B-SAFE User Manual

version 1.0

A. Stemke, O. Sailer, J.O. Turay, Dunfu Yang, Louise Whitehead

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1 Introduction

B-SAFE is an R-Shiny app. The app is an innovate software tool for statistical analysis of adverse event summary data. The app can enhance the descriptive analysis for a current trial with historical information on one or more treatment arms for increased precision. It features a Bayesian Meta-Analytic Predictive (MAP) Prior approach [1] and a robust extension [2], which incorporates historical information for safety analyses on adverse events into safety analyses for a new trial. The use of historical information has been used for efficacy analyses in the past and now being extended to safety analyses.

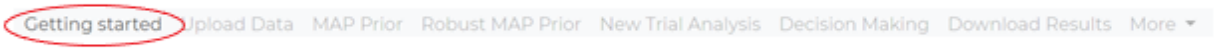
This user manual details how to use the app. The user manual documents and specifies the input parameters with their expected outputs. Refer to the Statistical Analysis Plan for the methodology used.

- Coding : Lin Feng Zou, Lars Andersen, Alexander Stemke
- Statistical Analysis: Oliver Sailer, Alexander Stemke
- Testing : Lars Andersen, Dunfu Yang
- Support by Steven Brooks, Kevin Kunzmann, Dooti Roy, Christina Schlecker, James O. Turay, Louise Whitehead

2 Using the App

This section introduces the user to the app and how to prepare the dataset for analysis. From this section on, we will use a simple example to demonstrate the usage of the entire application.

2.1 Getting Started



The **Getting Started** page is the first page you'll encounter on opening the app. It is expected that users move from left to right along the tabs at the top of the page. Each of the tabs will be explained in detail in the following sections. It provides an overview of the usage of the app. The app has two main uses:

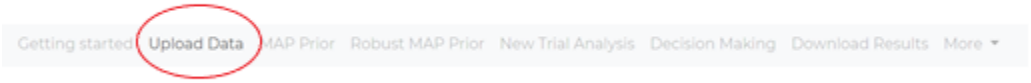
- A deep dive into a Bayesian MAP Prior analysis of a selected adverse endpoint
- A Posterior Probability analysis to compare a set of adverse events between two treatment arms

Analyses for Incidence Proportions and Exposure-Adjusted Adverse Event Rates (i.e., Incidence Rates) are available.

To begin any form of analysis, one must upload a dataset (see Section 2.2) that contains both the adverse events from historical data and the new trial data as a .csv file. A single dataset is uploaded that contains all relevant information.

You can then jump directly to the "Download Results" tab for a summary table with the default. Further analysis into specific Adverse Events (AEs) can be done if that is needed.

2.2 Upload Data - Data Preparation



The "Upload Data" tab makes provision for you to upload the data that will be used for your analysis.

2.2.1 Upload CSV File

Click on the Browse button in Figure 1 to upload a .csv file containing the collection of various studies you will use for the analysis. The data applicable for the MAP Prior analysis is then displayed on the right hand side of the page.

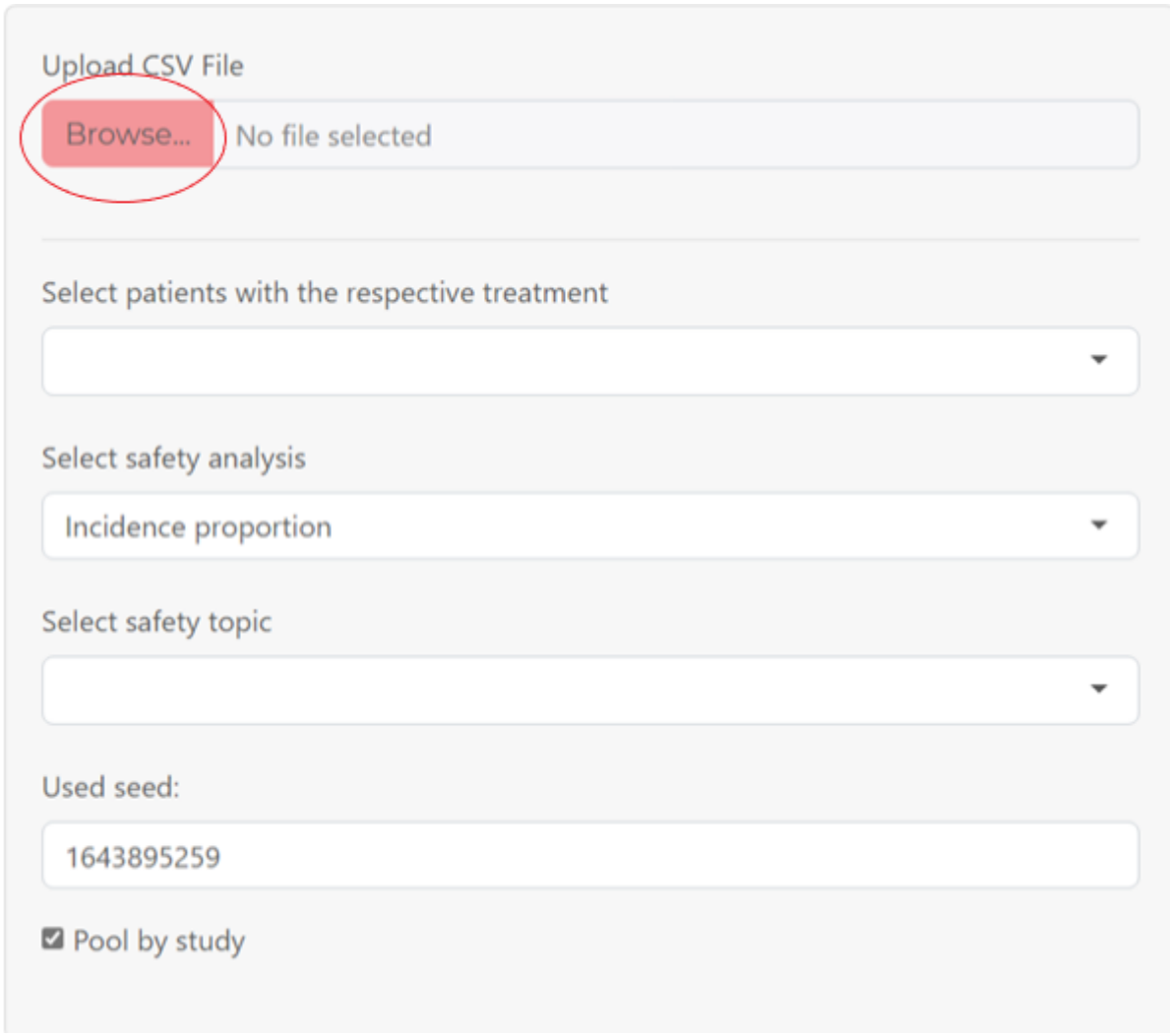


Figure 1: Browse File

STUDYID	HIST	DOSE	FREQ	LENGTH	TREAT	ARM	N	SAF_TOPIC	N_WITH_AE	TOT_EXP	REGION
0000-0001	1	0	1	365	Placebo	Placebo	200	DILI	4	200	China
0000-0001	1	0	1	365	Placebo	Placebo	200	Depression	3	190	China
0000-0001	1	0	1	365	Placebo	Placebo	200	MACE	5	210	China
0000-0002	0	0	1	365	Placebo	Placebo	100	DILI	2	100	East Asia
0000-0002	0	0	1	365	Placebo	Placebo	100	Depression	1	99	East Asia
0000-0002	0	0	1	365	Placebo	Placebo	100	MACE	3	105	East Asia
0000-0003	1	0	2	532	Placebo	Placebo	300	DILI	0	300	US
0000-0003	1	0	2	532	Placebo	Placebo	300	Depression	0	300	US
0000-0003	1	0	2	532	Placebo	Placebo	300	MACE	1	302	US
0000-0004	1	0	1	90	Placebo	Placebo	60	DILI	1	62	UK
0000-0004	1	0	1	90	Placebo	Placebo	60	Depression	2	67	UK
0000-0004	1	0	1	90	Placebo	Placebo	60	MACE	3	66	UK
0000-0004	1	150	1	90	ABC 150 mg	Treatment	120	DILI	10	130	Africa
0000-0004	1	150	1	90	ABC 150 mg	Treatment	120	Depression	20	135	Africa
0000-0004	1	150	1	90	ABC 150 mg	Treatment	120	MACE	15	137	Africa

Figure 2: Data

The dataset that is uploaded must include the variable columns shown in Table 1 to effectively run the analysis:

Table 1: Variable Columns

Variable	Data Type	Description
STUDYID	character/numeric	Study number or name
HIST	boolean	0 for current trial and 1 for historical trial
ARM	character/numeric	Defines the various treatment arms in the respective study
N	numeric	Total number of patients in the respective study
N_WITH_AE	numeric	Total number of patients for the respective study safety topic who experienced at least one adverse event
SAF_TOPIC	character	Describes the type of adverse event. Safety topic will be read in by your dataset, max 30 characters
TOT _ EXP	numeric	Total exposure time for the respective safety topic: sum of patients treatment exposure period until occurrence of first event. If no event occurs, use complete observation time

Note that TOT_EXP (total exposure time) is only needed for analysis of the Exposure Adjusted Incidence Rate.

Additionally, other variables including Dose, Freq (Frequency), Length (Length of treatment), Treat (Treatment) can be included, as shown in Table 2. With these additional variables, subgroup analysis can be done. Note that in Table 2, for variables Freq and Length, the unit does not have to be "day". The time scale depends on the input and should be consistent throughout the entire dataset.

The following simple example was manually generated for this introductory example.

Table 2: Additional Variables

Variable	Data Type	Description
Dose	numeric	Amount/weight of the medication the patient took
Freq(Frequency)	integer	Number of times in a day the medication was taken by the patient
Length	integer	Total number of days the patient was on the treatment
Treat	character	The specific treatment the patient was on

STUDYID	HIST	DOSE	FREQ	LENGTH	TREAT	ARM	N	SAF_TOPIC	N_WITH_AE	TOT_EXP	REGION
0000-0001	1	0	1	365	Placebo	Placebo	200	DILI	4	200	China
0000-0001	1	0	1	365	Placebo	Placebo	200	Depression	3	190	China
0000-0001	1	0	1	365	Placebo	Placebo	200	MACE	5	210	China
0000-0002	0	0	1	365	Placebo	Placebo	100	DILI	2	100	East Asia
0000-0002	0	0	1	365	Placebo	Placebo	100	Depression	1	99	East Asia
0000-0002	0	0	1	365	Placebo	Placebo	100	MACE	3	105	East Asia
0000-0003	1	0	2	532	Placebo	Placebo	300	DILI	0	300	US
0000-0003	1	0	2	532	Placebo	Placebo	300	Depression	0	300	US
0000-0003	1	0	2	532	Placebo	Placebo	300	MACE	1	302	US
0000-0004	1	0	1	90	Placebo	Placebo	60	DILI	1	62	UK
0000-0004	1	0	1	90	Placebo	Placebo	60	Depression	2	67	UK
0000-0004	1	0	1	90	Placebo	Placebo	60	MACE	3	66	UK
0000-0004	1	150	1	90	ABC 150 mg	Treatment	120	DILI	10	130	Africa
0000-0004	1	150	1	90	ABC 150 mg	Treatment	120	Depression	20	135	Africa
0000-0004	1	150	1	90	ABC 150 mg	Treatment	120	MACE	15	137	Africa

Figure 3: Simple Example

Figure 3 displays the example data. In this dataset, three historical trials will be used to generate the MAP prior for placebo arm.

