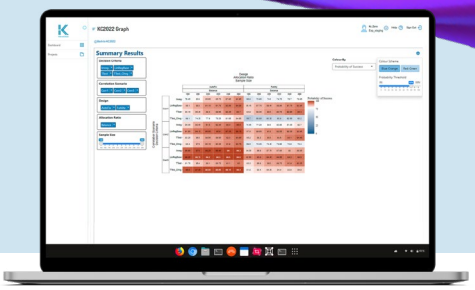
KerusCloud® 2022 Release

KerusCloud Tutorial: Evaluating Stroke Events

Hosted by Exploristics Principal Statistician, Alecia Nickless, PhD



KerusCloud Tutorial: Evaluating Stroke Events

Background

A drug regime for hypertension is being investigated and a long-term study planned to demonstrate that the drug combination effectively reduces the number of subjects having stroke. The study is planned to follow subjects for 4 years and hence it is expected that a fairly large number of subjects will not adhere to the treatment regime and may also drop out over time. This simulation is designed to investigate the effect that different levels of non-adherence and different levels of drop out have on the observed treatment effect. The result is shown through the probability of study success to meet criteria as defined below.

Adherence is difficult to measure as it depends on the subject owning up to deviating from the regime. Some studies use pill counting as a way to measure Adherence. Adherence can include any deviations from the set regime: subjects taking double doses one day because they forgot to take them the day before, subjects forgetting and so having gaps e.g., taking one dose a day instead of two, subjects losing motivation and so after a set amount of time stopping taking treatment altogether but still remaining in the study. For simplicity this simulation sets up different levels of adherence by assuming that a reduction in adherence equates to a reduction in the effectiveness of the treatment.

This tutorial shows how to build up the KerusCloud simulation in stages for a single scenario. Scenarios are defined to examine the effect that different distribution settings will have on the study outcome.

For more detailed instructions on how to use KerusCloud refer to the User Guide.

Stage 1: Virtual Population Wizard

The first step is to decide if there are different scenarios to compare the outcomes between. In this study we are going to create Advanced Scenarios to explore the effect that different amounts of missing data will have on the outcome.

Click on "View" next to the Advanced Option Scenarios option, and then click on "Activate". We're going to create four variables in this virtual population: 1). Treatment id, 2). Number of subjects who are Adherent, defined as a proportion of the total 3). The event rate for stroke 4). Systolic blood pressure distribution.

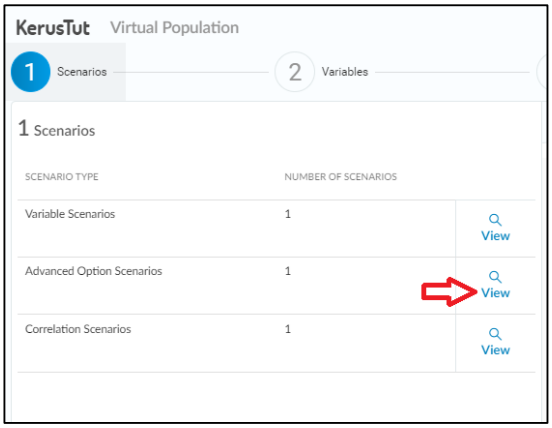
HOW TO:

Click on New Project. Create a name for the project and provide a description.

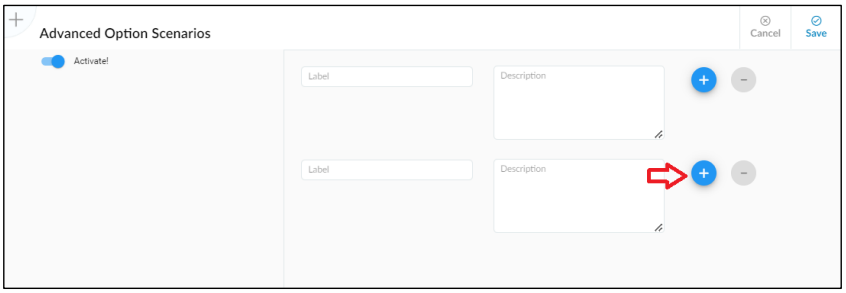
Click on "View" next to the Virtual Populations:

Define the Advanced Scenarios:

Click on "View" next to the Advanced Option Scenarios option, and then click on "Activate":

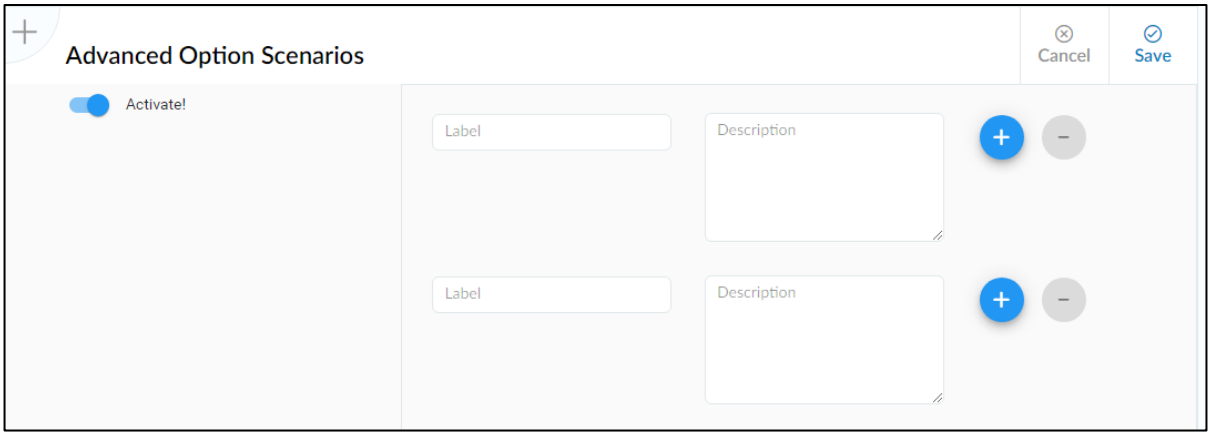


Click on + to create an extra level.

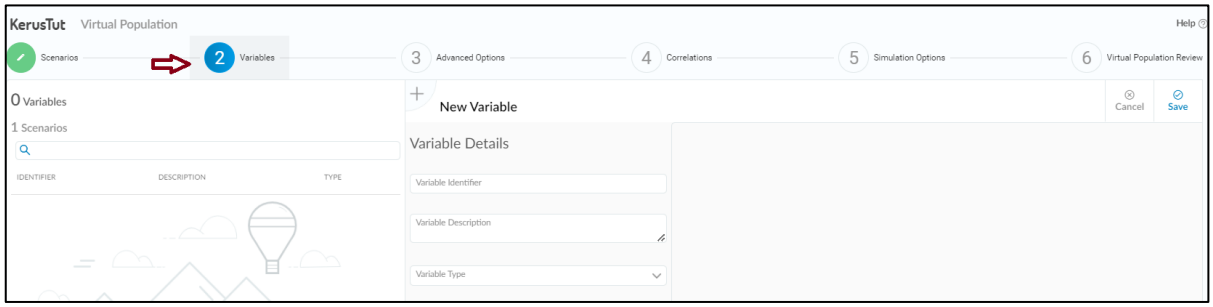


First level Label: Miss_0. Description: Negligible amount of missing data
Second level Label: Miss_Low. Description: Low % missing data
Third level Label: Miss_Hig. Description: High % of missing data

Click Save:



Click the Variables tab:



Create the Variables:

