B-Safe User Manual v. 0.0.5
for B-Safe v. 0.1

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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. Refer to the Statistical Analysis Plan for the methodology and deefault values used.

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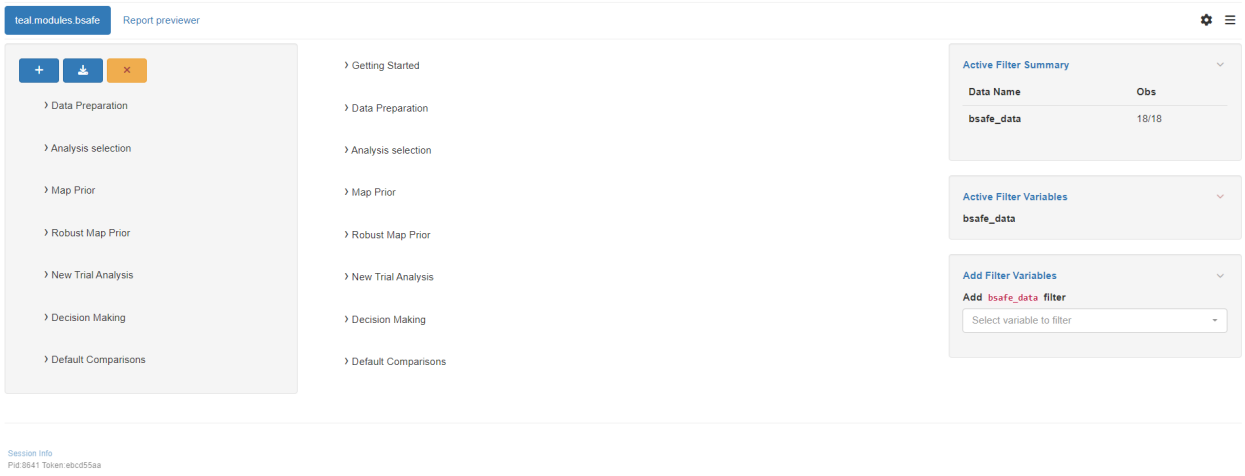
Using the App

CHECK TODO GOTFIX data example ref

This section introduces the user to the app and how to prepare the data set for analysis. From this section on, we will use example data (see section) to demonstrate the usage of the entire application. This simple data example is further specified in section @ref(tab:data_example).

Figure 1: Landing Page



You will land on a page similar to this. It is recommended to go trough the app from top to bottom. The left and middle panel in fig. correspond to each other. Each bullet point has a section within this manual.

Getting Started

The **Getting Started** page is the first bullet point from the top. 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.

As you are a user of the app, the first step has already been taken and the app was set up successfully. Therefore, you have to specify a dataset as `.csv` as described in table 1.

You can then jump directly to section Default comparisons **??** for a summary table with a default analysis.

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 time scale depends on the input and should be consistent throughout the entire dataset. Moreover, further variables could be included (see therefor also the data example 4).

Data Preparation

Once you have set up the app, under data preparation the available data is displayed. In the following section the data set will be introduced. Afterwards in section , the `teal` functionality of data filtration will briefly introduced, before we prepare an `ARM` to analyze.

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.

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 the medication was taken by the patient per time unit
Length	integer	Total number of time units the patient was on the treatment
Treat	character	The specific treatment the patient was on

Data example

The following data set example was generated for this introduction.

In brief those three studies are presented. Each study has a `STUDYID` which corresponds in this case with its `ARM`. `Study#1` includes historical (`HIST = 1`) and non historical (`HIST = 0`) information. And has only for the Placebo treatment historical and current information. `Study#2` includes only current data (`HIST = 0`) and `Study#3` only historical (`HIST = 1`).

All additional information, that are not releveant for the `B-SAFE` module, are displayed in table 4. In addition to the predefined additional variables (section 2), this dataset also includes information on the region of the study.

It is important to understand, that for the meta-analysis, the data subset which will be used is defined by the variable `ARM`. Accordingly the creation of a arm will be explained next.

Adding an Arm

Each analysis is performed for the data defined by the variable `ARM`. Before we use the predefined arms, or add a new arm, it is crucial to note, that the filtering via `TEAL` in fig. 2, has to be done, before any arm is created.

By collapsing 1. in fig. 2 you can view your data and by 2. in fig. 2 you can collapse the `TEAL` filtration.