2.2.2 Creation of New Arm

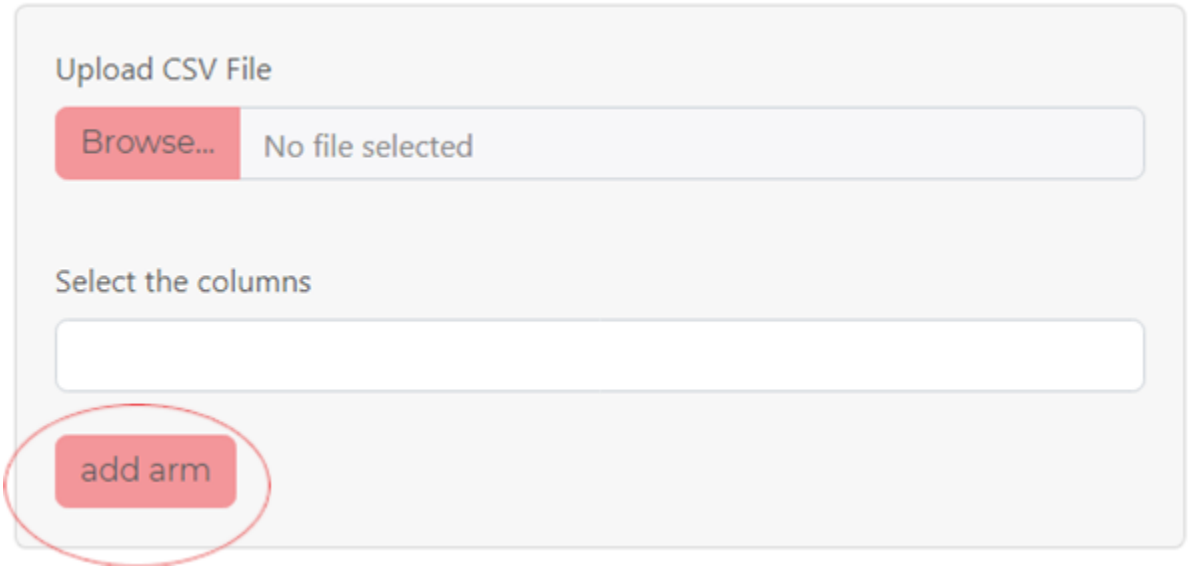
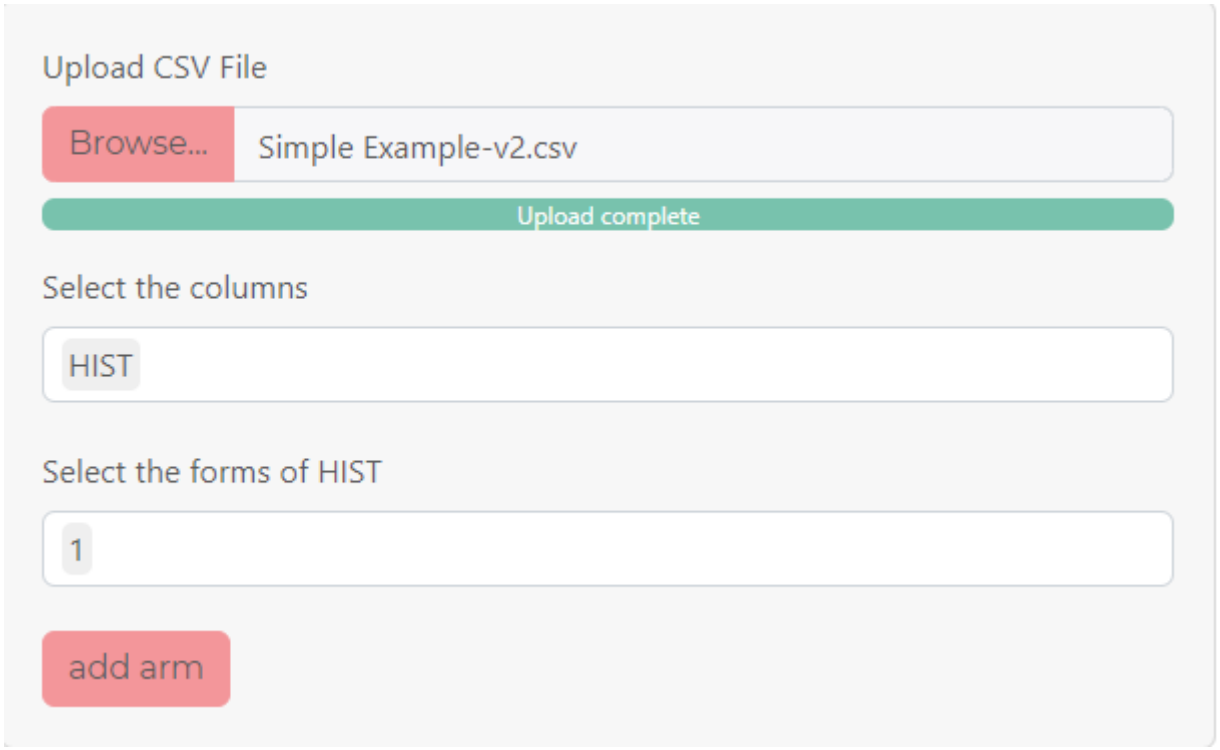


Figure 4: Add Arm

Upon uploading the csv file, the user can create a new arm (which will be used to form the MAP Prior) as shown in Figure 4. Various variable columns can be selected for consideration in the creation of the arm. On creating the new arm, it is added to the dataset and displayed on the right hand side of the page. This newly created arm can create sub-groups for which comparisons and sub-group analysis can be done.

In the example, as shown in Figure 5, only historical summary data was selected for deriving the MAP prior and we named it as "hist".



STUDYID	HIST	DOSE	FREQ	LENGTH	TREAT	ARM	N	SAF_TOPIC	N_WITH_AE	TOT_EXP	REGION
0000-0001	1	0	1	365	Placebo	hist	200	DILI	4	200	China
0000-0001	1	0	1	365	Placebo	hist	200	Depression	3	190	China
0000-0001	1	0	1	365	Placebo	hist	200	MACE	5	210	China
0000-0003	1	0	2	532	Placebo	hist	300	DILI	0	300	US
0000-0003	1	0	2	532	Placebo	hist	300	Depression	0	300	US
0000-0003	1	0	2	532	Placebo	hist	300	MACE	1	302	US
0000-0004	1	0	1	90	Placebo	hist	60	DILI	1	62	UK
0000-0004	1	0	1	90	Placebo	hist	60	Depression	2	67	UK
0000-0004	1	0	1	90	Placebo	hist	60	MACE	3	66	UK
0000-0004	1	150	1	90	ABC 150 mg	hist	120	DILI	10	130	Africa
0000-0004	1	150	1	90	ABC 150 mg	hist	120	Depression	20	135	Africa
0000-0004	1	150	1	90	ABC 150 mg	hist	120	MACE	15	137	Africa

Figure 5: Select Historical Summary Data

The filtered data "hist" is then being selected for the "Select patients with the respective treatment" option.

2.2.3 Select Patients with the Respective Treatment

If there are different treatment options in the uploaded dataset file, one can choose a specific treatment from the drop-down menu in Figure 6. The filtered data is then displayed on the right hand side of the screen.

Figure 6: Treatment Selection

2.2.4 Select Safety Analysis

The drop-down menu in Figure 7 provides two analyses options to choose from:

- Incidence Proportion: sometimes known as Adverse Event Rate which describes the proportion of patients with at least one of the Adverse Event of interest in our trial, i.e., $Incidence\ Proportion = \frac{\sum N\_WITH\_AE}{\sum N}$ where $\sum N\_WITH\_AE$ = total number of patients with AE and $\sum N$ = total number of patients.

  Incidence proportion can also be described as the estimated probability of a patient having one or more AEs during the specific period.

- Exposure Adjusted Event Rate: sometimes referred to as Incident rate, which describes the incident rate of AEs per patient per unit time assuming a constant hazard rate. This could be interpreted

as the number of patients having one or more adverse events per unit time under assumption of constant risk over the observational period. $\textit{Exposure Adjusted Event Rate} = \frac{\sum N\_WITH\_AE}{\sum t_i}$ where $\sum N\_WITH\_AE$ = number of subjects who had at least one AE, t_i = subject i's total exposure time to first AE or censoring.

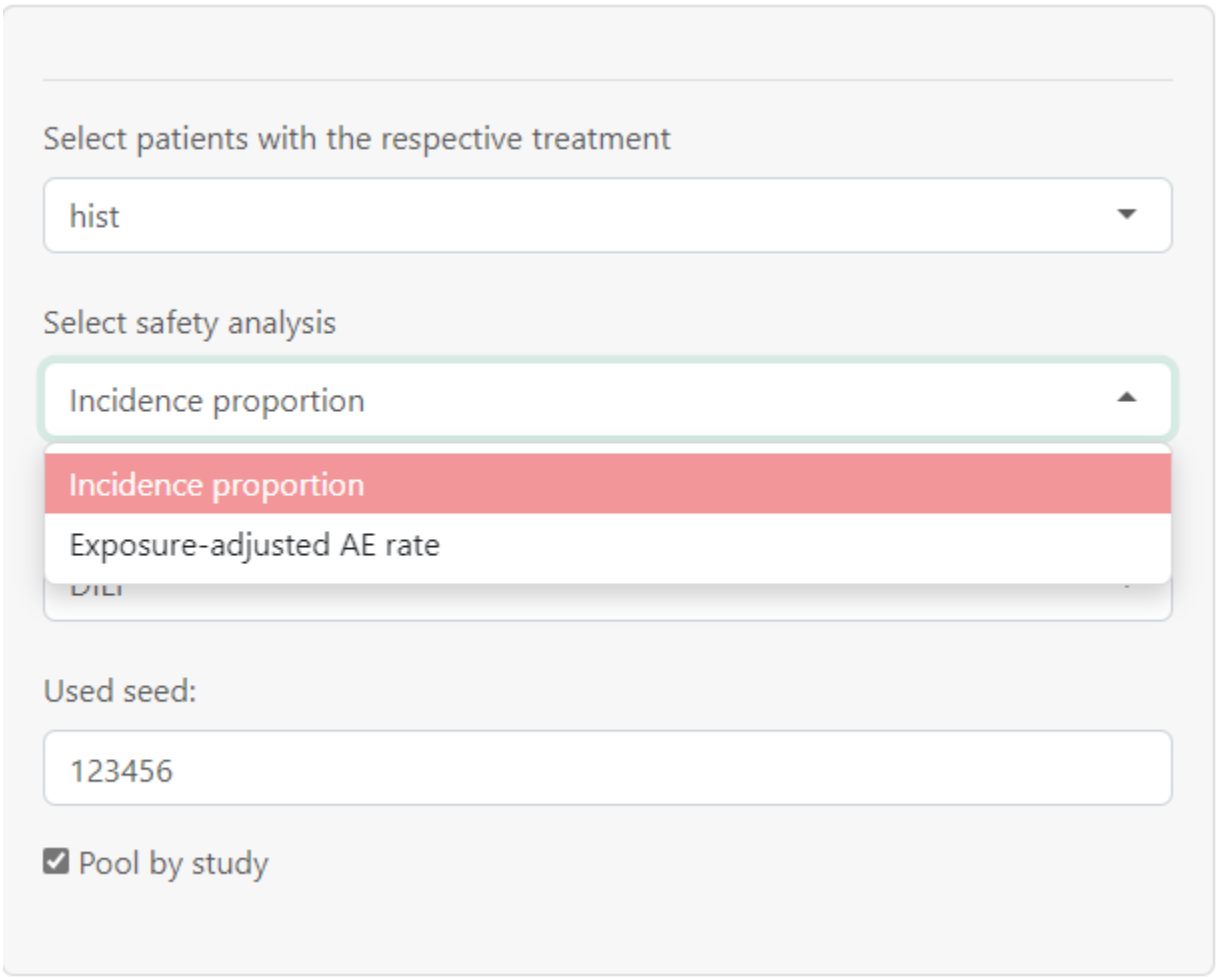


Figure 7: Safety Analysis

The choice of Safety Analysis option is based on the need of the user.

The selection of the Safety Analysis option does not affect the filtered data that is displayed.

2.2.5 Select Safety Topic

The user should select a safety topic (AE endpoint) that a (robust) MAP Prior will explore from the drop-down menu in Figure 8. The filtered data will be displayed on the right hand side of the screen.