Variable 1: Define treatment variable

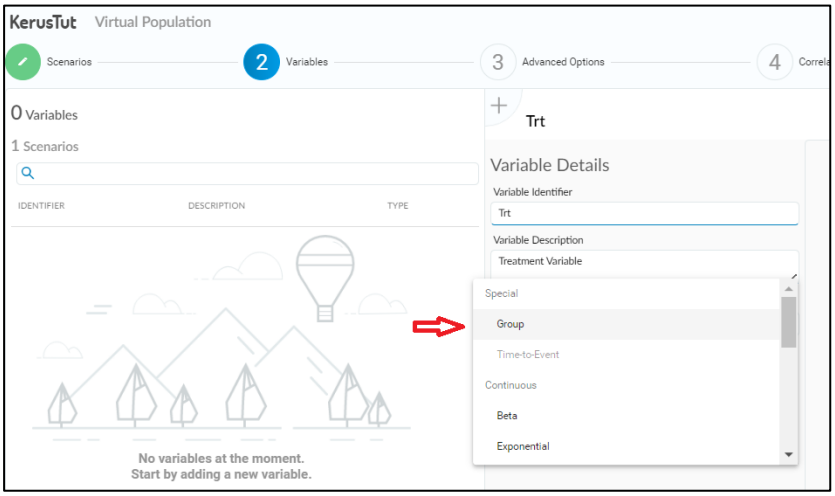
Variable Identifier: Trt

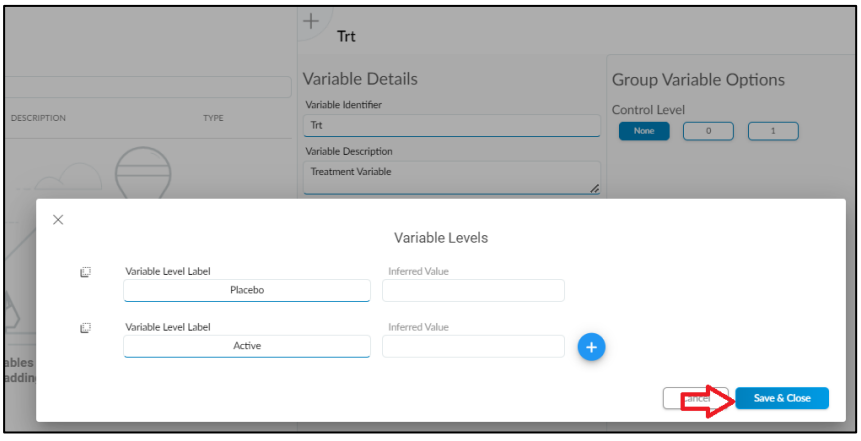
Variable Description: Treatment

Variable Type: Group

Customise Variable Levels: Change the '0' Label to 'Placebo' and '1' Label to 'Active'.
No need to enter any Inferred Values. Save & Close.

Click Save in top right.





Variable 2: Define a variable to indicate if subject has adhered to treatment regime or not.

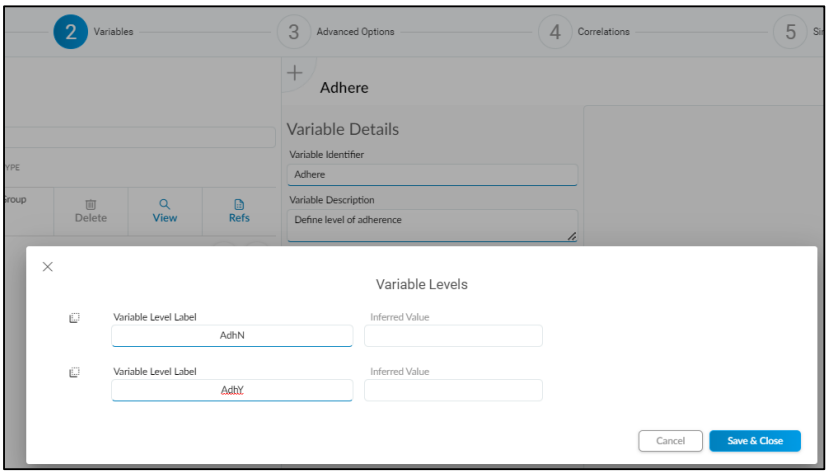
These 2 subgroups will be used when defining event rates for stroke in Variable 3.

Variable Identifier: Adhere

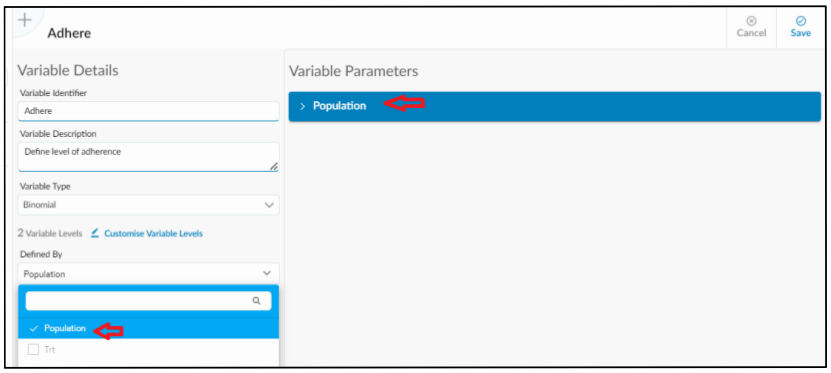
Variable Description: Define level of adherence

Variable Type: Binomial

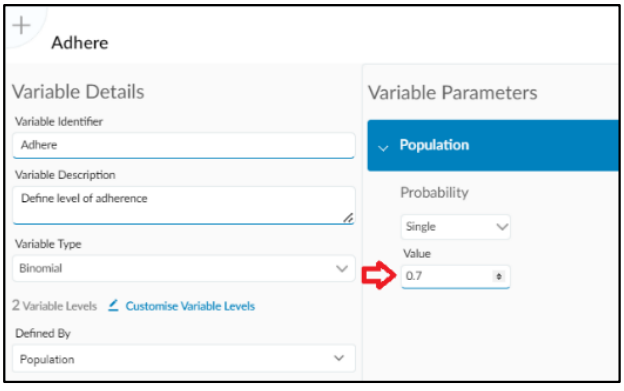
Customise Variable Levels: Change the '0' Label to 'AdhN' and '1' Label to 'AdhY'.
No need to enter any Inferred Values. Save & Close.



Defined By: Select Population. This implies that the level of adherence is the same across both treatment groups.



Variable Parameters: Enter 0.7 for the Single probability under Population. This will create a virtual dataset where 70% of the subjects are defined as adhering and consequently 30% as non-adhering.



Click Save in the top right.

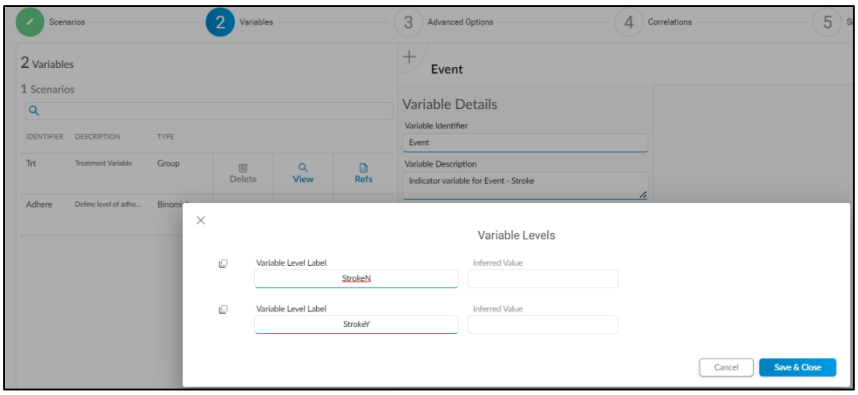
Variable 3: Event rate for stroke

Variable Identifier: Event

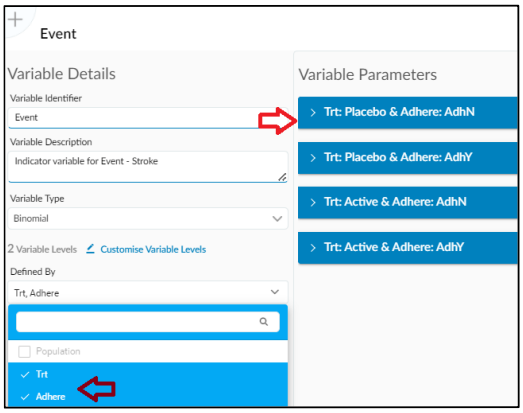
Variable Description: Indicator variable for Event - Stroke

Variable Type: Binomial

Customise Variable Levels: Change the '0' Label to 'StrokeN and the '1' Label to 'StrokeY'.
No need to enter any Inferred Values. Save & Close.