It is possible to filter for each variable of the dataset. 1. (see fig. 3) select the variable you would like to filter. In this example we choose the total exposure time and the region. 2. we chose an exposure under 500 and America and Eurasia as a region. Any further arm creation or analysis would be performed on this subset.

For now, we don't need further filtration, this feature is very useful, if you would like to investigate certain subgroup characteristics or see directly a potential arm creation; under 3. it is displayed how many observations remain in this subset. For any further information, please refer to `TEALs` documentation.

Starting with our original data set we will now create a data subset called an arm, which we will investigate further.

Table 3: Data example

	STUDYID	HIST	ARM	N	SAF_TOPIC	N_WITH_AE	TOT_EXP
1	Study#1	1	g1	143	vomitting	34	257.98
2	Study#1	1	g1	120	vomitting	26	338.18
3	Study#1	1	g1	198	vomitting	27	318.65
4	Study#1	1	g1	179	insomnia	36	316.20
5	Study#1	1	g1	200	insomnia	33	334.95
6	Study#1	1	g1	156	insomnia	32	262.24
7	Study#1	0	g1	200	insomnia	34	193.03
8	Study#2	0	g2	109	vomitting	65	334.73
9	Study#2	0	g2	190	vomitting	57	263.33
10	Study#2	0	g2	119	insomnia	55	203.99
11	Study#2	0	g2	124	insomnia	59	273.15
12	Study#2	0	g2	187	vomitting	58	226.69
13	Study#3	1	g3	138	vomitting	58	226.69
14	Study#3	1	g3	114	vomitting	65	334.73
15	Study#3	1	g3	121	vomitting	55	203.99
16	Study#3	1	g3	200	insomnia	59	213.91
17	Study#3	1	g3	183	insomnia	57	263.33
18	Study#3	1	g3	163	insomnia	36	316.20

Starting with 1. (see fig. 4) select the variables we are interested in. In this case we chose `DOSE` and `TREAT`. 2. choose the variables characteristics. In this case, we are interested to borrow information from the Placebo treatments. In general it is discouraged to borrow information from treatment arms that are not Placebo or standard of care. 3. you add the arm, by doing so a pop up will open and requests naming your arm and to 4. accept your naming.

In this case the subset of dose 500 and Placebo treatment is identical, but especially with an increasing number of studies to borrow from, it is better to ensure your correct choices. On our example `ARM: Placebo500` we will now perform any further analysis.

Analysis selection

The filtered data is then displayed on the right hand side of the screen when 1. in figure 5 is collapsed.

Under 2. in fig. 5 we have several options, we will explain each of them next.

Select patients with the respective treatment

If there are different treatment options in the uploaded dataset file, and you have created different `ARMS` you can 2. choose a specific `ARM` from the drop-down menu in figure 5. In this case we choose our created `ARM` Placebo500. g1 would not be a wise choice, it includes different treatments.

Select Safety Analysis

The drop-down menu in figure 5 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.

Table 4: Data example: Additionl Variables

	STUDYID	DOSE	FREQ	LENGTH	TREAT	REGION
1	Study#1	150	2	120	AgentA	Africa
2	Study#1	250	3	240	AgentB	America
3	Study#1	500	1	365	Placebo	Eurasia
4	Study#1	150	3	365	AgentA	Eurasia
5	Study#1	250	1	120	AgentB	Africa
6	Study#1	500	2	240	Placebo	America
7	Study#1	500	2	240	Placebo	Eurasia
8	Study#2	250	1	240	AgentB	America
9	Study#2	500	2	365	Placebo	Africa
10	Study#2	150	3	120	AgentA	Eurasia
11	Study#2	250	1	365	AgentB	America
12	Study#2	150	3	240	AgentA	Eurasia
13	Study#3	150	3	240	AgentA	Africa
14	Study#3	250	1	365	AgentB	America
15	Study#3	500	2	120	Placebo	Africa
16	Study#3	150	2	240	AgentA	Eurasia
17	Study#3	250	3	365	AgentB	America
18	Study#3	500	1	120	Placebo	Africa

- Exposure Adjusted Adverse 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.

The choice of Safety Analysis option is based on the need of the user. Later section will be divided into subsection to give a proper insight to the use of the app.

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 5. The filtered data will be displayed on the right hand side of the screen.

By default, the first AE endpoint (ordered alphabetically) will be selected and displayed. In our example we choose also vomitting.