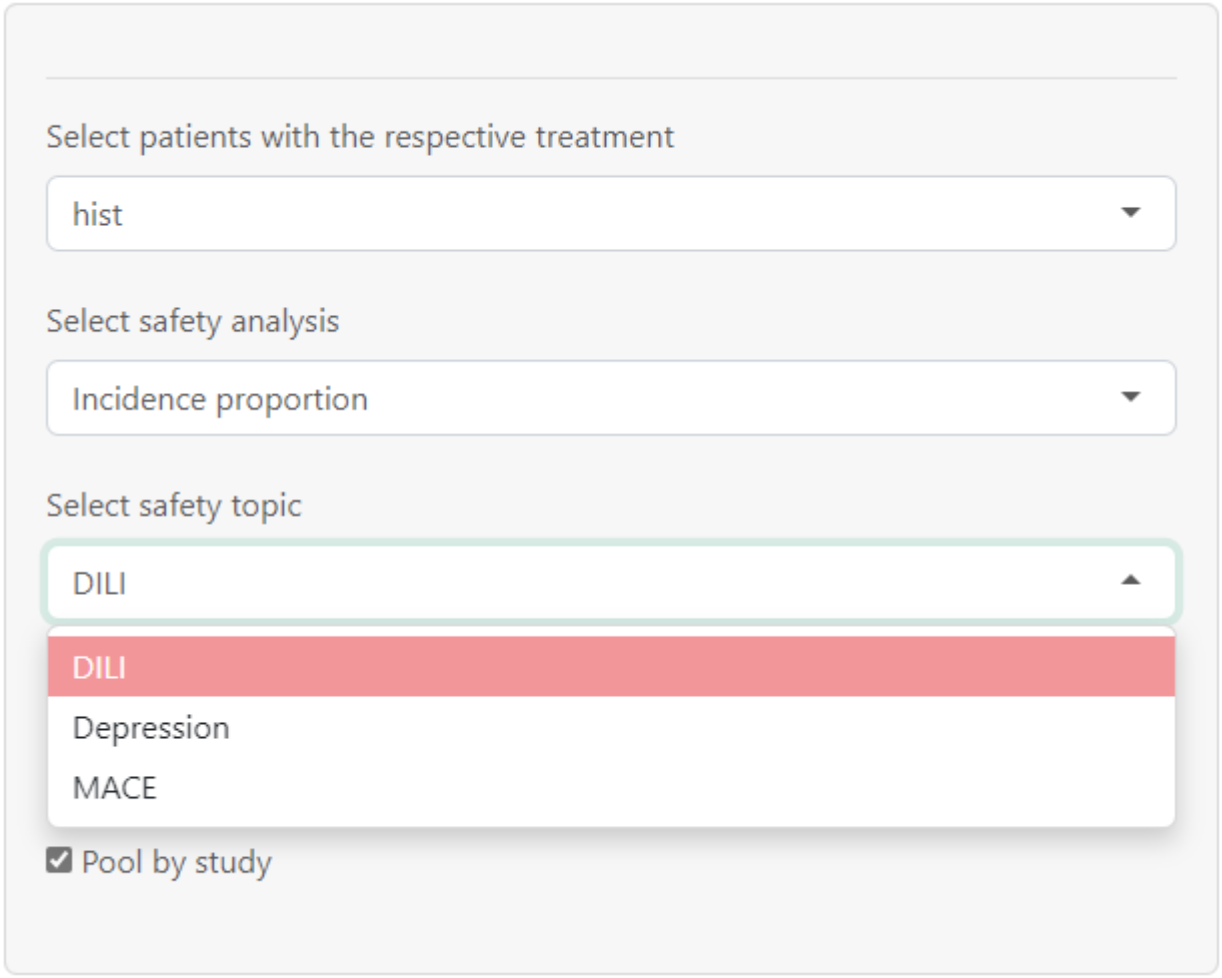


Figure 8: Safety Topic

By default, the first AE endpoint (ordered alphabetically) will be selected and used for analysis.

2.2.6 Used Seed

The user can manually set the seed for reproducibility of results of the Markov Chain Monte Carlo simulations (see Figure 9).

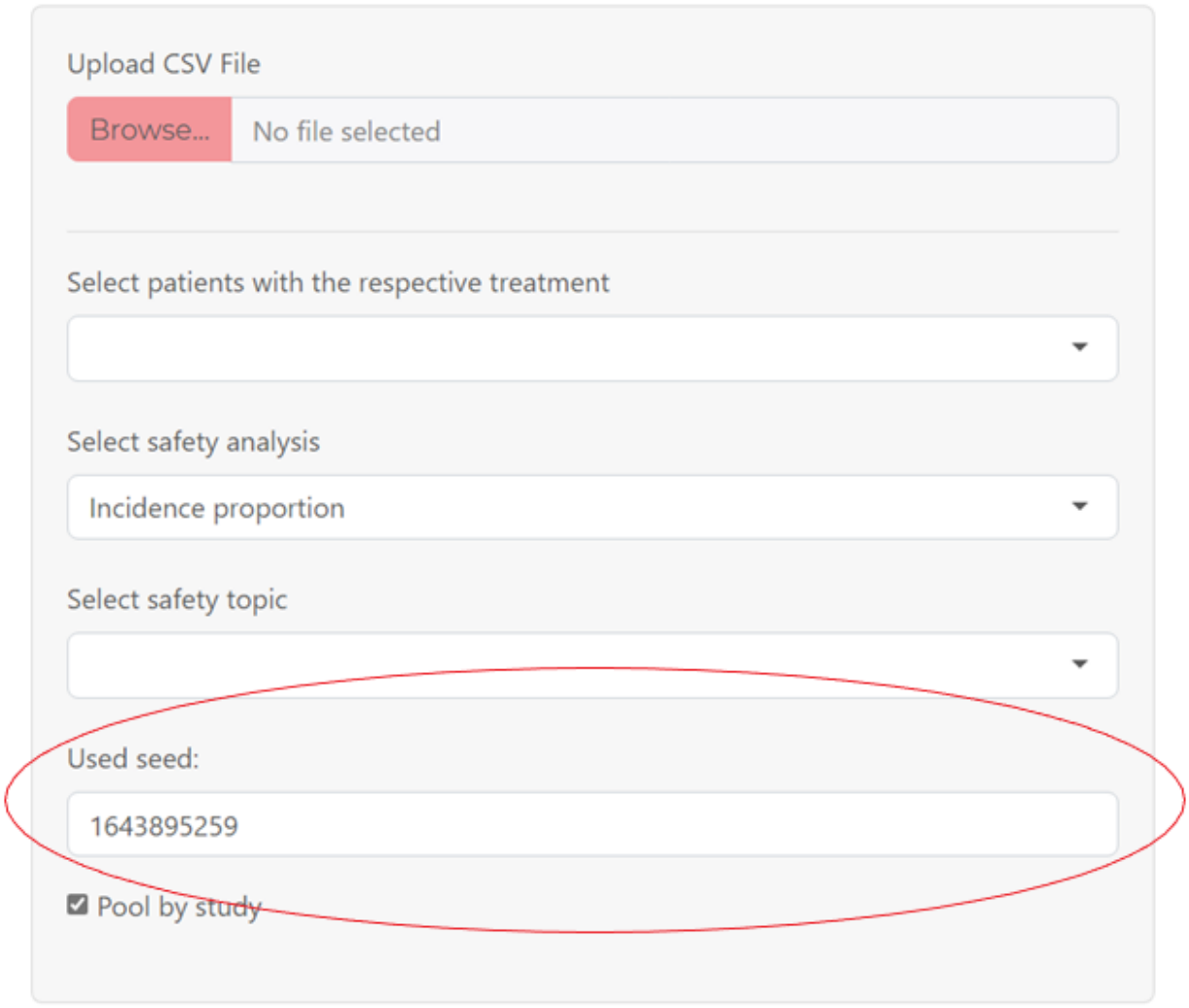


Figure 9: Used Seed

2.2.7 Pool by Study

If the defined treatment arm includes subsets within the trial, e.g., several different doses, the user can choose to pool these together or keep them separated for the purpose of MAP Prior analysis. The default option is to pool the studies together (see Figure 10).

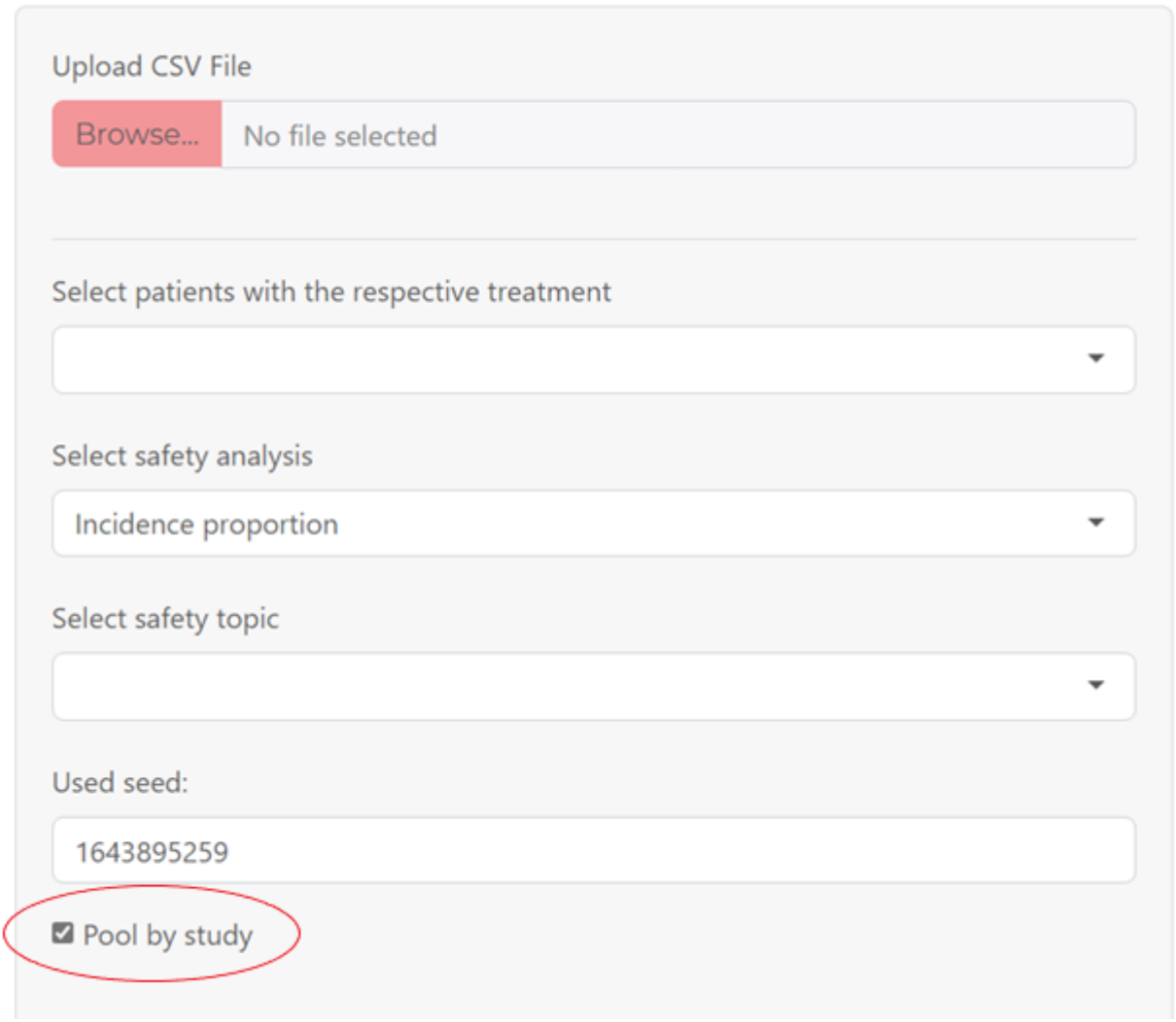


Figure 10: Pool Study

For the simple example, suppose here our target is to estimate the probability of a patient having at least one of the AE of interest in our trial. Therefore, we select "Incidence Proportion" for the "Safety Analysis" option. By default, the first AE endpoint DILI (by alphabetic order) will be selected and used for analysis. Seed number 123456 was used for reproducibility of the results.

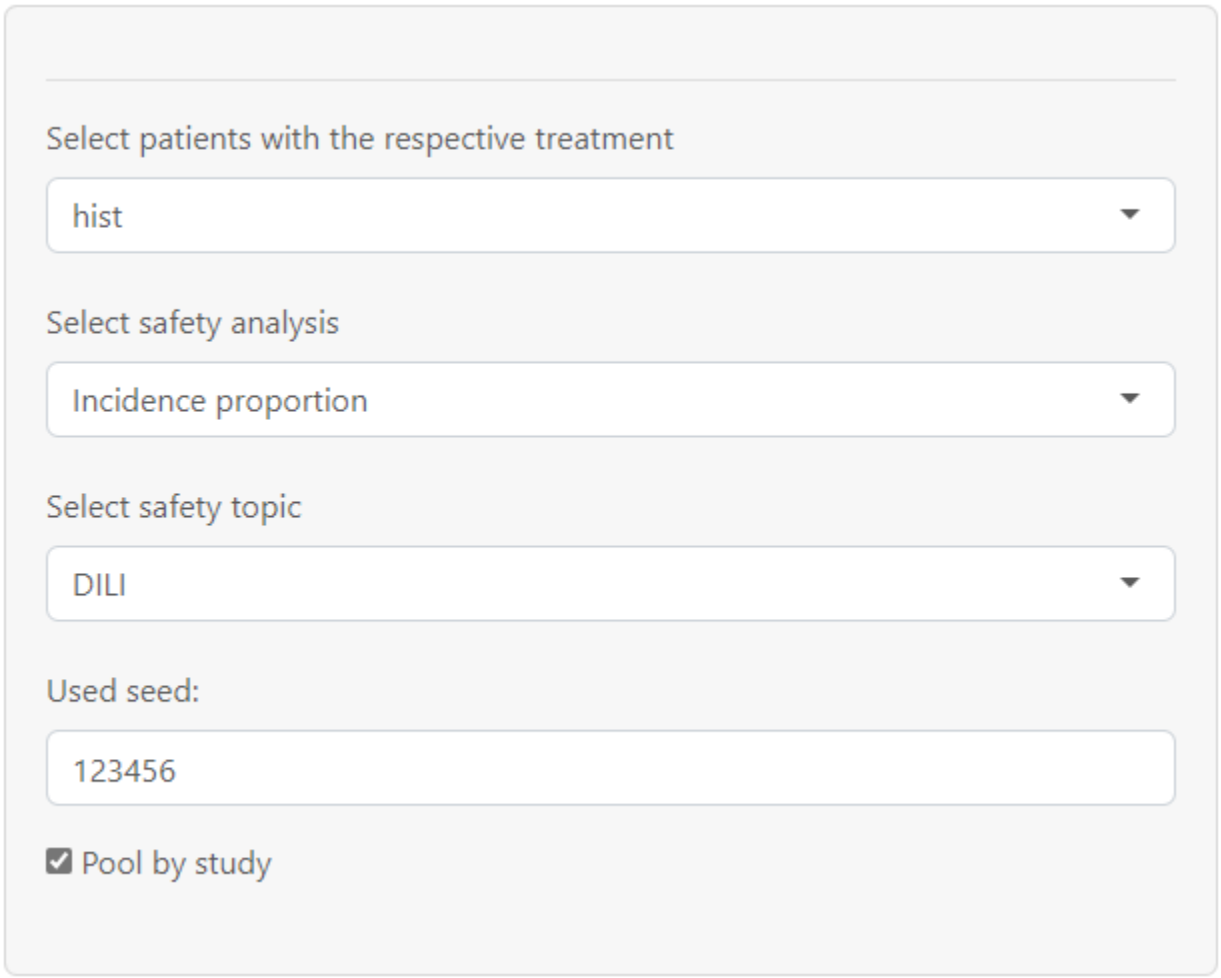
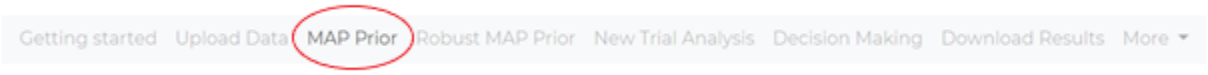


Figure 11: Select Safety Analysis

3 MAP Prior



The MAP Prior as proposed in [1] is estimated using a meta-analytic predictive model which accounts for the between-trial heterogeneity leading to discounting of the historical information.