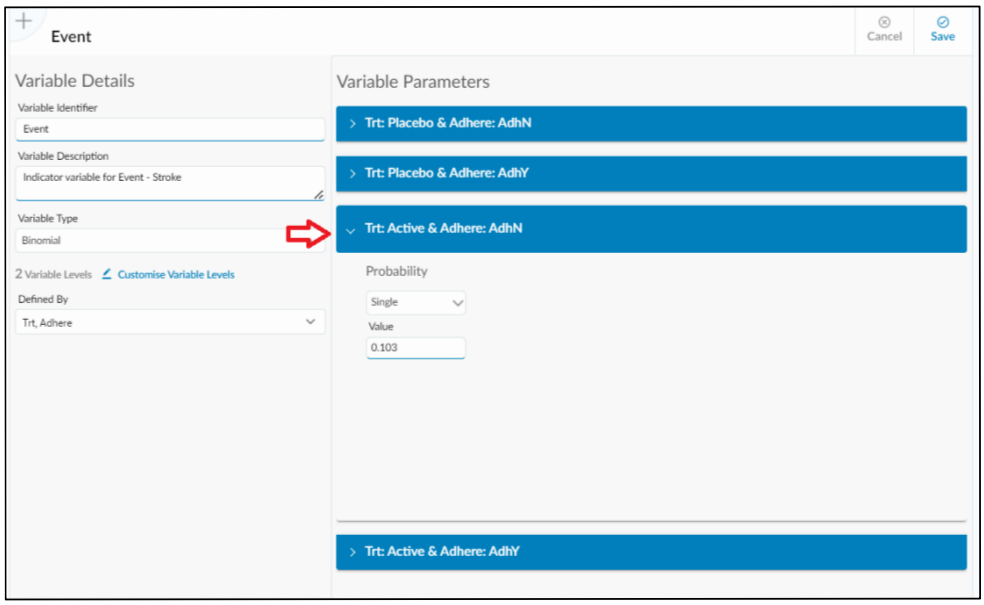
Defined By: Select Trt and Adhere. This implies that the probability of a stroke occurring depends on whether the subject is adhering or not and that the probability will be different for subjects on placebo and active treatment.



Variable Parameters: each of the following parameters are defined at the 'Single' level as no scenarios are set up yet. For a rationale on the numbers entered here follow this link.

- Adhere: AdhY & Trt: Placebo: **enter 0.144** (14.4% of all subjects on Placebo are expected to have a stroke during the 4 year course of the study)
- Adhere: AdhY & Trt: Active: **enter 0.085** (8.5% of fully adhering subjects on Active treatment are expected to have a stroke)
- Adhere: AdhN & Trt: Placebo: **enter 0.144** (non-adherence in a placebo group should not affect the risk of stroke)
- Adhere: AdhN & Trt: Active: **enter 0.103** (30% of subjects non-adhering increases the risk of stroke in this sub group)

Click Save in the top right.



Variable 4: systolic blood pressure variable

Variable Identifier: sBP

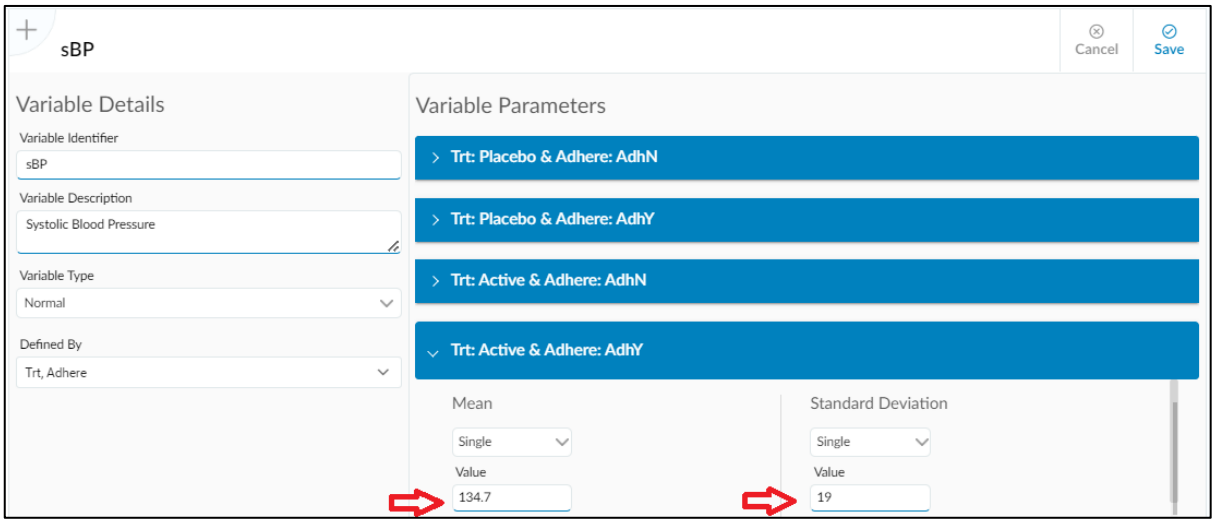
Variable Description: systolic blood pressure

Variable Type: Normal

Defined By: Select Trt and Adhere. This implies that the blood pressure reading depends on whether the subject is adhering or not and also will depend on which treatment they have been assigned to.

Variable Parameters: each of the following parameters are defined at the 'Single' level as no scenarios are set up yet. For a rationale on the numbers entered here follow this link.

- Adhere: AdhY & Trt: Placebo: under Mean **enter 147** and under SD **enter 19**
- Adhere: AdhY & Trt: Active: under Mean **enter 134.7** and under SD **enter 19**
- Adhere: AdhN & Trt: Placebo: under Mean **enter 147** and under SD **enter 19**
- Adhere: AdhN & Trt: Active: under Mean **enter 140.9** and under SD **enter 19**



Advanced Options:

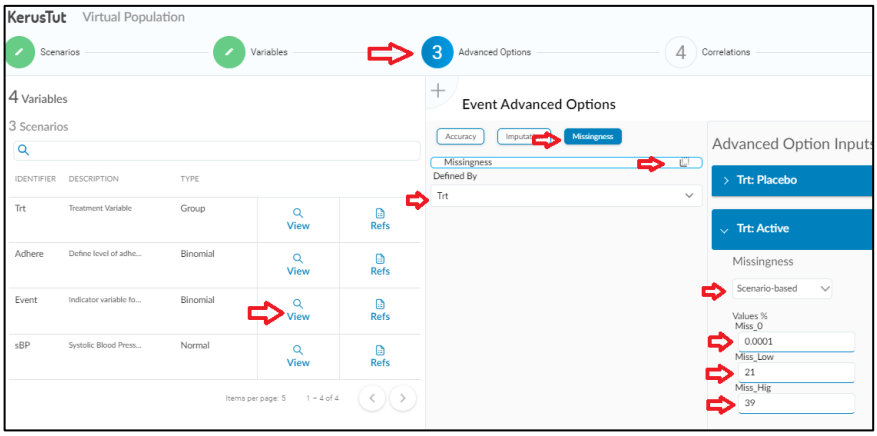
Click View on the Event variable: Click on the bubble labelled Missingness. This will turn blue and a Missingness input row will appear. Click this newly appeared line which will present Defined by options. Under Defined By select Trt. Change the Missingness option from Single to Scenario-based.

Under Placebo enter the following:

- Miss_0: 0.0001%
- Miss_Low: 29%
- Miss_Hig: 47%

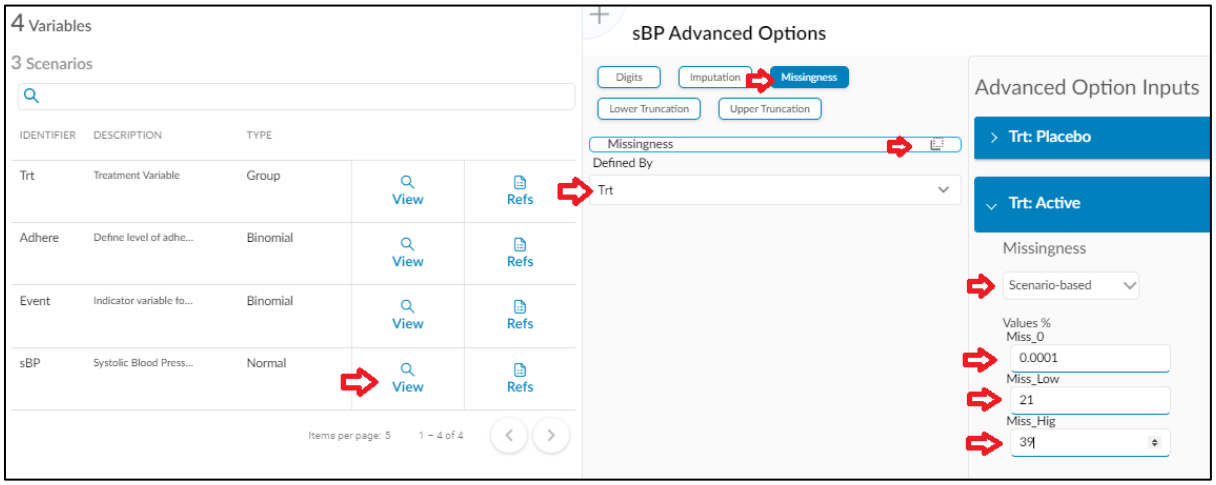
Under Active enter the following:

