stages in the trial, ranging from 2 to 6.

Patient at Each Stage: The number of total patients at each stage. Users can specify them after selecting the number of arms and stages and clicking on the **'Assign Patients'** button. Click on **'Save'** to save the assignments, click on **'Reset'** to reset all the entries. Once the number of stages is changed, all entered numbers will be reset.

Allocation Ratio: The allocation ratio of control to treatment. In MAMS design, we assume the allocation ratio is fixed and all treatment arm has the same number of patients.

Futility Boundary: The futility boundary**,** futility ($C_{F,jk}$), should between 0 and 1.

Efficacy Boundary: The efficacy boundary**,** efficacy ($C_{E,jk}$), should between 0 and 1 and larger than the futility boundary.

Clinically Significant Difference: The clinically significant difference δ to be detected in the trial.

Predictive Probability: If this box is checked, the simulation will include calculating predictive probabilities. If not, the simulation will finish after simulating interim analysis.

Number of New Patients: The number of total patients planned to add to these arms, based on the same allocation ratio.

Success Boundary: C_P is the threshold to reject the null hypothesis $H_0 : \tilde{p}_{jK} - \tilde{p}_{0K} \leq \Delta$.

Use Same Clinically Significant Difference or Specify a New Value: Sometimes users may want to use a different clinically significant difference value for the predictive probability, that is, $\Delta \neq \delta$. If the box is checked, then the same value as in the interim analysis will be used, otherwise a new value must be entered.

Method of Calculation: The method used to find the pairs that will lead to the conclusion. **'Bisection Search Method'** is recommended for its speed when number of patients is large. The **'Critical Look-up Table'** is also useful but should be used in caution because the clinically significant difference used to generate the table should be consistent with the one specified in the simulation.

Load CVL Table: If users select the **'Critical Look-up Table'**, they can load a pre-generated table, otherwise a new table will be calculated in the simulation.

Results

Average Success: The average cumulative count of patients with success outcomes for each treatment arm at each stage.

Conditional Futility: The conditional probability of stopping a treatment arm for futility at each stage. For each arm each stage, that is calculated from dividing the cumulative number of stops for futility by number of simulations.

Unconditional Futility: The unconditional probability of stopping a treatment arm for futility at each stage. For each arm each stage, that is calculated from dividing the number of stops for futility at that stage by number of simulations.

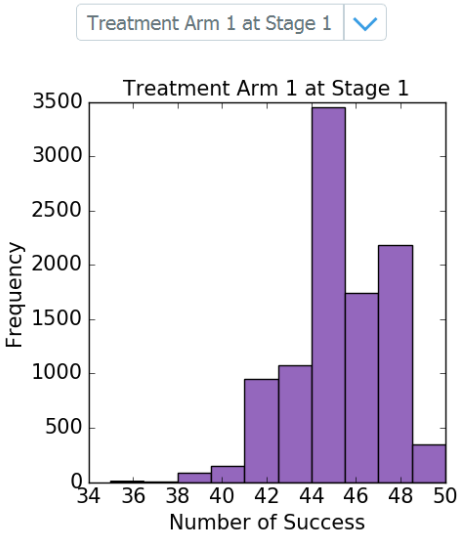
Conditional Efficacy: The conditional probability of stopping a treatment arm for efficacy at each stage. For each arm each stage, that is calculated from dividing the cumulative number of stops for efficacy by number of simulations.

Unconditional Efficacy: The unconditional probability of stopping a treatment arm for efficacy at each stage. For each arm each stage, that is calculated from dividing the number of stops for efficacy at that stage by number of simulations.

Predictive Probability: The posterior predictive probability of each treatment arm. This measures how likely the trial will reach a successful outcome given a number of future patients.

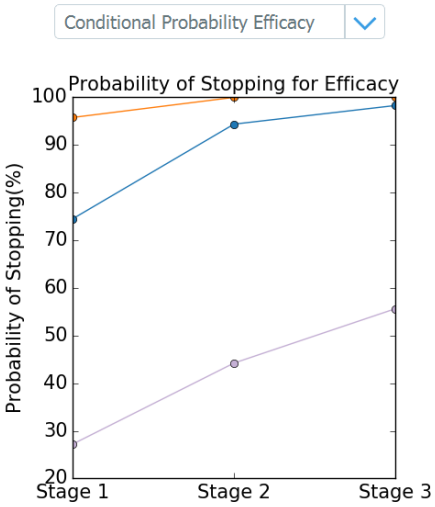
Plots

Simulated Data



The histograms of the simulated outcome for each arm at each stage. The data comes from the same arm will be plotted in the same color.