The B-SAFE app uses the Half-normal distribution as a prior distribution for the between trial heterogeneity parameter τ as seen in Figure 12 which is a special case of the normal distribution that is truncated to values greater than or equal to zero.

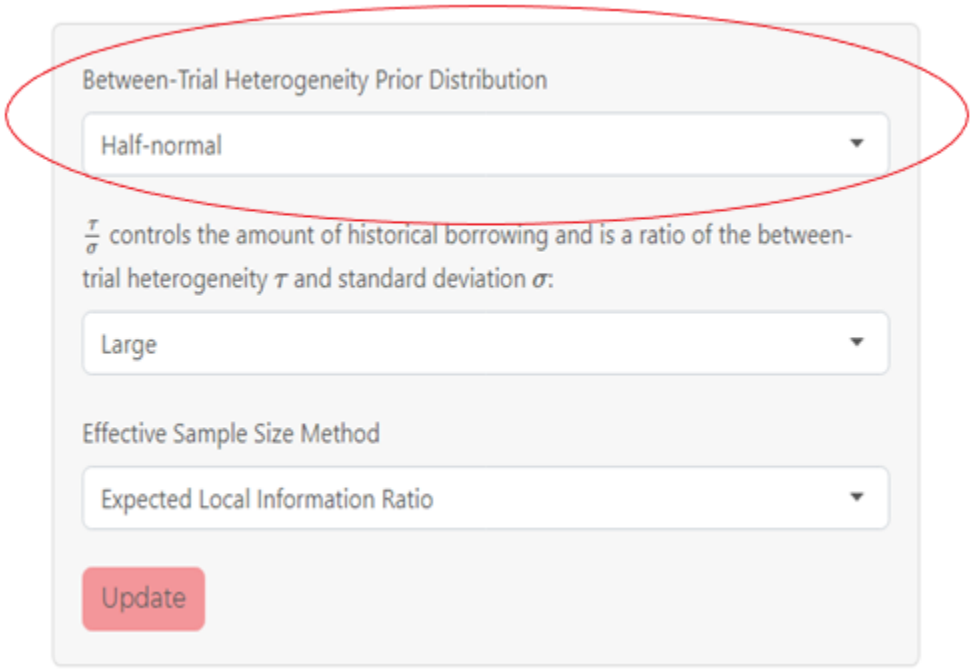


Figure 12: Between-Trial Heterogeneity

To control the amount of information borrowed, the drop-down menu in Figure 13 gives the user control of how much historical information to borrow using the recommendation in [3] as shown in Table 3. The amount of information to be borrowed depends on the confidence the user has on the similarity between the new and historical data. In the app, the (default) hyperparameter for τ representing between-trial heterogeneity has been set to 'large' [4]. Therefore, the amount of historical information borrowed is 'small'.

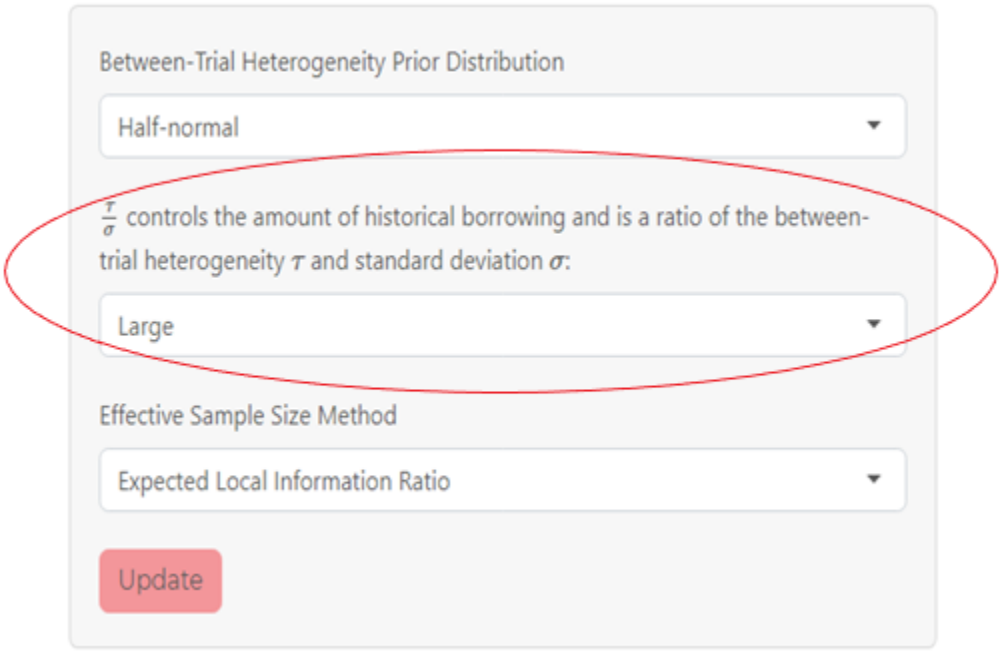


Figure 13: Amount of Historical Information Borrowed

Heterogeneity	τ/σ
small	0.0625
moderate	0.125
substantial	0.25
large	0.5
very large	1

Table 3: Amount of Historical Borrowing

For the Expected Sample Size method, the Expected Local Information Ratio proposed in [5] is used . This is due to its predictive consistency, i.e., the posterior expected sample size on average, if the data are generated from the prior, equals the sum of the prior expected sample size and the current trial sample size. The expected sample size calculated from the MAP Prior is rounded down.

On the top-right corner of Figure 14, is the Model Estimate of which a forest plot displays the frequentist estimates for the strata (dashed lines) and the lower part shows the mean distribution and the MAP prior of the mean.

On the bottom-right corner of Figure 14, a density curve and summary statistics is obtained for the MAP Prior.

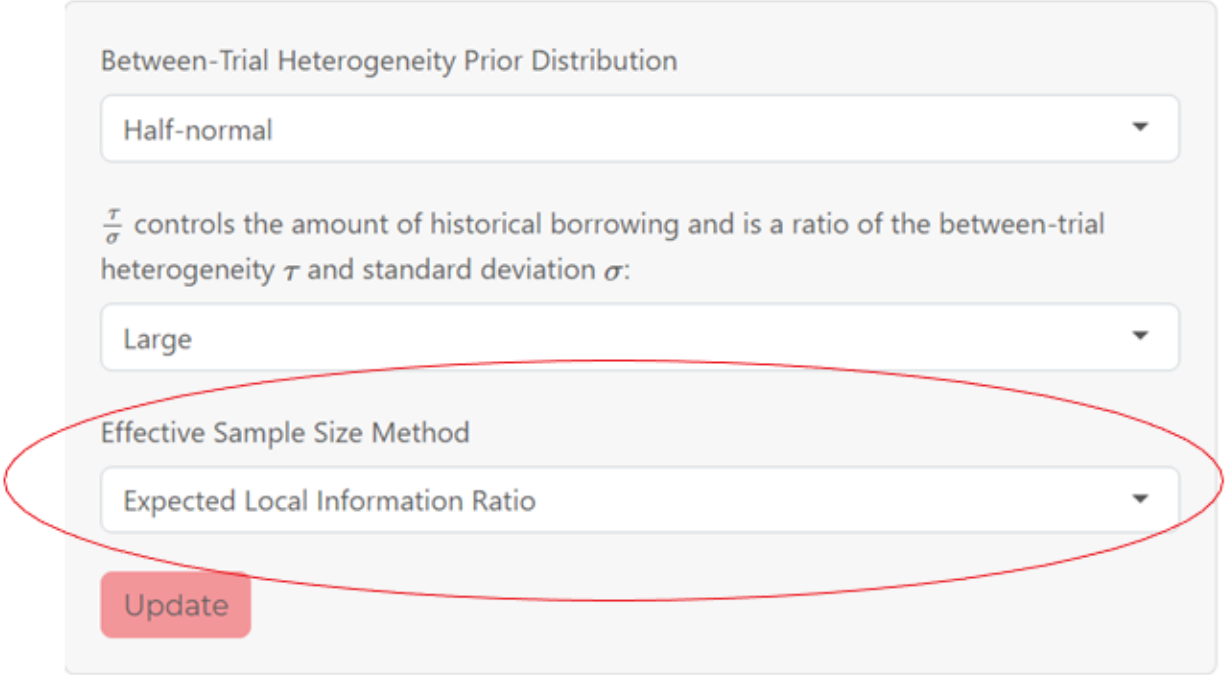


Figure 14: Effective Sample Size

Should the type of analysis be changed, the update button should be pressed. If not, the beta values for the previous analysis will be used leading to wrong estimated values for the mean, standard deviation, median, 95% credible interval and effective sample size.

One thing to note is that when no historical information is available, a noninformative prior derived from the current data will be used. On the contrary, if there is no current data, the MAP prior will be used.

3.1 Incidence Proportion

The mean distribution in Figure 15 is the meta-analysis of the incidence proportion of the various historical data. The MAP Prior distribution is the predicted true incidence proportion of the population in the new trial based on the historical data.

The MAP prior for the incidence Proportion is generated by MCMC samples and then approximated by mixture of three Beta distributions.