- Miss_0: 0.0001%
- Miss_Low: 21%
- Miss_Hig: 39%



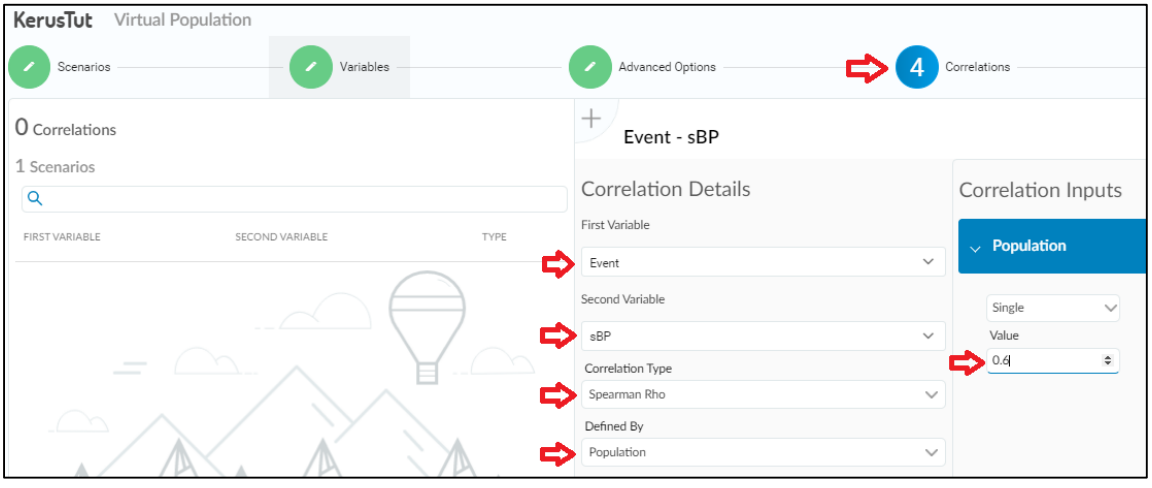
Click Save in the top righthand corner.

Click View on the sBP variable: Click on Missingness. Under Defined By select Trt. Change the Missingness option from Single to Scenario-based and enter the same values as above. Click Save in the top righthand corner when completed.



Correlations:

Under First Variable select Event and under Second Variable select sBP. Under Correlation Type select Spearman Rho and under Defined By select Population. Enter 0.6 for the Correlation Input. A positive correlation will generate data where subjects who have a stroke have higher average blood pressure than those who don't have a stroke. Click Save in the top righthand corner.

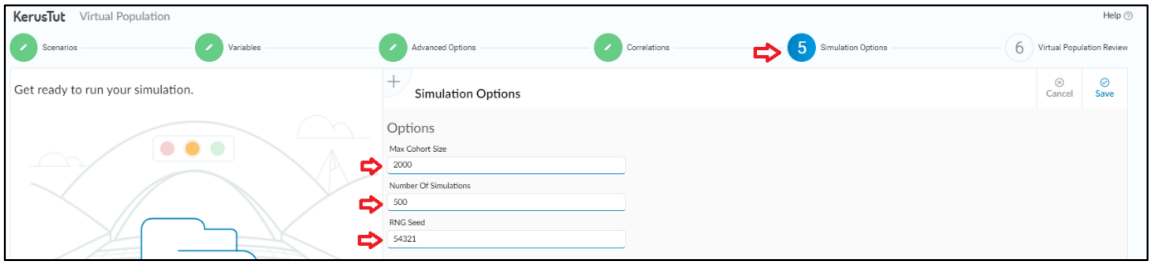


Simulation Options:

Max Cohort Size: Enter 2000. This is the largest sample size per arm that we will define at the design stage.

Number of Simulations: Enter 500. This can be any number up to 10000 but the more requested the longer the simulation takes.

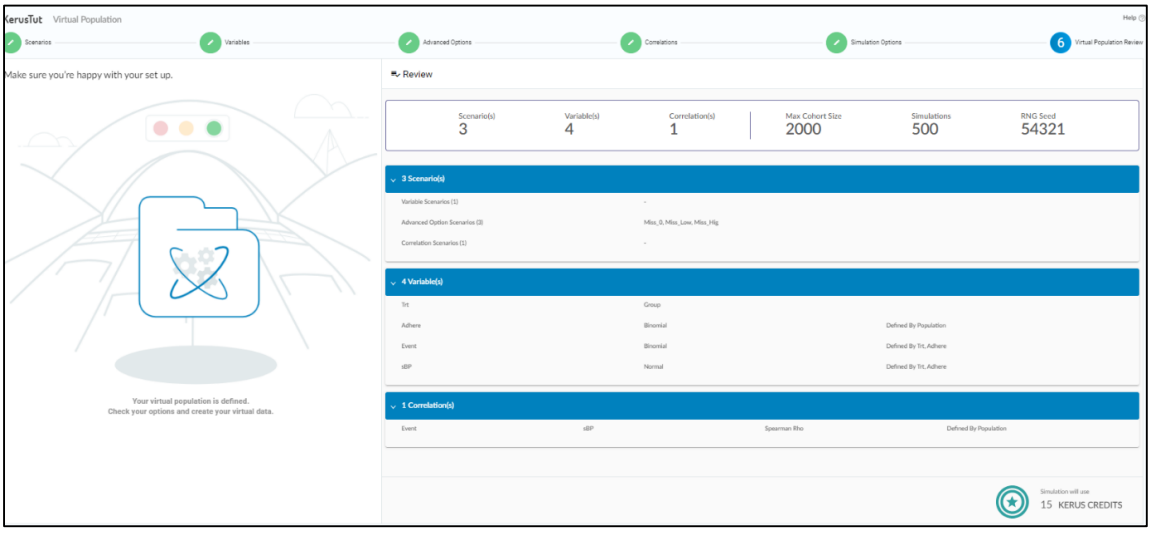
RNG Seed: enter a random number of your choice



Click on Save in the top righthand corner.

Click Next to move to the final window of the Virtual Population Wizard. Review the population set up and click 'Go' in the bottom righthand corner.

Congratulations! You have successfully set up and run your Virtual Population with 4 variables and requested 500 simulations of size 2000 under three missingness scenarios. Kerus will produce 500×3 = 1500 datasets, each containing 2000 rows per treatment arm.

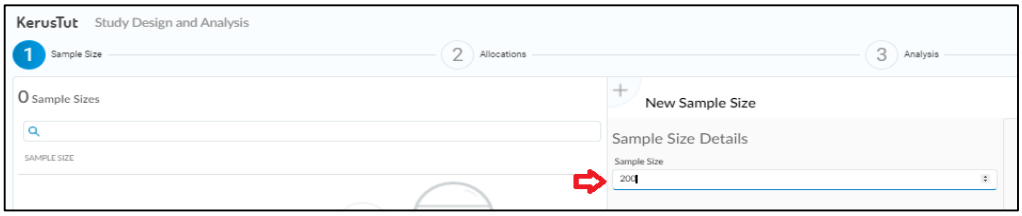


Stage 2: Study Design and Analysis

In the next section we will set out which sample sizes we wish to consider, what allocation ratio we will used to allocate participants to the treatment arms, which analyses will be carried out, and what study design we wish to use. In this example we will use a 1:1 allocation ratio and use a fixed study design.