Used Seed

The user can manually set the seed for reproducibility of results of the Markov Chain Monte Carlo simulations and other random draws (see figure 5). Be aware that reproducibility is only guaranteed, while you are in the same session. For more information, please refer to the statistical analysis plan. For more information how to save your analysis please see section TODO

By default, a seed is given, but you can always overwrite the seed.

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 1. figure 6).

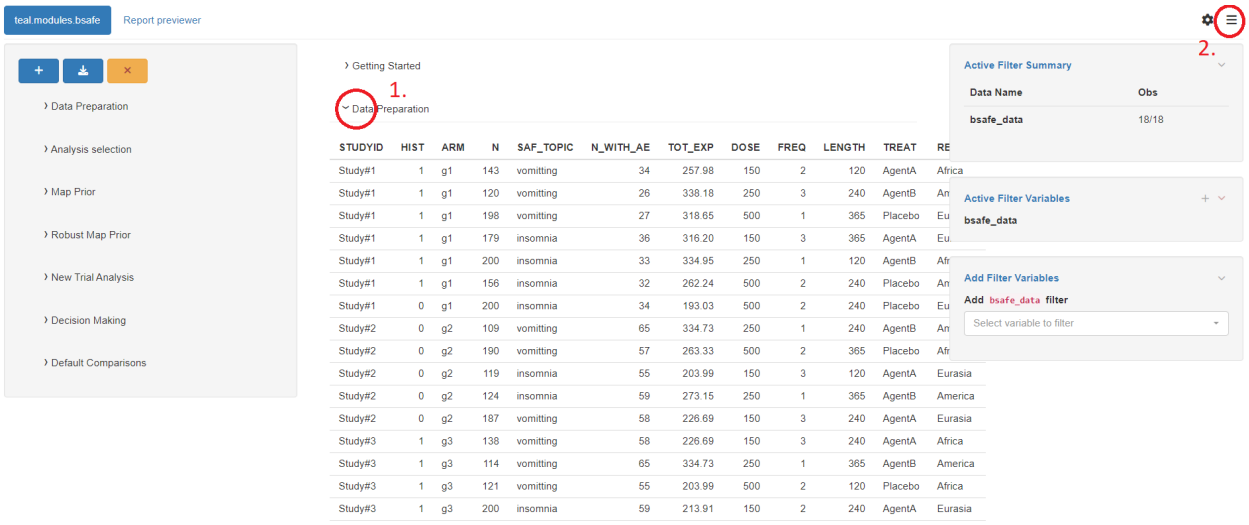


Figure 2: TEAL filtration

As can be seen in 2. the sum over the study is taken, if the studies won't be pooled, each subgroup is treated as a own group within the hierarchical model. For the demonstration we changed the `ARM` to g1. If we 3. select no pooling we get the three different subgroups from different regions with different frequency.

For the reminder of the demonstration using Placebo500, there is no difference whether we pool or not.