Interim Analysis



The plots for conditional/unconditional futility and efficacy. Each line represents a treatment arm.

Reference

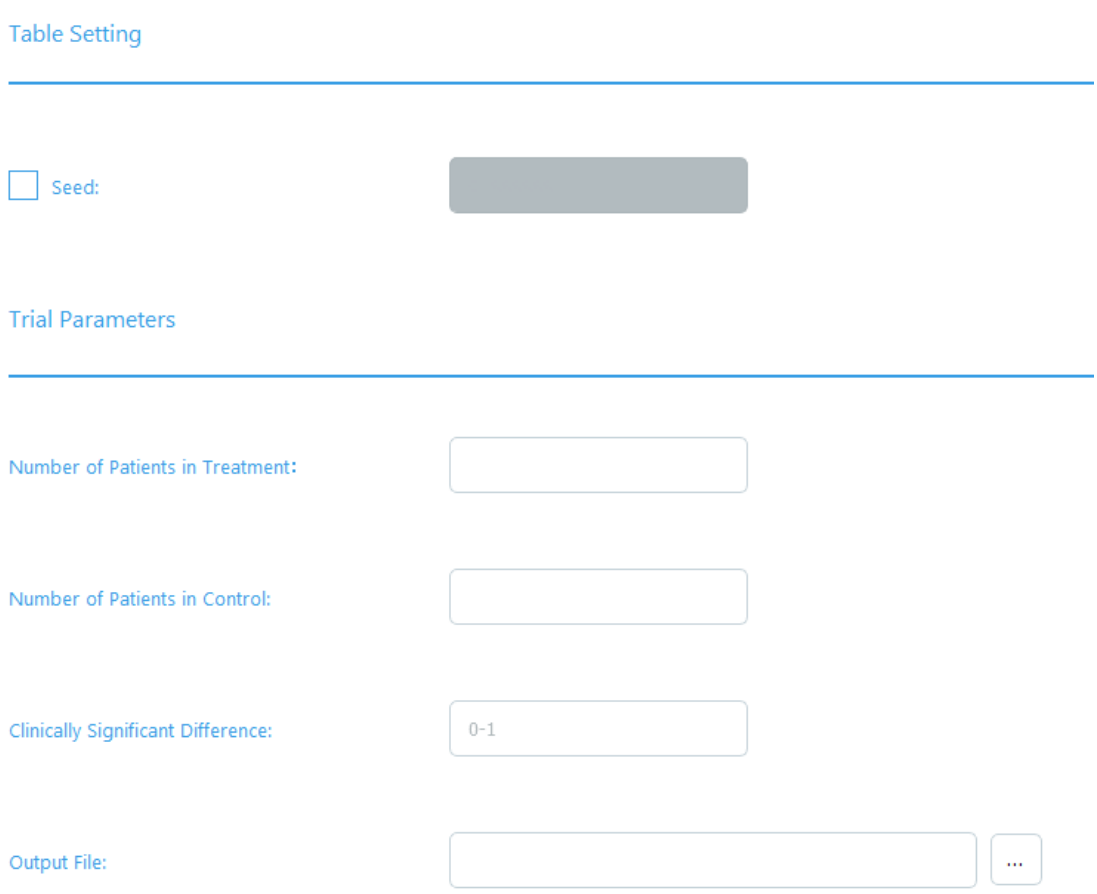
Royston, P., Barthel, F. M.-S., Parmar, M. K. B., Choodari-Oskooei, B., & Isham, V. (2011). Designs for clinical trials with time-to-event outcomes based on stopping guidelines for lack of benefit. *Trials*, *12*(1), 81. http://doi.org/10.1186/1745-6215-12-81

Critical Value Look-up Table

Introduction

It is useful to generate a look-up table to store critical values for all possible outcomes that could be observed at each analysis, to avoid redundant calculations.

Setting



Users can specify the followings in creating critical value look-up table:

Seed: The seed to generate the look-up table. With the same seed the same table will be generated.

Number of Patients in the Treatment: The number of patients in the treatment arm.

Number of Patients in the Control: The number of patients in the control.

Clinically Significant Difference: The clinically significant difference.

Output File: Specify the output directory for the generated table.

Results

The output file will be in csv format. The first column is the number of success in the treatment, the second column is the number of success in the control and third column is the critical value calculated from the observed outcome.