HOW TO:

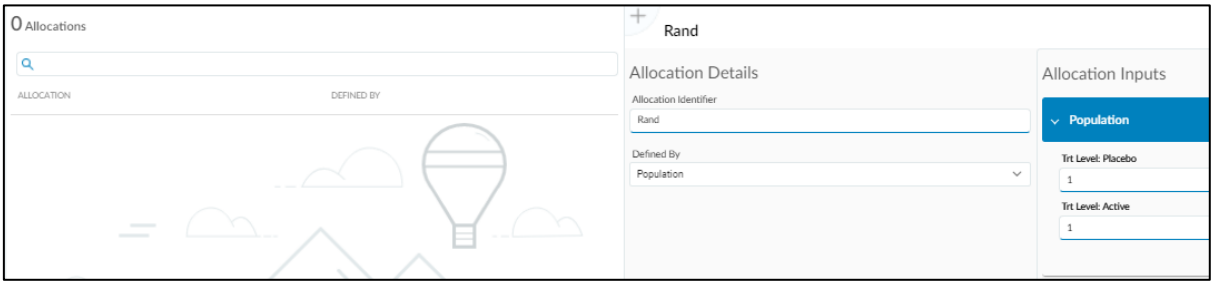
Sample Size tab: Under New Sample Size enter the range of sample sizes to be investigated. Enter 10 sample sizes: 200, 400, 600, 800, 1000, 1200, 1400, 1600, 1800, 2000. Enter each sample size separately under Sample Size and click the Save button in the top righthand corner after you have entered each sample size.



Once you have clicked Save after the last sample size entered, then click Next in the bottom righthand corner.

Allocation tab: Specify the allocation ratio of treatment to subjects. Enter the label name 'Rand' into the Allocation field. Under Defined By click on Population

Under Allocation Inputs enter 1 into both the Placebo and Active fields. This specifies that equal numbers of subjects will be allocated to each treatment arm. Click Save in the top righthand corner.



Then we move on to the Analysis tab. We will set up an analysis for the binary event variable data using a chi-squared test and then set up an analysis for the blood pressure variable using an analysis of variance test.

HOW TO:

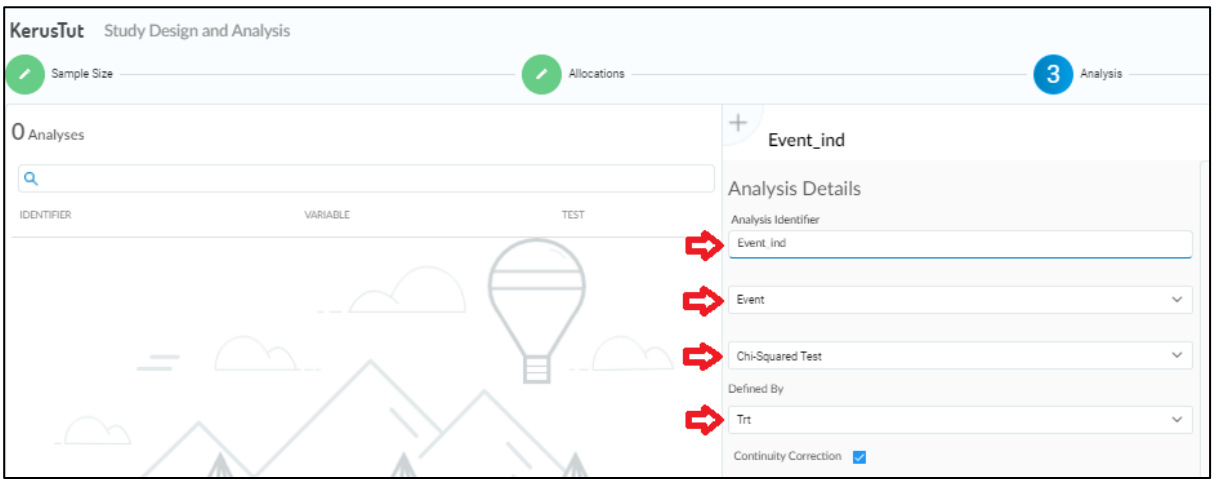
Analysis 1:

Under the Analysis tab type in an Identifier for the analysis: Event_ind

Select Event and select Chi-square Test

Under Defined By select Trt

Click on Save in the top righthand corner



Analysis 2:

Under Analysis Identifier type in an identifier for the analysis: systolic_BP

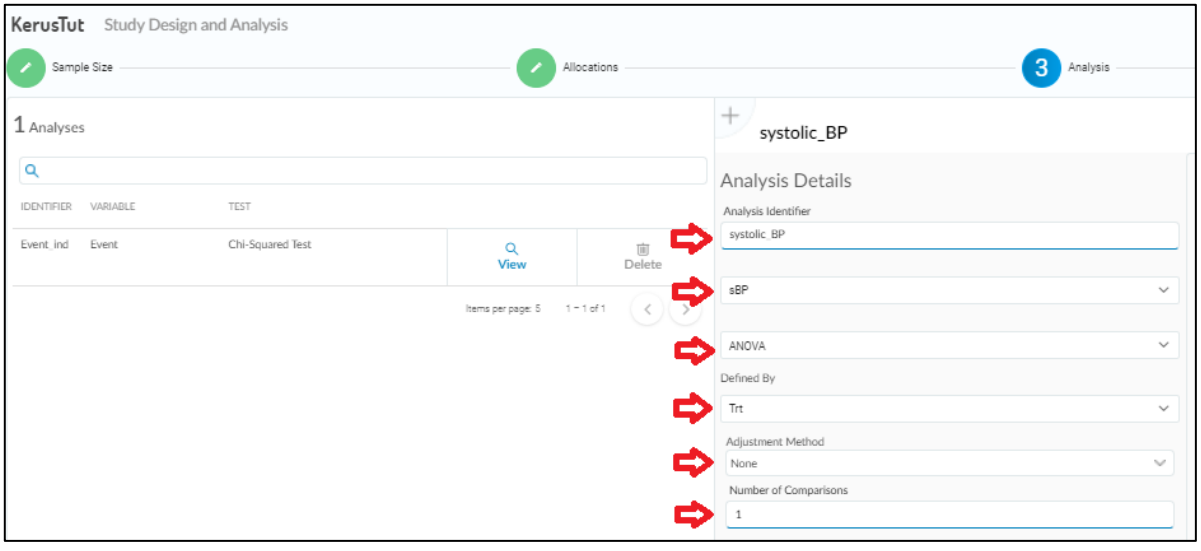
Under Select Variable select sBP and under Select Test select ANOVA

Under Defined By select Trt

Under Adjustment Method select None

Under Number of Comparisons select 1

Click on Save in the top righthand corner



Click Next to move on to Designs.

Under the Designs tab you are able to choose between a fixed design, or a number of adaptive design options.

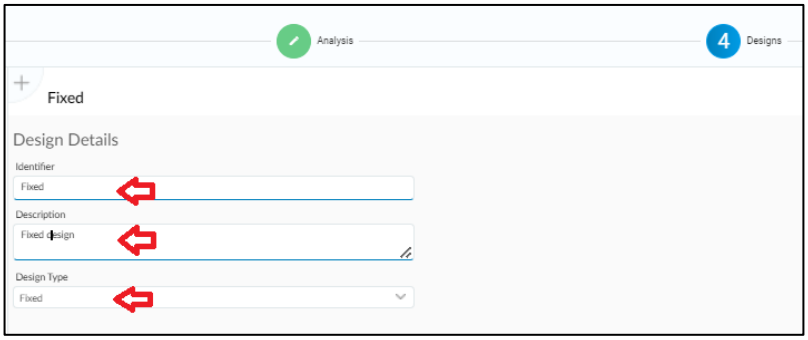
HOW TO:

Under Identified enter 'Fixed' for the design label.