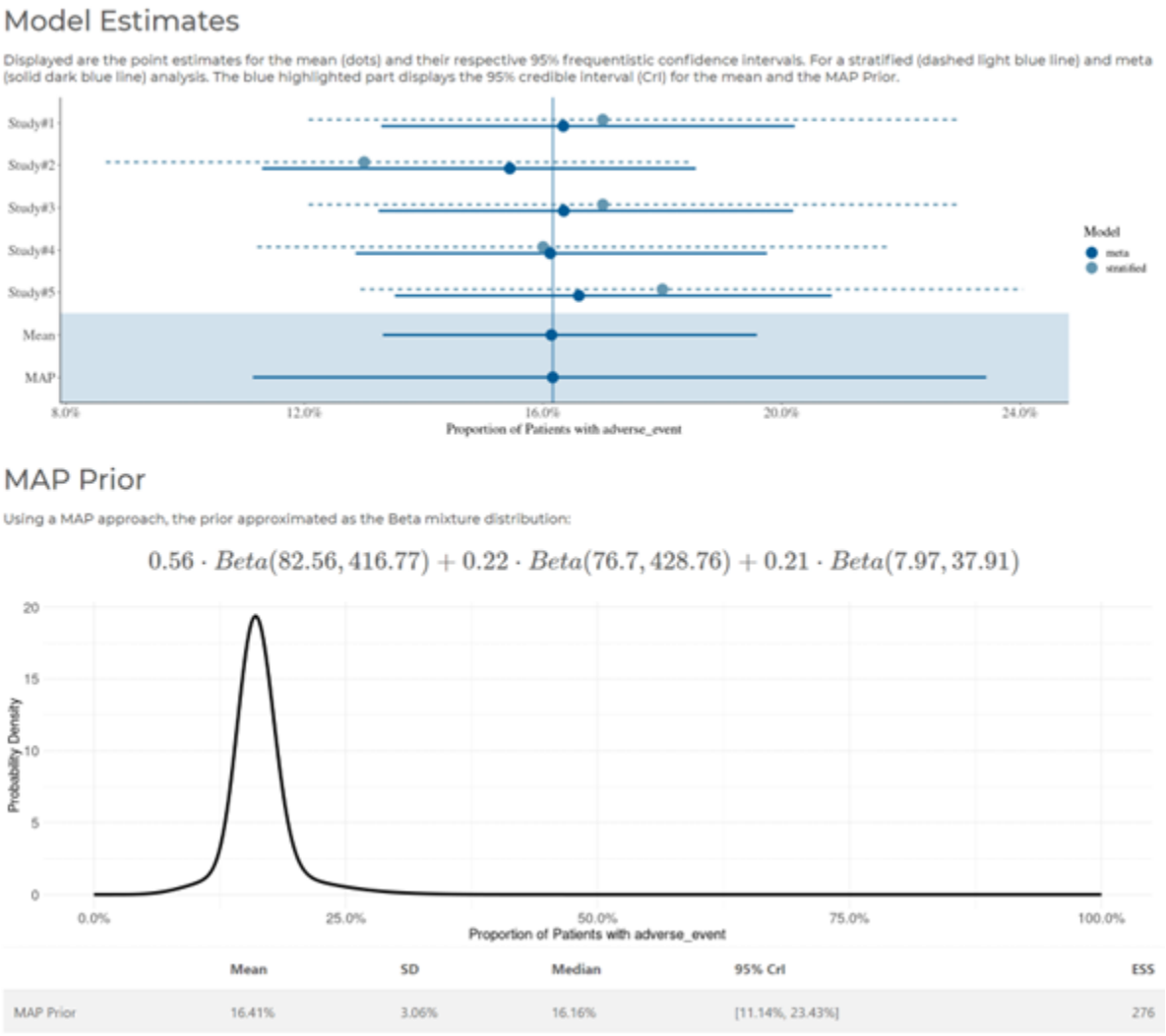


Figure 15: Model Estimates and MAP Prior for Incidence Proportion Analysis

3.2 Exposure-Adjusted Adverse Event Rate

Exposure-Adjusted Event Rate is estimated as the log hazard rate using the asymptotic normal distribution. The MAP Prior for the log hazard is approximated by mixture of three normal distributions (see Figure 16).

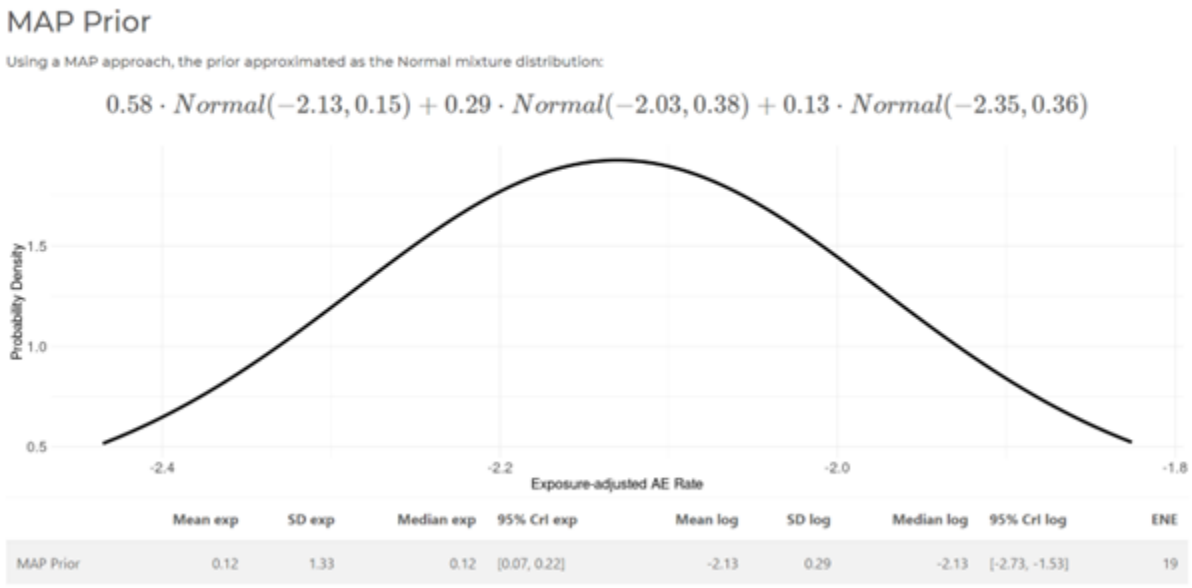


Figure 16: MAP Prior for Exposure-Adjusted Adverse Event Rate

In Figure 16 the variable mean exp, SD exp, Median exp and 95% CrI exp refers to the mean, standard deviation, median and the 95% Credible Interval of the MAP Prior on the hazard rate scale.

By default, the between trial heterogeneity was set to "Large" so that the amount of information borrowed would be "small". By clicking the "Update" button, a forest plot, density curve, and summary statistics were obtained for the MAP prior as shown in Figure 17 and Figure 18. The parametric distribution of the MAP prior was approximated by a mixture of three Beta distributions. The effective sample size is 67.

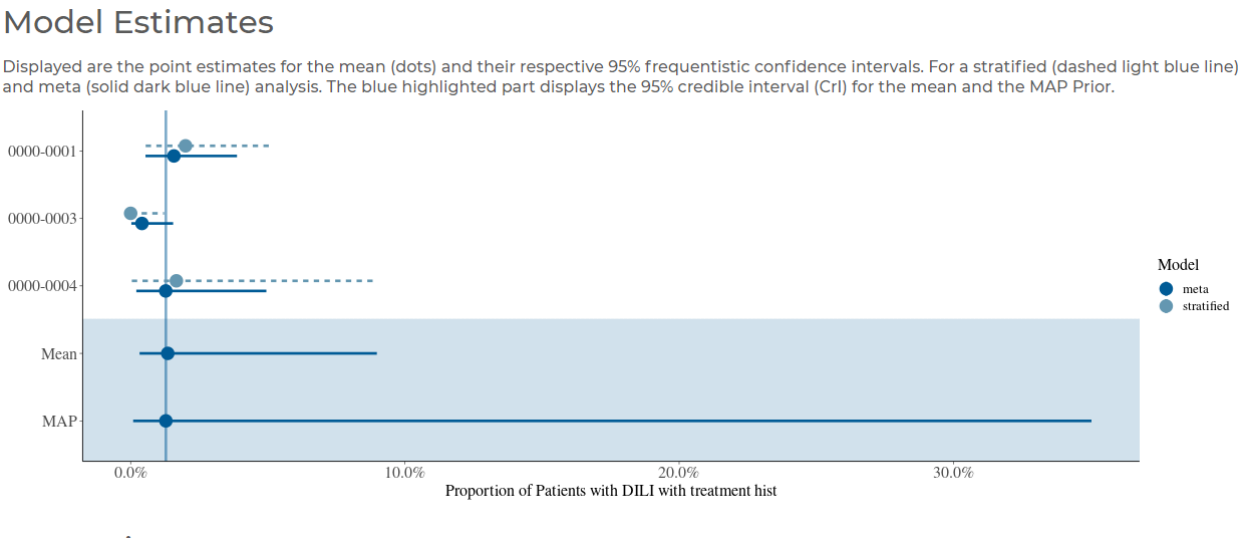
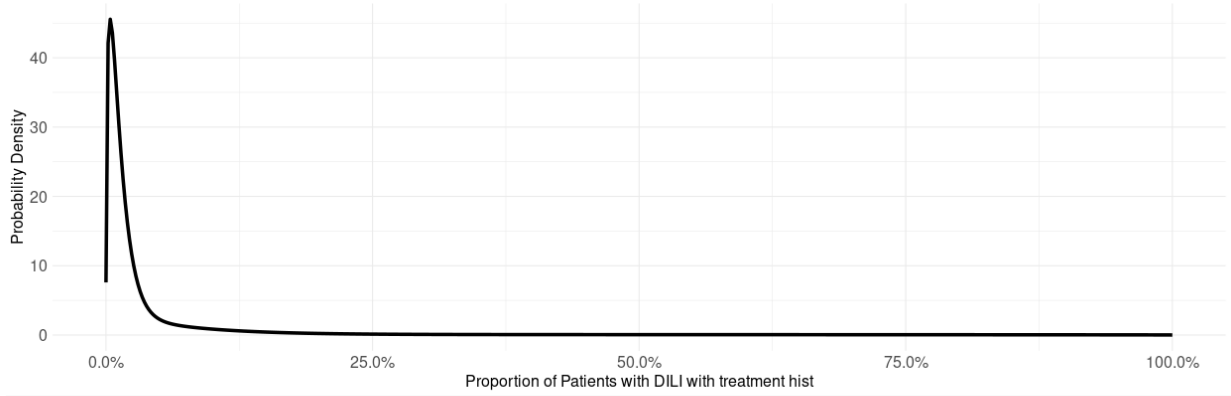


Figure 17: Forest Plot

MAP Prior

Using a MAP approach, the prior approximated as the Beta mixture distribution:

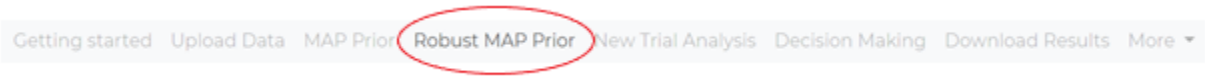
$$0.73 \cdot Beta(1.46, 116.07) + 0.22 \cdot Beta(1, 14.52) + 0.05 \cdot Beta(1, 1.39)$$



	Mean	SD	Median	95% CrI	ESS
Prior	4.32%	10.79%	1.28%	(0.09%, 2.87%)	67

Figure 18: MAP Prior

4 Robust MAP Prior



To protect against prior-data conflict, MAP priors should be robustified [6]. This adds a weakly informative component to the (informative) MAP prior distribution, such that the more the historical data differs from the observed data, the more robust MAP Prior will down-weight/discount the information from the historical data thus preventing prior data conflict. The default prior weight on the weakly informative component has been set to 0.2 (20%) discounting factor.

Depending on the expected comparability between the historical data and the observed data, the user can choose the weight of the weakly informative robust prior component. The smaller the weakly-informative prior weight figure, the more confidence the user has in the historical data and the less discount in the historical data.

The amount of robustification (i.e., the weakly-informative prior weight) can be manipulated using the the slider as shown in Figure 19.

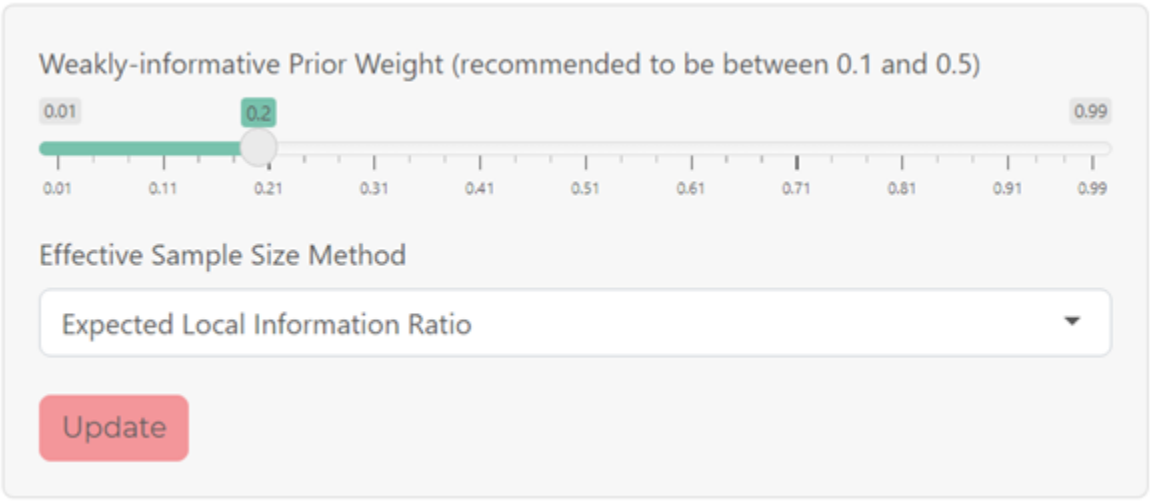
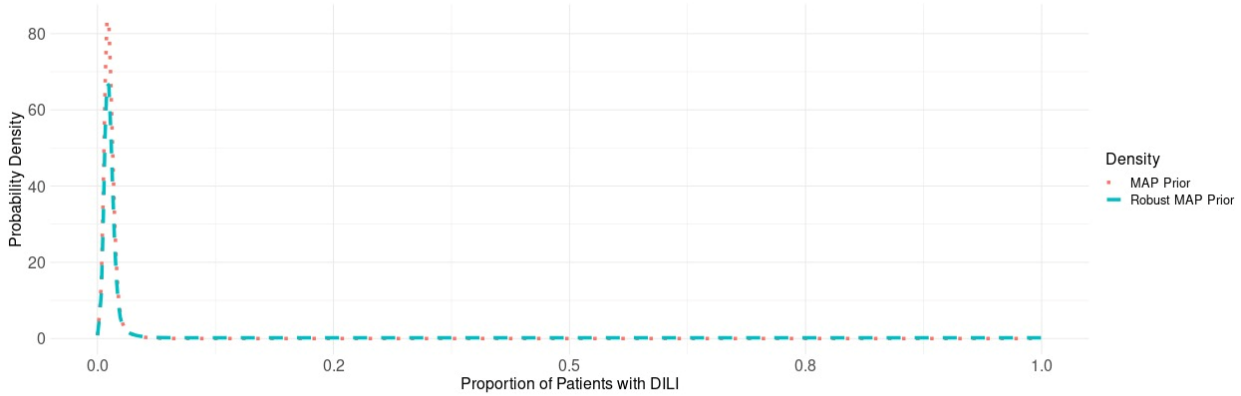


Figure 19: Robustification

A graph depicting both the MAP Prior and Robust MAP Prior is the generated on the right hand side of the page, shown in Figure 20.