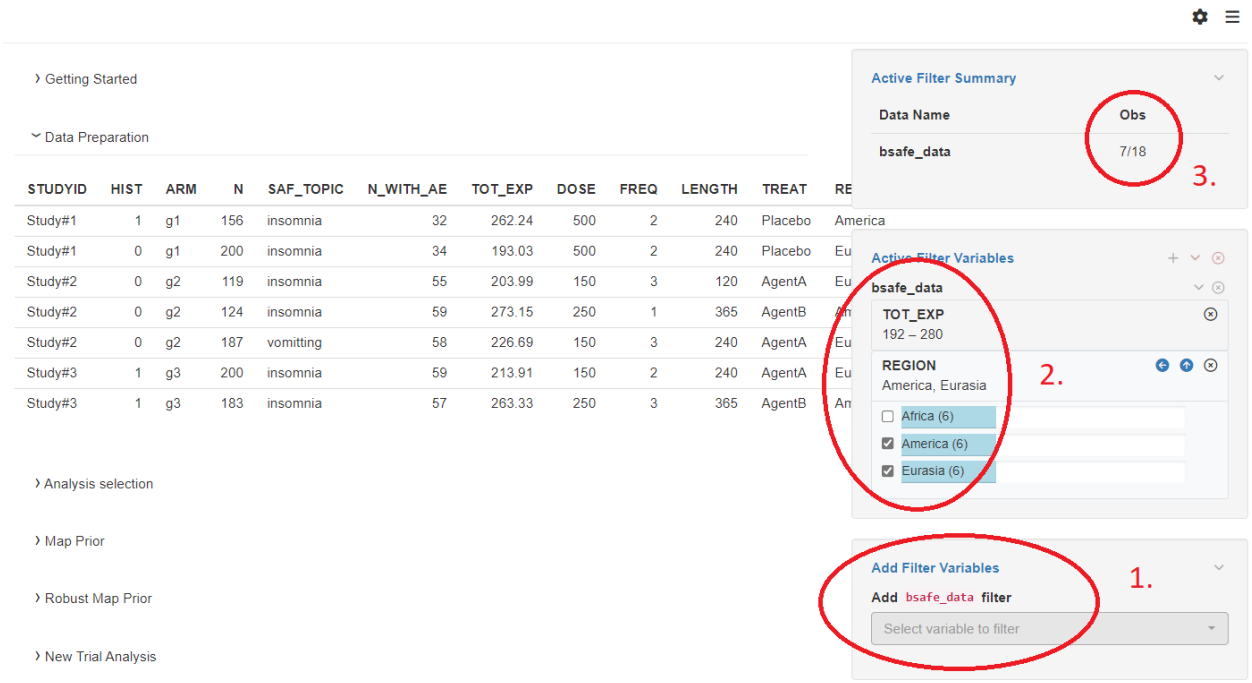


Figure 3: TEAL filtration selection

MAP Prior

The MAP Prior as proposed (see [1]) is estimated using a meta-analytic predictive model which accounts for the between-trial heterogeneity.

First collapse the section under 1. in fig. 7. Under 2. you have different options. The `B-SAFE` module uses the Half-normal distribution as a prior distribution for the between trial heterogeneity parameter τ as seen in fig. 7 which is a special case of the normal distribution that is truncated to values greater than or equal to zero.

To control the amount of information borrowed, the drop-down menu in fig. 7 gives you control of how much historical information to borrow using the recommendation (see [3]) as shown in Table 5. Generally, with larger heterogeneity less information will be borrowed.

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

Table 5: Heterogeneity

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].

For the Expected Sample Size method, the Expected Local Information Ratio proposed in [5] is used . This is due to its predictive consistency.

In fig. 7 the most important button is 3. For any relevant changes, the MCMC sample has to be calculated

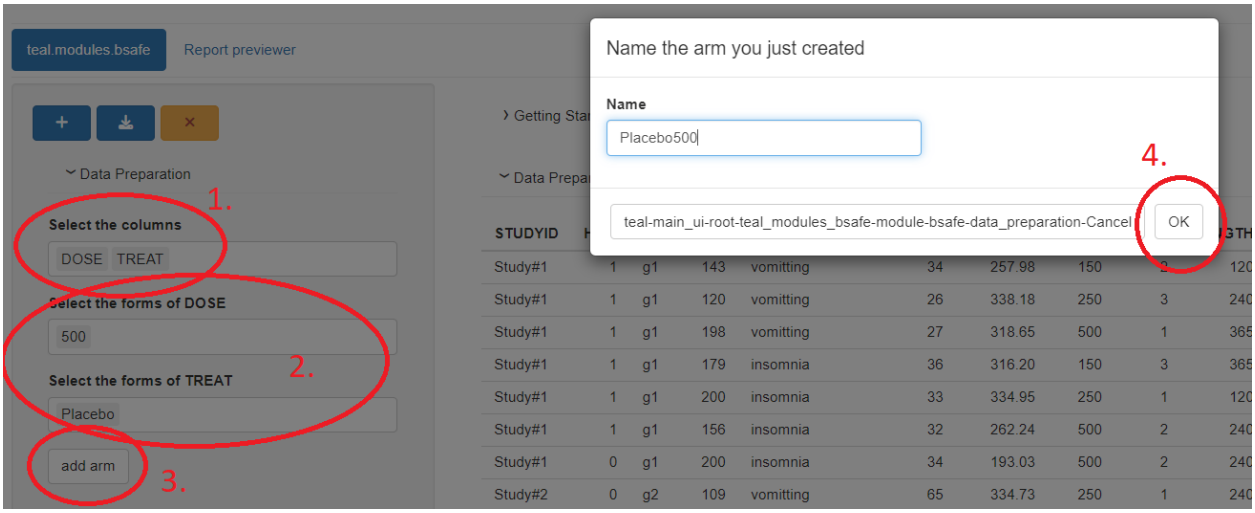


Figure 4: Add Arm

again. If no MAP prior was calculated, or any changes where done, then 4. is displayed.

For our example we use the default settings and continue with the incidence proportions and will investigate the exposure adjusted adverse event rate.