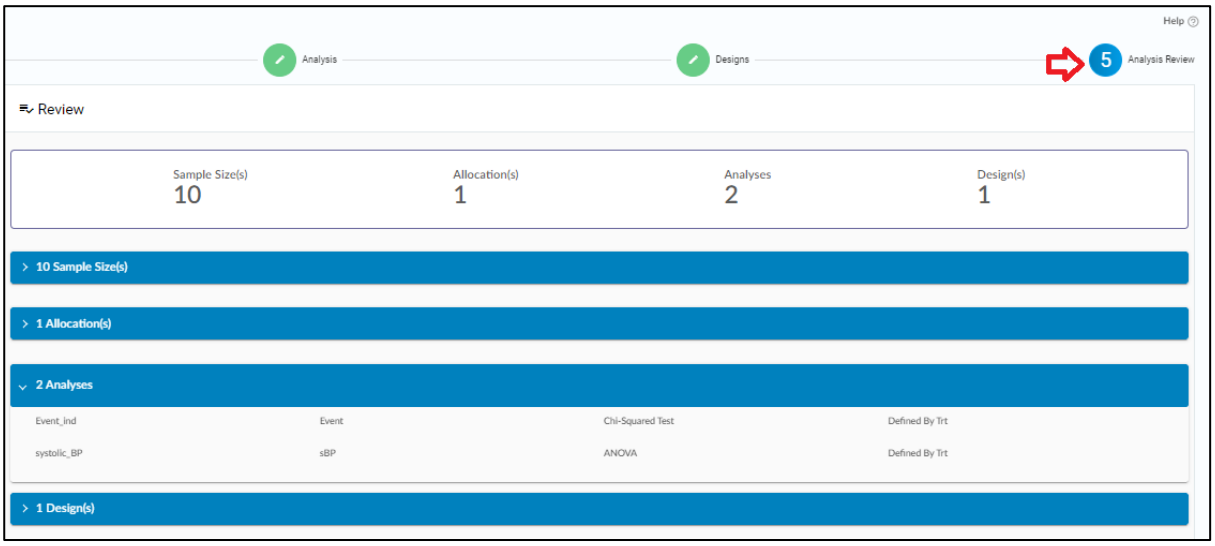
Under Description enter 'Fixed design'

Under Design Type select Fixed

Click Save in the top righthand corner



Finally, click Next to move on to the Review panel. Click Go.



Congratulations! You have successfully run the analyses for all 500 of the virtual populations created in the Population Wizard for each sample size, treatment allocation ratio and design scenario.

Stage 3: Decision Criteria Wizard

In this section we are defining thresholds that will determine success from our analysis output. In our example four criteria will be set up: 3 based on the event analyses and 1 based on the blood pressure data.

HOW TO:

Enter the first Decision Criteria for the event analysis

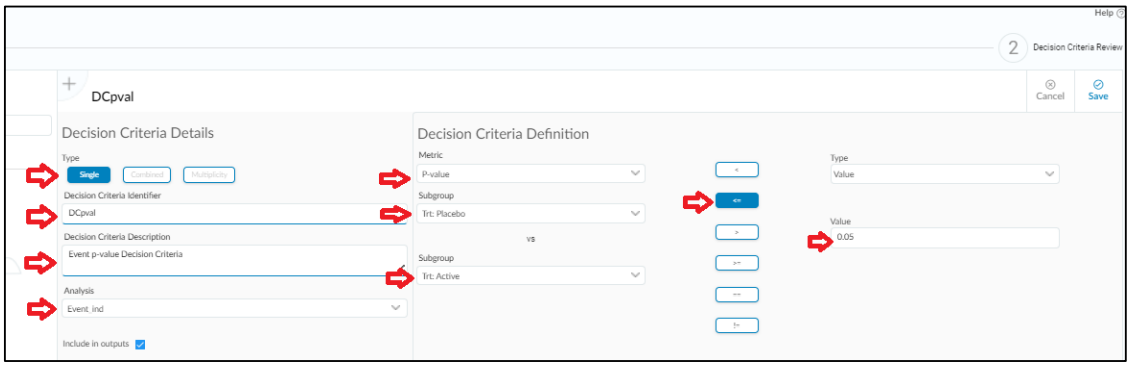
Under Type select Single

Under Decision Criteria Identifier type DCpval (or another label of your choice)

Under Decision Criteria Description type 'Event p-value Decision Criteria'

Under Analysis select Event_ind

Under Decision Criteria Definition select P-value as the Metric and Trt:Placebo vs Trt:Active as the subgroups. Select the box for '<=' and select Type as Value, then enter the value as 0.05. Click Save in the top righthand corner.



Enter another Single Decision Criteria for the event analysis

Under Type select Single

Under Decision Criteria Identifier type DC_OR (or another label of your choice)

Under Decision Criteria Description type 'Event Odds Ratio Decision Criteria'

Under Analysis select Event_ind

Under Decision Criteria Definition select Odds Ratio as the Metric and Trt:Active vs Trt:Placebo as the subgroups. In the calculation of the odds ratio, the odds of the first subgroup will be in the numerator and the odds of the second subgroup will be in the denominator. Select the box for '<=' and select Type as Value, then enter the value as 0.8. Click Save in the top righthand corner.

Enter a combined Decision Criteria for the event rate analysis

Under Type select Combined

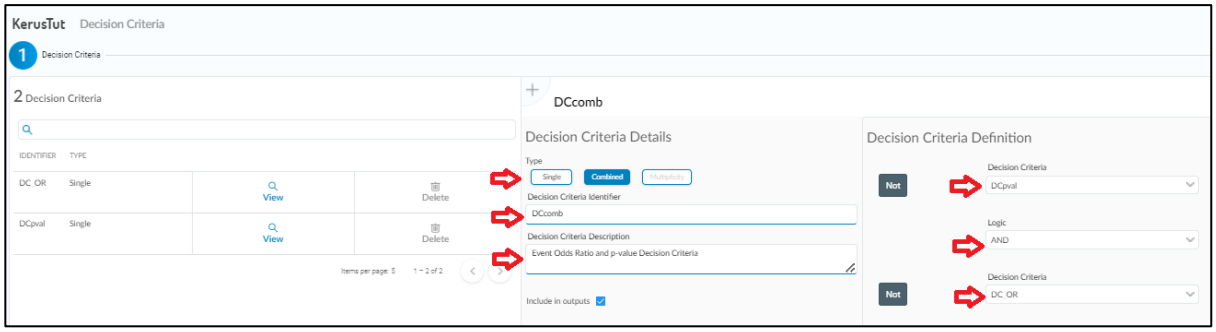
Under Decision Criteria Identifier type DCcomb (or another label of your choice)

Under Decision Criteria Description type 'Event Odds Ratio and p-value Decision Criteria'

Under Decision Criteria Definition select DCpval in the first box and DC_OR in the second box

Under Logic select AND. This means that only analysis which meet both criteria will be considered a successful outcome

Click Save in the top righthand corner



Enter a single Decision Criteria for the blood pressure data

Under Type select Single

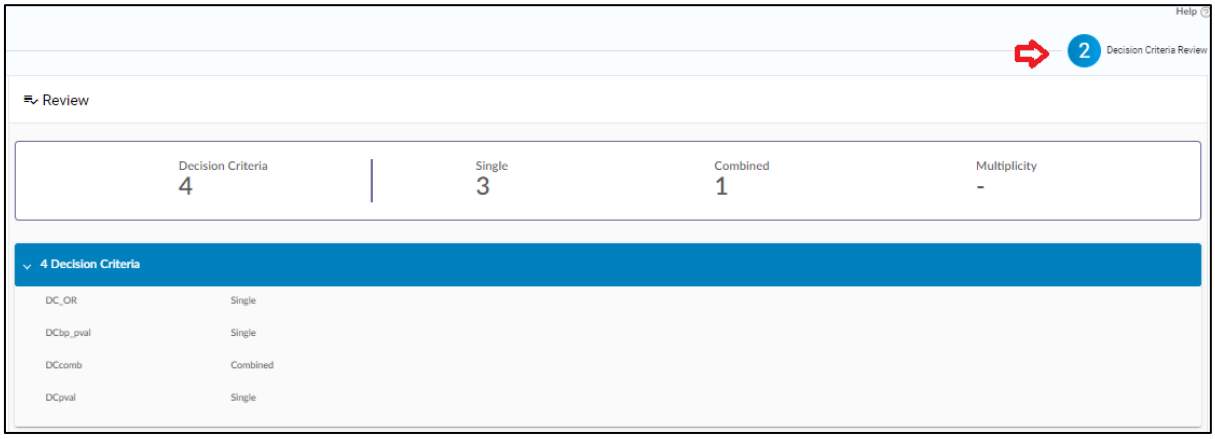
Under Decision Criteria Identifier type DCbp_pval (or another label of your choice)

Under Decision Criteria Description type 'sBP p-value Decision Criteria'