Based on a weakly informative conjugate component with weight 0.2 and mean 0.5 the robust MAP prior is approximated as $w \cdot (\text{MAP prior}) + (1 - w) \cdot (\text{weakly informative prior})$:

$$0.38 \cdot Beta(8.67, 784.18) + 0.26 \cdot Beta(12.52, 846.25) + 0.16 \cdot Beta(1.74, 107.7) + 0.2 \cdot Beta(1, 1)$$



	Mean	SD	Median	95% CrI	ESS
MAP Prior	1.0%	1.0%	1.0%	[0.0%, 3.0%]	441
Robust MAP Prior	11.0%	12.9%	11.0%	[0.4%, 87.5%]	346

Figure 20: Robust MAP Prior

For incidence proportion analysis, the uninformative mean is set to 50% and thus a Beta(1,1) distribution is chosen as the weakly-informative prior. For exposure-adjusted adverse event rate, a weakly-informative prior mean (hazard ratio) as in Figure 21 is also selected for the robust MAP prior to be calculated and the mean value is supposed to be chosen by the user. Note that if the SD for the robustified MAP prior is larger than 1, this means that the robustification turns to be informative so that we suggest not to borrow any information.

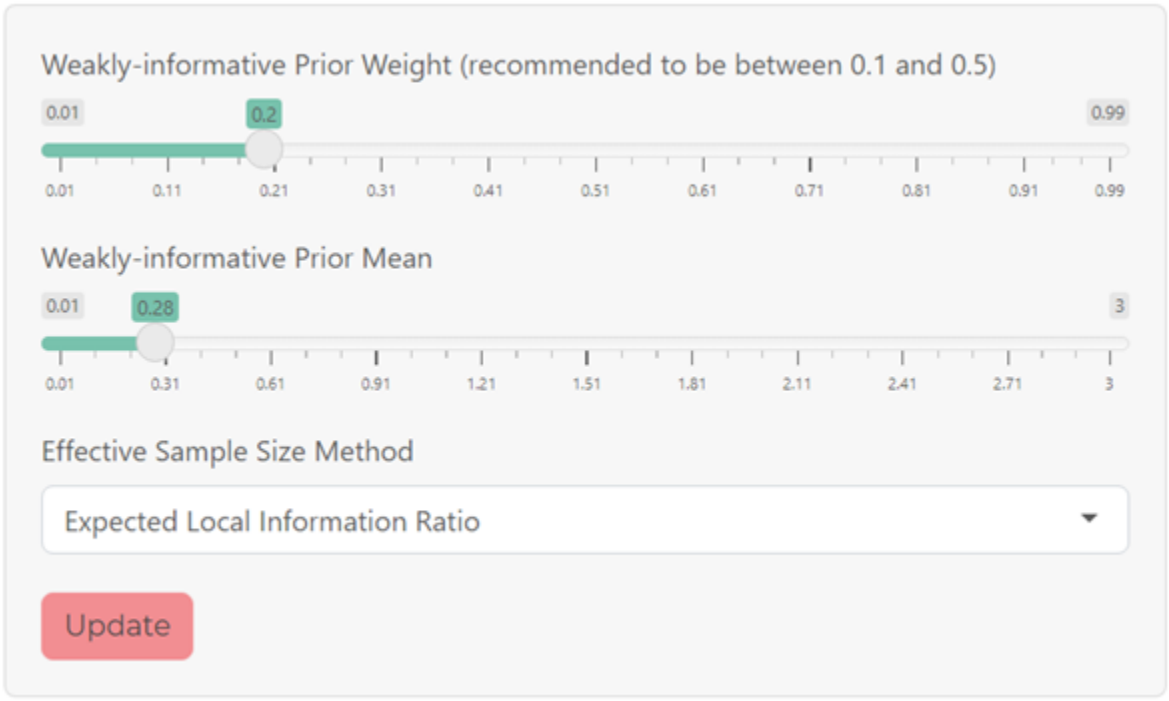
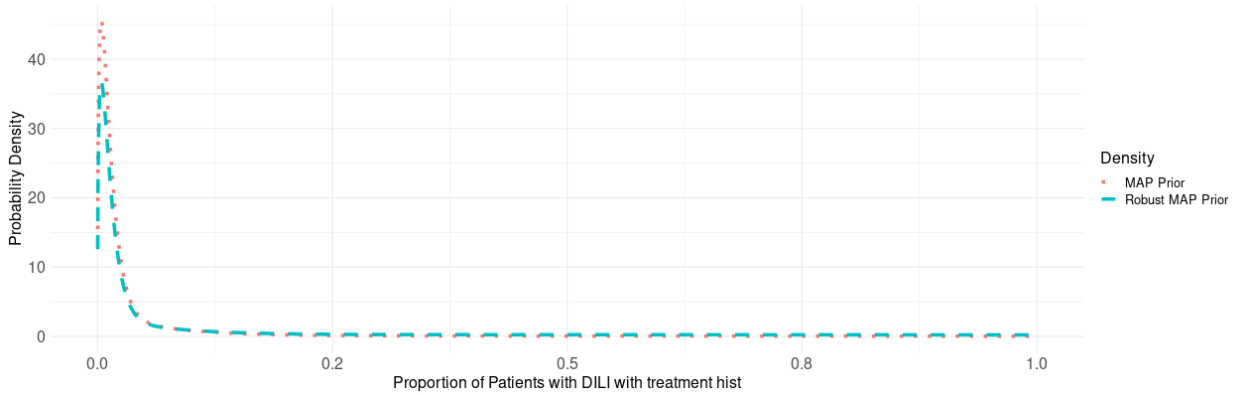


Figure 21: Robust MAP Prior for Exposure-Adjusted Adverse Event

For the simple example, to protect against prior data conflict, the default weight 20% (i.e., 20% on weakly-informative part and 80% on informative part) was set as discounting factor. Figure 22 depicts both the MAP prior and robustified MAP prior. By adding the non-informative part, now the robustified MAP prior is approximated by four Beta distributions. The former three Beta component were down weighted so that the effective sample size reduces to 52.

Here note that the mode/peak of the distribution you see in the plot might be different from the mean shown in the table underneath the plot in that both the prior and robustified prior are mixture of multiple densities.

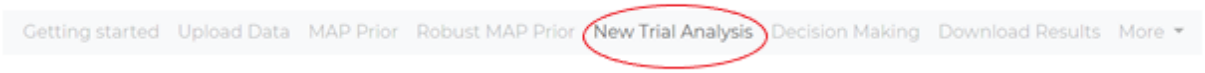
$$0.58 \cdot Beta(1.46, 116.07) + 0.18 \cdot Beta(1, 14.52) + 0.04 \cdot Beta(1, 1.39) + 0.2 \cdot Beta(1, 1)$$



	Mean	SD	Median	95% CrI	ESS
MAP Prior:	4.32%	10.79%	1.28%	[0.09%, 35.03%]	68
Robust MAP Prior	13.48%	14.19%	12.84%	[0.11%, 88.45%]	52

Figure 22: Robust MAP Prior

5 New Trial Analysis



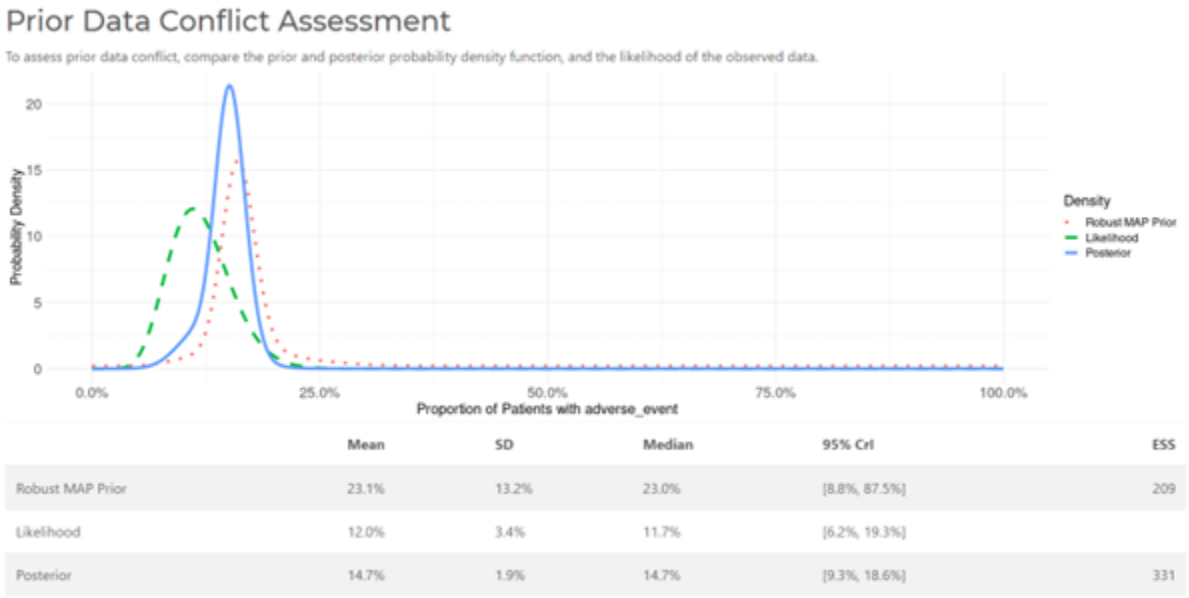
The new trial analysis portion of the application is mainly used for exploratory purposes.

To input the results of the observed trial (for the arm for which the (robust) MAP prior was generated), manipulate the slider in Figure 23 which has a separate slider for both the total number of patients and the number of patients with the adverse events. The example shown is for incidence proportions.

The maximum number of patients that can be entered is 200.

Figure 23: Input for New Trial (using data from the same arm for which the (robust) MAP prior was generated)

The Robust MAP Prior obtained in Figure 20 is then updated with the observed data from the respective arm (data from the new trial). This provides a Bayesian Posterior Analysis of the observed data. This could be data from an actual current trial or a hypothetical trial. The summary of the Robust MAP Prior, Likelihood and Posterior is generated graphically as shown in Figure 24. The generated graph allows the user to asses for potential prior data conflict.



	Mean	SD	Median	95% CrI	ESS
Robust MAP Prior	23.1%	13.2%	23.0%	[8.8%, 87.5%]	209
Likelihood	12.0%	3.4%	11.7%	[6.2%, 19.3%]	
Posterior	14.7%	1.9%	14.7%	[9.3%, 18.6%]	331

Figure 24: Trial Data Conflict Assessment

The Robust MAP Prior describes the historical data.

The Likelihood describes the observed/current data.

The Posterior distribution describes the synthesis of historical prior and the observed trial data from which decisions can then be made.

For the simple example, after obtaining the robustified MAP prior for a particular arm, we now input concurrent trial data for the same arm.

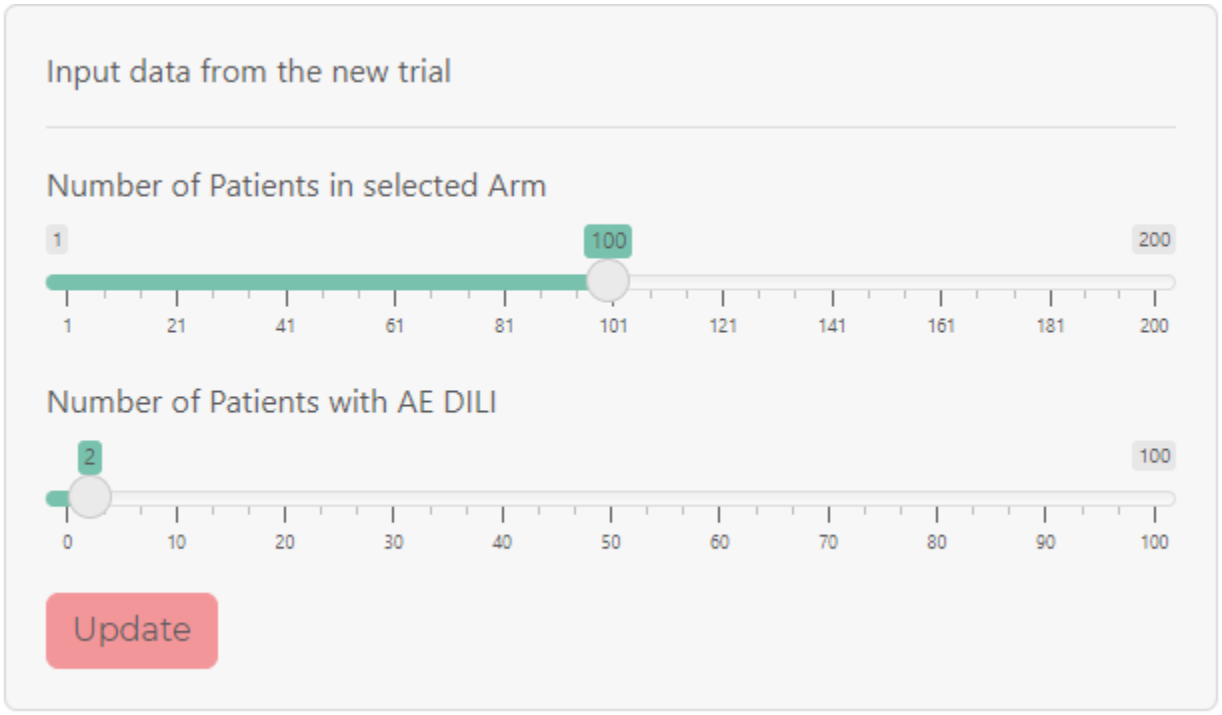
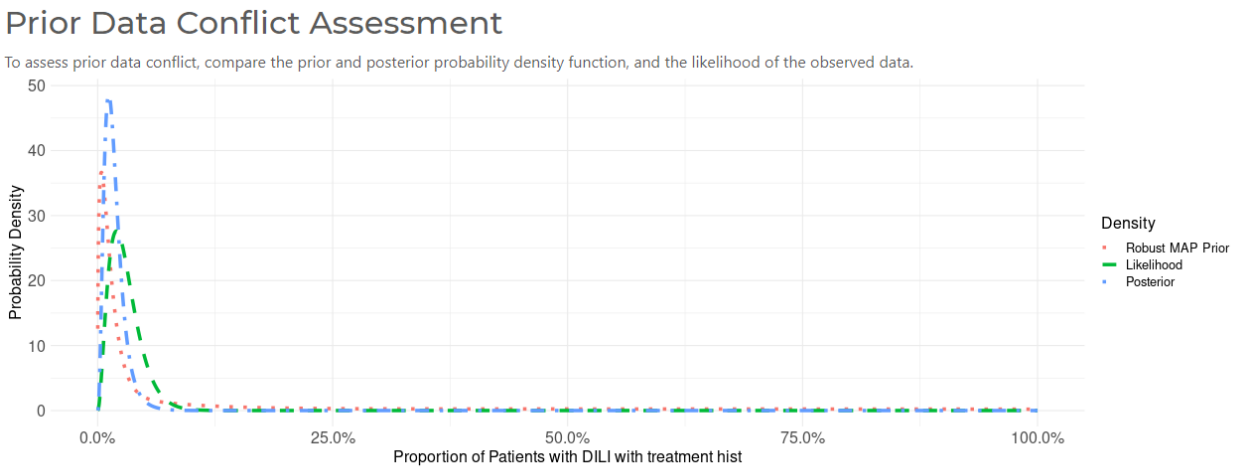


Figure 25: Concurrent Trial Data

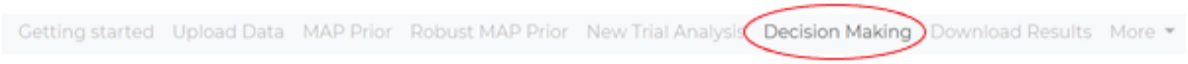
By clicking the "Update" button, the posterior distribution is obtained by combining the robustified MAP prior and the observed data. The summary of the robustified MAP prior, likelihood, and posterior is generated graphically as shown in Figure 26.



	Mean	SD	Median	95% CrI	ESS
Robust MAP Prior	13.5%	14.2%	12.8%	[0.1%, 88.5%]	52
Likelihood	2.9%	1.7%	2.6%	[0.6%, 7.0%]	
Posterior	1.8%	1.0%	1.6%	[0.4%, 4.5%]	

Figure 26: Posterior Distribution

6 Decision Making



The Decision Making tab allows statistical inferences to be made based on the Likelihood, MAP Prior, Robust MAP Prior and the Posterior distribution. These options can be obtained by assessing the drop-down menu in Figure 27. Note that the inference based on the likelihood is with respect to the observed data, in contrast to which based on the prior/posterior are with respect to the underlying parameter.

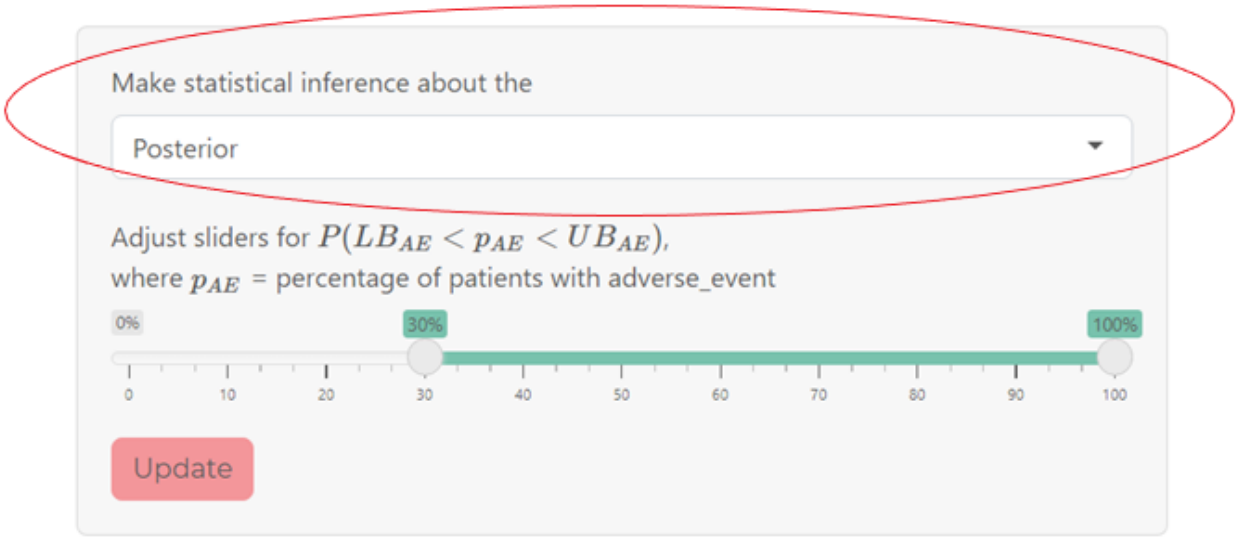


Figure 27: Statistical Inferences

Probabilities can be obtained for values exceeding/not-exceeding/between limits that can be specified using the slider as shown in Figure 28 on the left hand-side of the page.

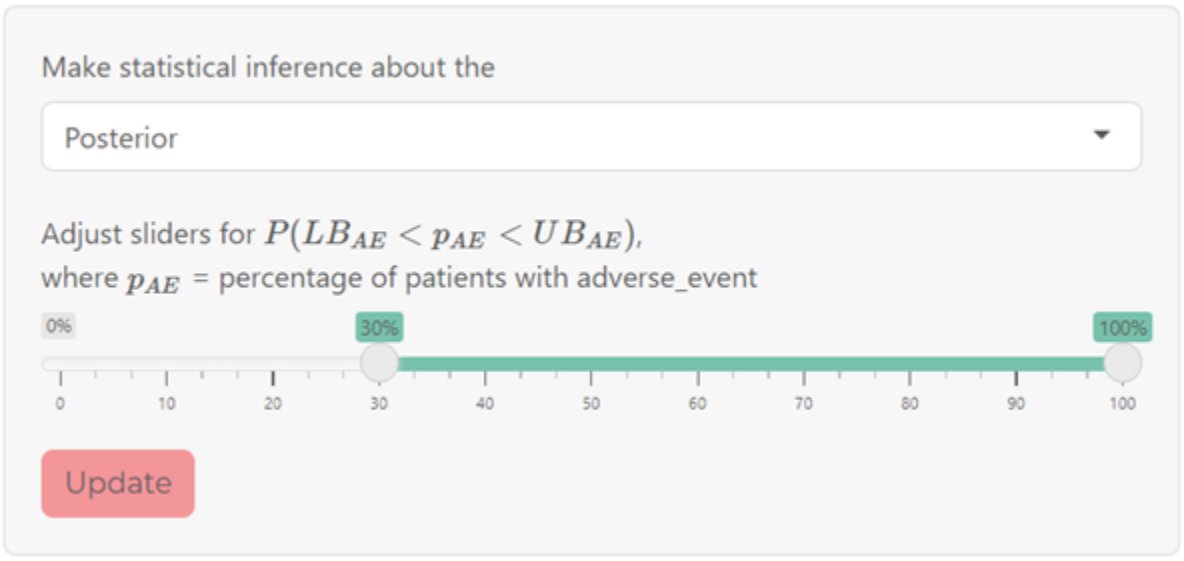


Figure 28: Making Statistical Inferences

A graph is then generated on the right hand-side of the page.

Additionally, inferences are made with 90%, 95% and 99% probabilities as shown in Figure 29, e.g., from Figure 29 there is a 1% certainty that the proportion of patients with adverse_event is greater than 30%.

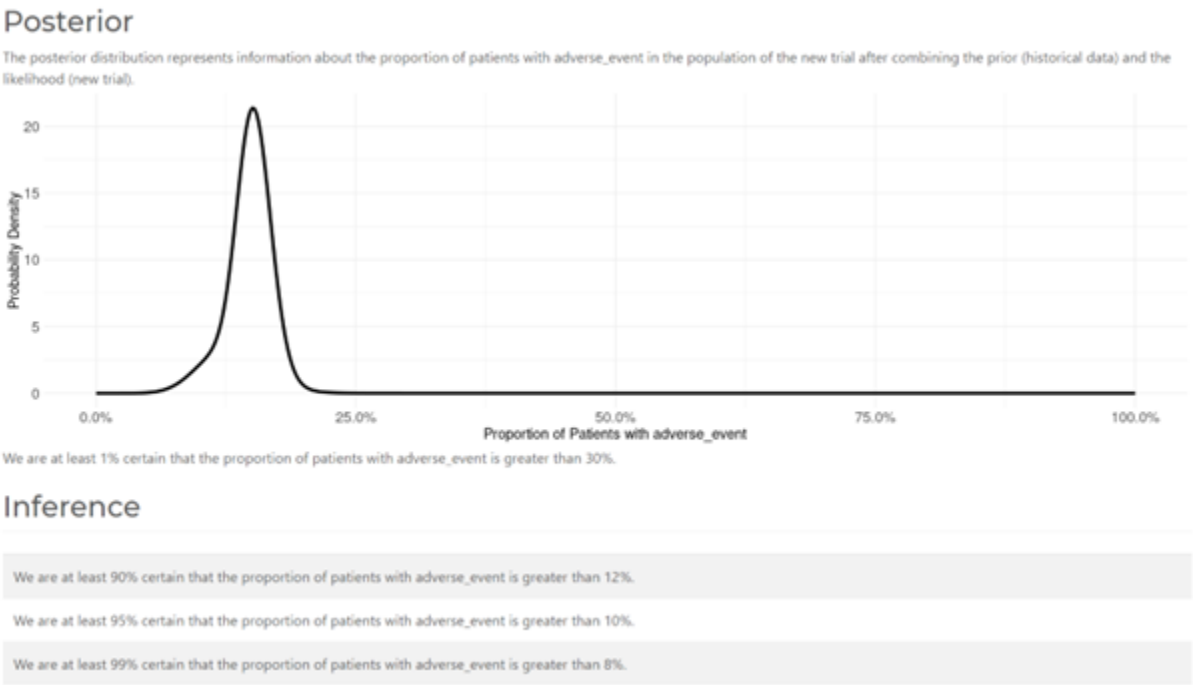


Figure 29: Inferences

For the simple example, given the posterior, we want to know the probability of percentage of patients with DILI greater than 3%. By moving the left endpoint of the slider to 3% and clicking the "Update" button, the

cumulative probability right to 3% under the posterior density is shown in Figure 31. The conclusion is that we are at least 12% certain that the proportion of patients with DILI is greater than 3%.