Under Analysis select systolic_BP

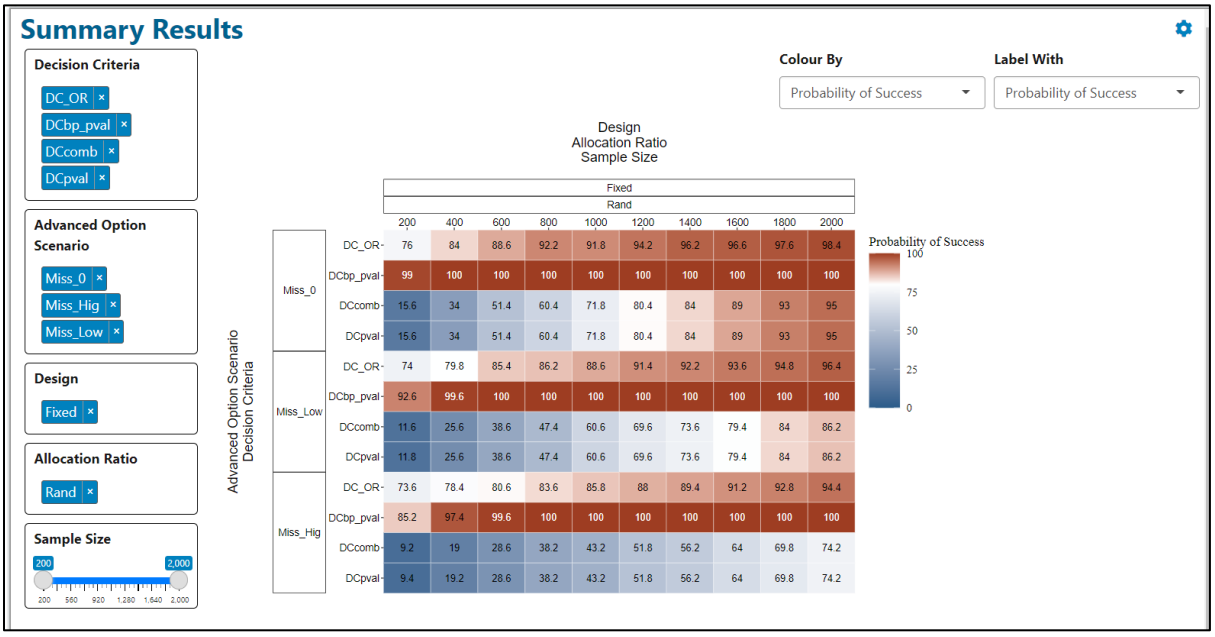
Under Decision Criteria Definition select P-value as the Metric and Trt:Placebo vs Trt:Active as the subgroups. Select the box for '<=' and select Type as Value, then enter the value as 0.05. Click Save in the top righthand corner.

Click Next to move to the final window of the Decision Criteria Wizard. Review the set up and click 'Go' in the bottom righthand corner.



Congratulations! You have successfully run the Decision Criteria to assess the probability of success for your study calculated from the analysis results across all 500 simulations and for each sample size, allocation ratio and scenario.

Once all Wizards have run go to Decision Criteria Visualisations and click View to see a heatmap containing the probability of success for each sample size and decision criteria. We can download the datasets by clicking Generate Data in the Virtual Population Data window. We will need to wait for the datasets to be created and then we can download a zipped file containing all the datasets, together with a manifest which describes which scenarios each dataset is associated with.

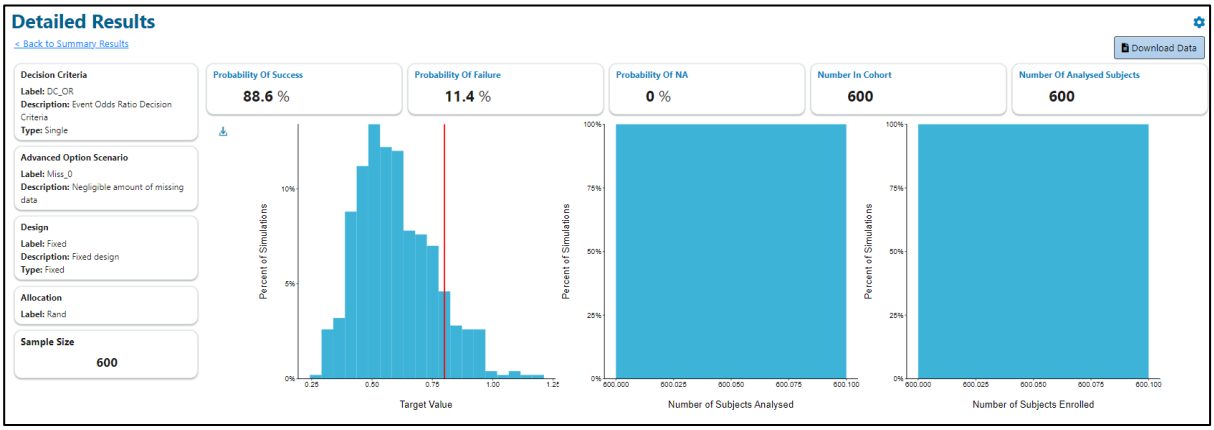


In the heatmap, the percentage value that is displayed by default in the cells, and which is used to colour the cell according to the colour bar on the righthand side of the display, is the percentage of simulated trials which met the decision criteria, i.e. the probability of success. You can modify the displayed percentage and the colour to be the two different values, such as the probability of failure, the average number in cohort (for adaptive designs) and the average number in analysis.

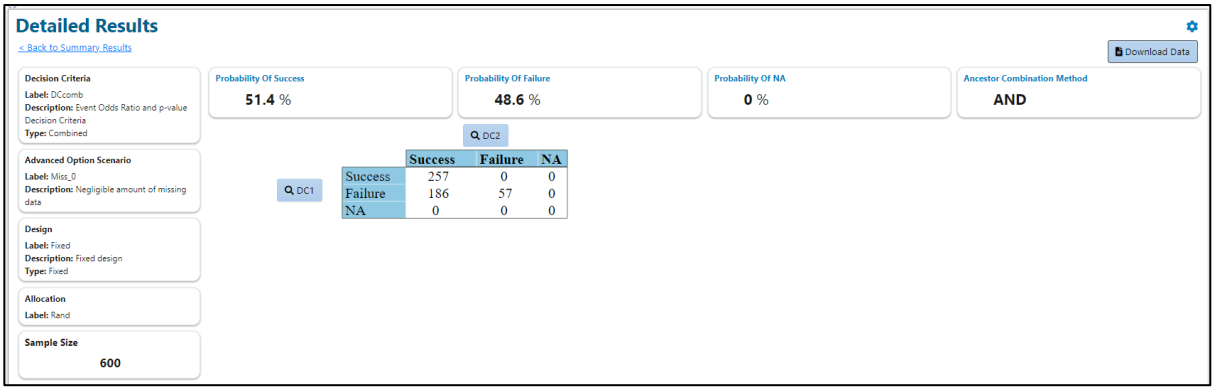
You can mouse over the cell to get a full summary. If you click on the cell it will take you through to another page which provides a further breakdown of the outcomes for the simulated trials in the form of figures and tables. The summary information provided will depend on the analysis type (fixed or adaptive design) and whether your decision criteria is single or combined.

You are also able to download the individual trial decision criteria outcomes by clicking on the Download Data tab in the top righthand corner.

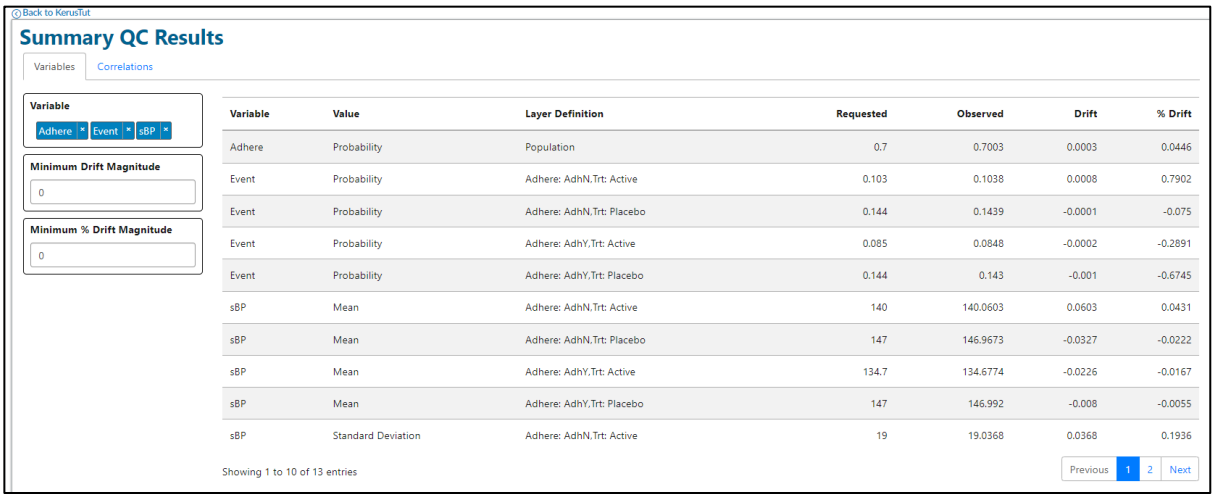
Single Decision Criterium with Fixed Design:



Combined Decision Criteria with Fixed Design:

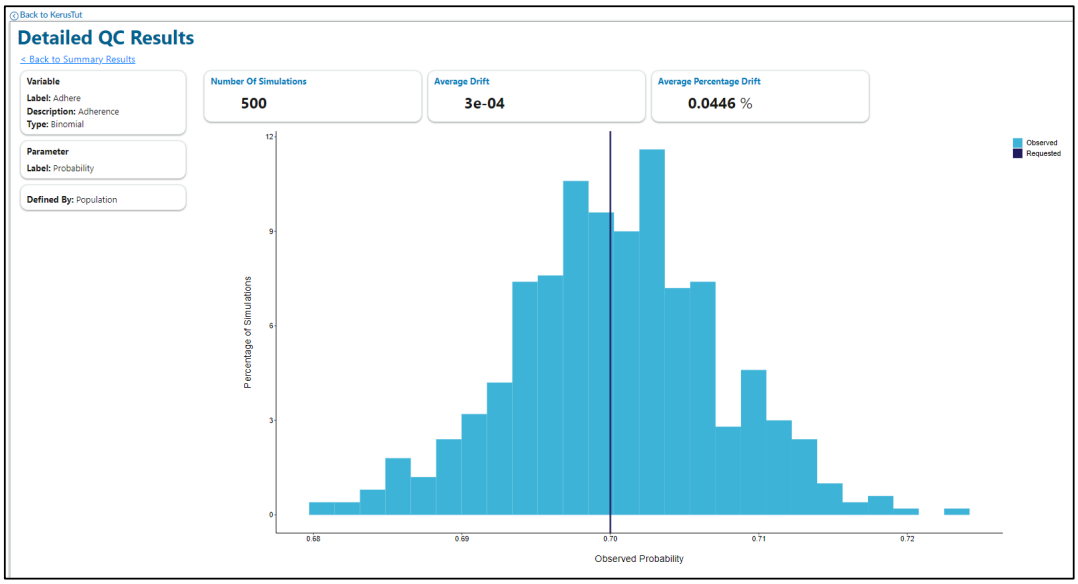


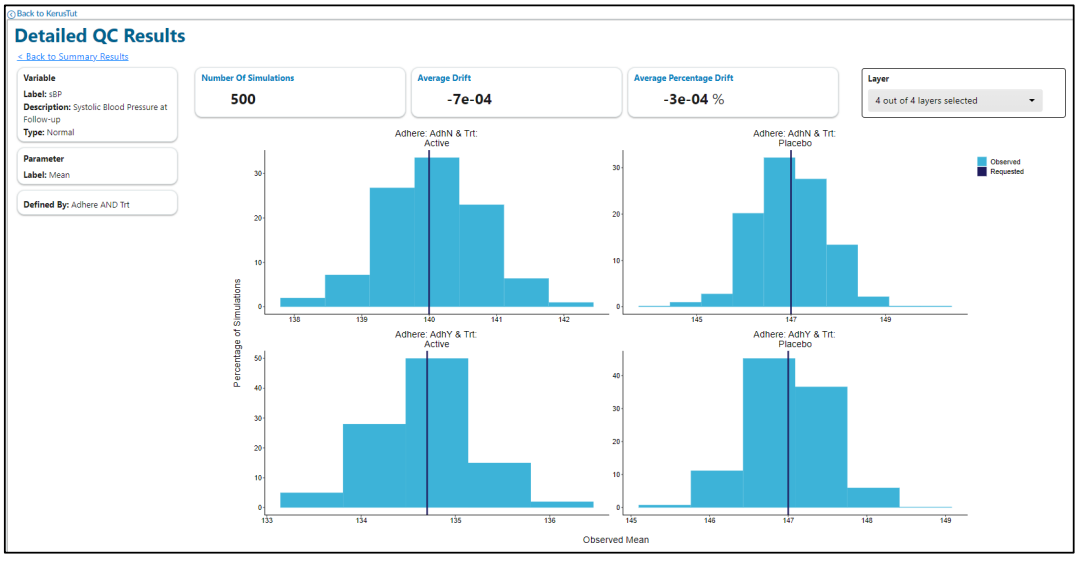
If you wanted to confirm that the virtual population reflects the parameters that were specified in the Virtual Population section, you can go to the Virtual Population QC window, and click on Generate QC. Once this has completed, you can then click View and access a table with summaries of the sample parameters over all the simulated datasets. The table will show for each distribution parameter and correlation specified in the Virtual population the summary statistics of the matching sample parameters calculated from the datasets generated by KerusCloud.



Variable	Value	Layer Definition	Requested	Observed	Drift	% Drift
Adhere	Probability	Population	0.7	0.7003	0.0003	0.0446
Event	Probability	Adhere: AdhN,Trt: Active	0.103	0.1038	0.0008	0.7902
Event	Probability	Adhere: AdhN,Trt: Placebo	0.144	0.1439	-0.0001	-0.075
Event	Probability	Adhere: AdhY,Trt: Active	0.085	0.0848	-0.0002	-0.2891
Event	Probability	Adhere: AdhY,Trt: Placebo	0.144	0.143	-0.001	-0.6745
sBP	Mean	Adhere: AdhN,Trt: Active	140	140.0603	0.0603	0.0431
sBP	Mean	Adhere: AdhN,Trt: Placebo	147	146.9673	-0.0327	-0.0222
sBP	Mean	Adhere: AdhY,Trt: Active	134.7	134.6774	-0.0226	-0.0167
sBP	Mean	Adhere: AdhY,Trt: Placebo	147	146.992	-0.008	-0.0055
sBP	Standard Deviation	Adhere: AdhN,Trt: Active	19	19.0368	0.0368	0.1936

If you click on a specific parameter in the table, you will be taken to additional visualisations of the sample parameters, presented as a histogram. If you defined the parameter by Population, then you will get one histogram, and if you have defined by one or more categorical group variables, then you will get a histogram for each subgroup.





Background to the parameter estimates

go back

The parameter estimates were taken from an article published in the Lancet journal: Vol 358 Sept 29 2001 'Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack'. The study described was set up as a collaboration between many groups with patients recruited from around the world. The collaboration was named PROGRESS and funded by grants from Servier, the Health Research Council of New Zealand, and the National Health and Medical Research Council of Australia.

The results of the study were used to give estimates for the Kerus simulation and to assess the effect that non-adherence would have on study outcomes.

Event Rate

go back

The estimates for the event rate were taken from Figure 5: percentage of stroke events for the combination therapy. This showed that over the course of the study 14.4% of subjects had a stroke in the placebo group and 8.5% in the combination therapy group.

An assumption was made that subjects not adhering to their treatment regime would have a reduced level of protection from the active treatment. Thus, if a subject was only taking 70% of their pills the risk of stroke would increase from 0.085 (8.5%) to 0.103 (10.3%). If a subject was only adhering half the time and hence only getting half the expected benefit, then the risk of stroke would increase from 0.085 to 0.1145 (11.45%).

The risk of stroke in the placebo group remains at 0.144 (14.4%) regardless of whether the subject was adhering or not due to the belief that missing doses of placebo won't have any true effect on the risk of stroke.

Blood pressure

go back

The estimates for average blood pressure were taken from the text. Claims that under combination treatment the systolic BP reduced by 12.3 from a placebo value of 147. The estimate for SD was taken from the baseline characteristics table as 19.

An assumption was made that subjects not adhering to their treatment regime would have a reduced level of protection from the active treatment. Thus, if a subject was only taking 70% of their pills the average blood pressure would increase from 134.7 to 138.39. If a subject was only adhering half the time and hence only getting half the expected benefit, then the average systolic blood pressure would increase from 134.7 to 140.85.

The average response of subjects in the placebo group remains at 147 regardless of whether the subject was adhering or not due to the belief that missing doses of placebo won't have any true effect on blood pressure.