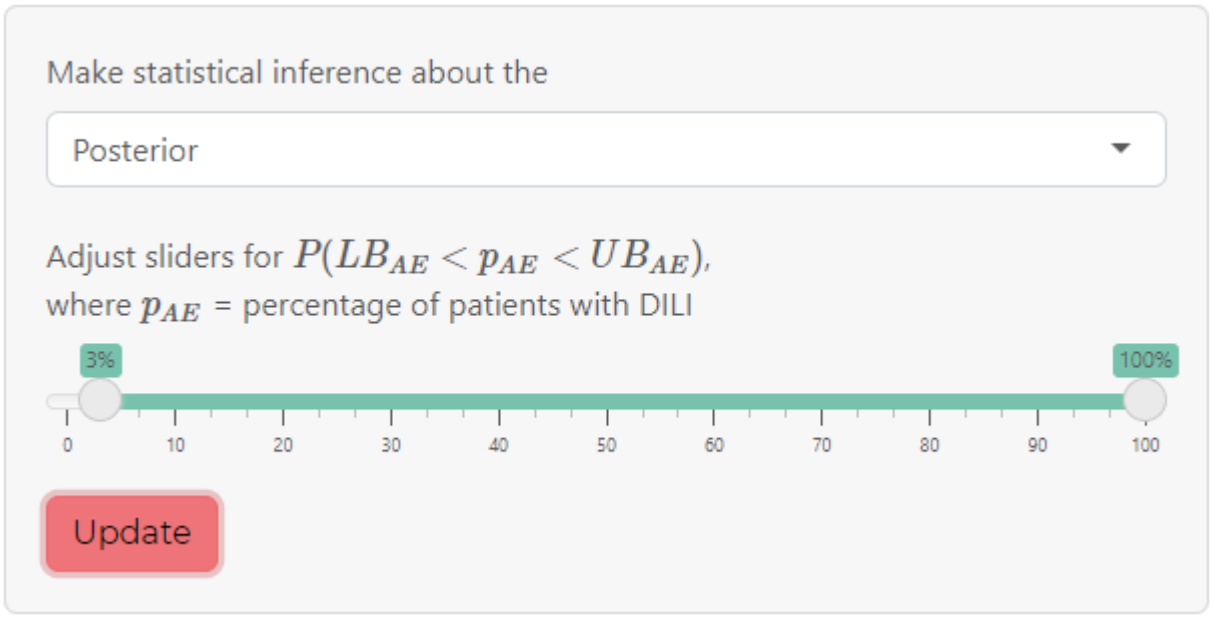


Figure 30: Decision Making

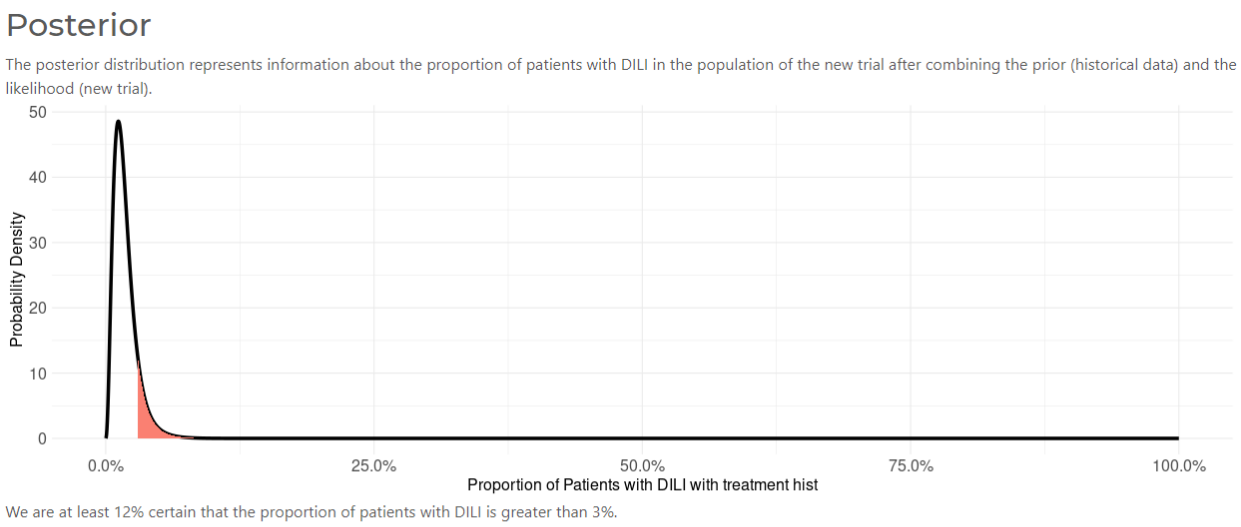
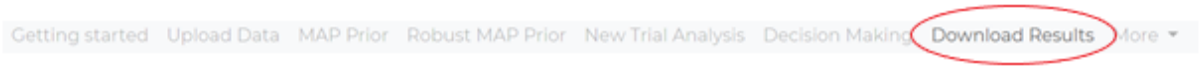


Figure 31: Decision Making

7 Download Results



Summary tables are produced that contain the posterior probability analysis for all the adverse events in the uploaded dataset. There are also tables for the Incidence Proportion and Exposure-adjusted Adverse Event Rates for all the adverse events in the dataset.

The values that are used in exploring the uploaded dataset has no effect in generating the summary tables of the analysis as the default settings are used.

Summary tables are generated for all adverse events in the dataset and not only those that were explored.

On clicking the show/hide Comparison button in Figure 32, the user selects the treatment and control arms that is to be compared as shown in Figure 33. The user can make up to five different treatment arm comparisons. The slider in Figure 32 can be moved based on the number of comparisons the user wants to do. On increasing the number of comparisons needed as in Figure 32, the number of show/hide comparison options also increases for which the respective treatment and control arms can be selected as in Figure 33.

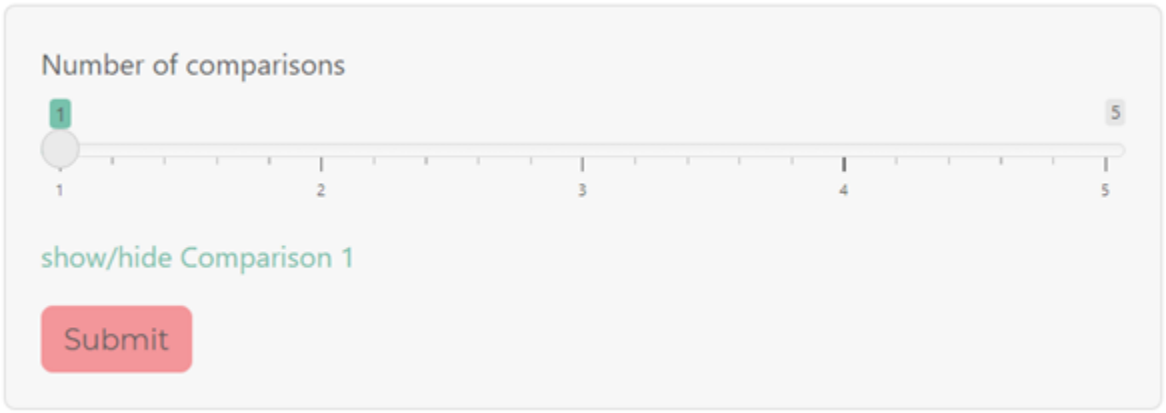


Figure 32: Number of Comparisons

Figure 33: Treatment Arms Comparison

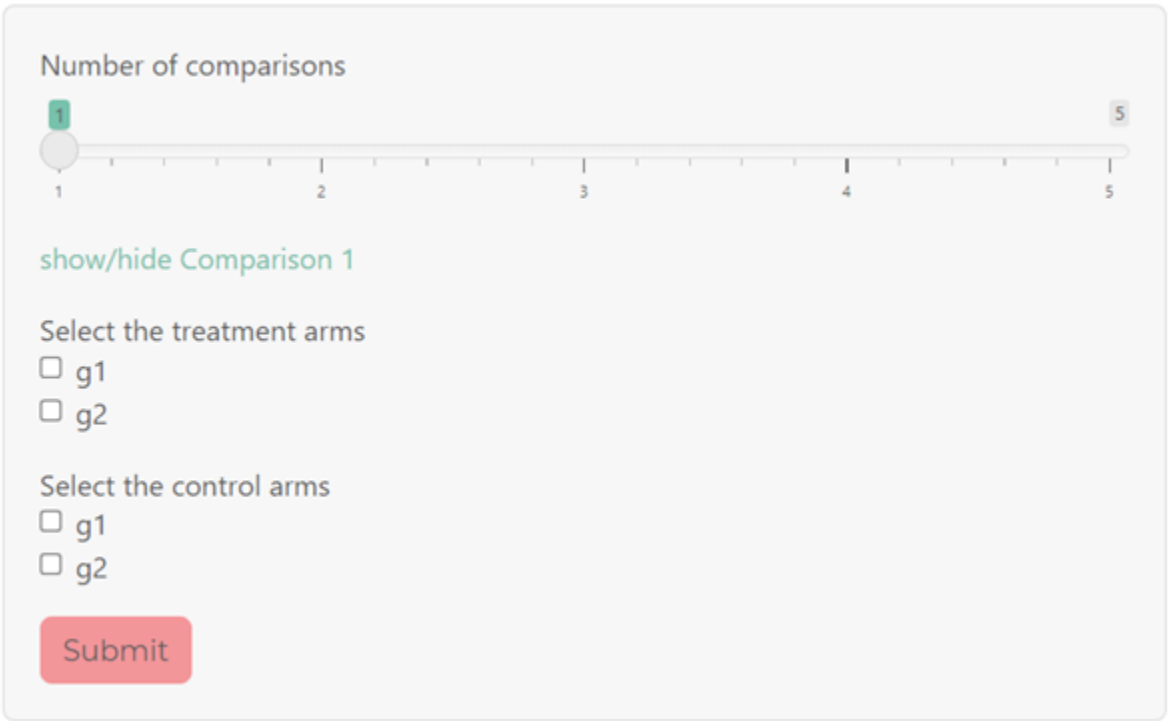


Figure 34: Treatment Arms Comparison

Once the Treatment and Control arms has been selected by the user, click the Submit button. The user then waits for the simulation/calculation to be completed. A progress bar Figure 35 is displayed on the bottom-right corner. Depending on the number of Adverse Event Endpoints and the number of comparisons done, this simulation process can take some time.

Figure 35: Simulation Progress

Once the simulation is completed, the chosen comparisons are then displayed (from Figure 36 to Figure 37) on the right-hand side on the page.

Figure 36: Before Completing Simulation

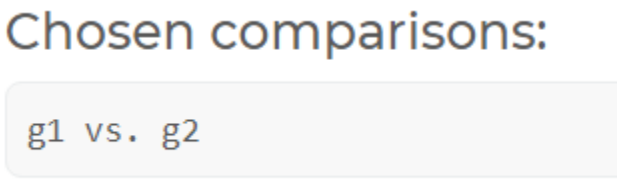


Figure 37: After Completing Simulation

On completion of the simulation, the results which is presented in a tabular form which can be downloaded as a .pdf file by clicking the Download All AE Summary Tables as shown in Figure 38.

Figure 38: Download Button

For each comparison, five different tables are produced:

- Table 1 lists the different trials that makes up each arm (Treatment and Control) of the comparison.
- Table 2 indicates the number of patients that experienced each Adverse Event r, the total number of patients n, and the proportion (%) of patients with AE in the population. Posterior summary shows the Posterior Distribution mean, median and the 95% credible interval.
- Table 3 estimates the Risk Difference and the Risk Ratio calculated from the number of patients with the event r and the total number of patient n (Incidence Proportion). Posterior summary shows the Posterior Distribution mean, median and 95% credible interval.

- Table 4 shows the Exposure-Adjusted Adverse Event rate, the rate of patients with event per patient year at risk. Naive estimates shows the (pooled) number of patients with event r, divided by the (pooled) total exposure time. Posterior summary shows the Posterior Distribution mean, median and 95% credible interval.
- Table 5 estimates the Risk Difference and Risk Ratio calculated from (pooled) number of patients with event r and (pooled) number of patients (Exposure-Adjusted Adverse Event Rate). Posterior summary shows the Posterior Distribution mean, median and 95% credible interval.

8 Troubleshooting, Issues and Remarks

This app is not yet validated.

If the app does not open or does not work as intended, possible ways to troubleshoot are:

- Install the most recent version of R and RStudio
- Install the most recent version of the R Shiny Package

9 Contact

For questions and feedback please contact:

- Alexander Stemke alexander.stemke@boehringer-ingelheim.com
- Quic team

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[5] Neuenschwander, B., Weber, S., Schmidli, H. and O'Hagan, A. (2020). Predictively consistent prior effective sample sizes. *Biometrics* **76** 578–87.

[6] Schmidli, H., Gsteiger, S., Roychoudhury, S., O'Hagan, A., Spiegelhalter, D. and Neuenschwander, B. (2014). Robust meta-analytic-predictive priors in clinical trials with historical control information. *Biometrics* **70** 1023–32.