After 3. Updating the MAP prior, a small idle token (see fig. 8) will appear on the bottem right corner and then the results instead of 3.

MAP Prior - Incidence Proportion

On the top-right corner of Figure 9, 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 10, a density curve and summary statistics is obtained for the MAP Prior.

The MAP prior for the incidence Proportion is generated by MCMC samples and then approximated by mixture of three Beta distributions (see figure 10).

MAP Prior: 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 fig).

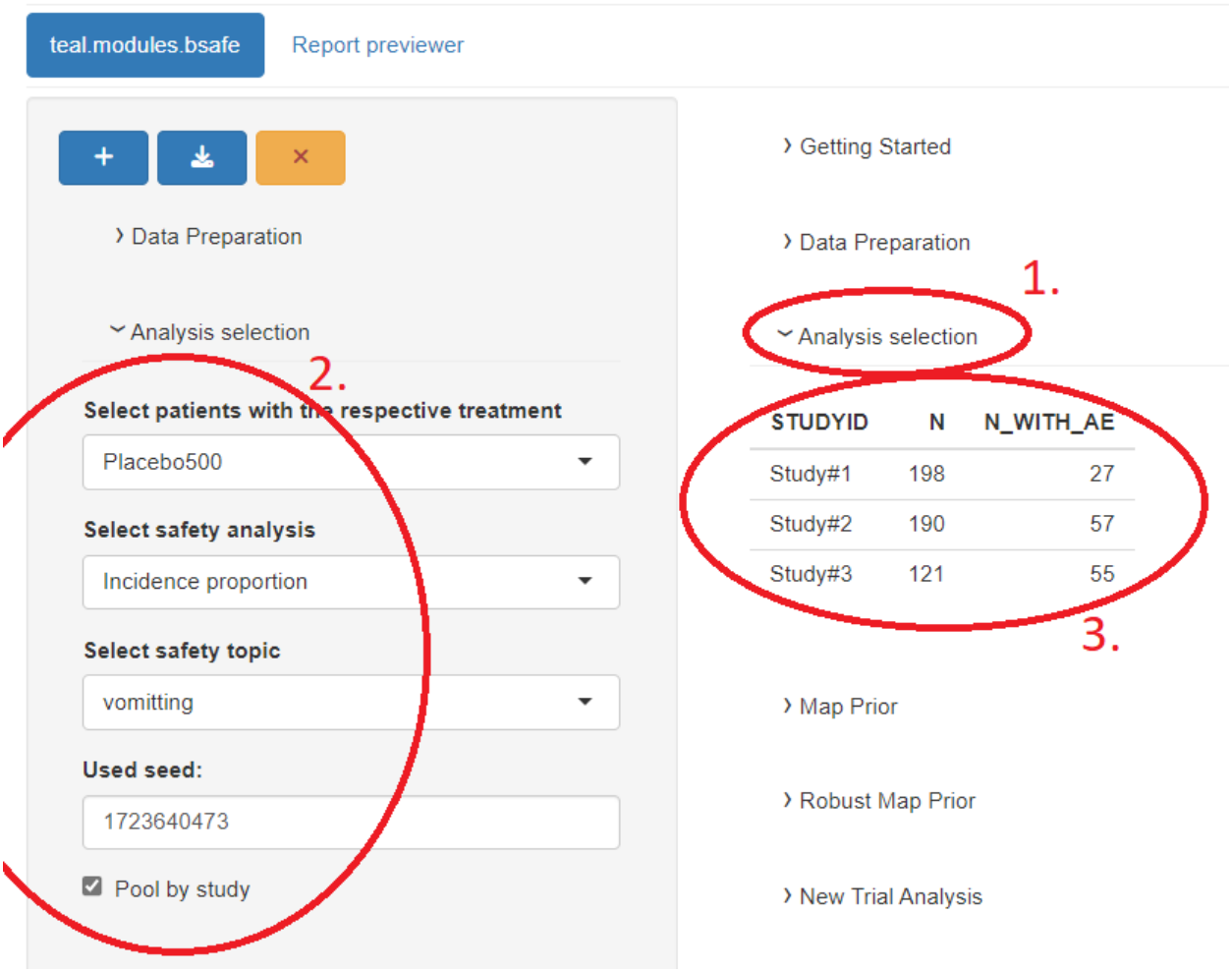


Figure 5: Analysis Selection

Contact

For questions and feedback please contact:

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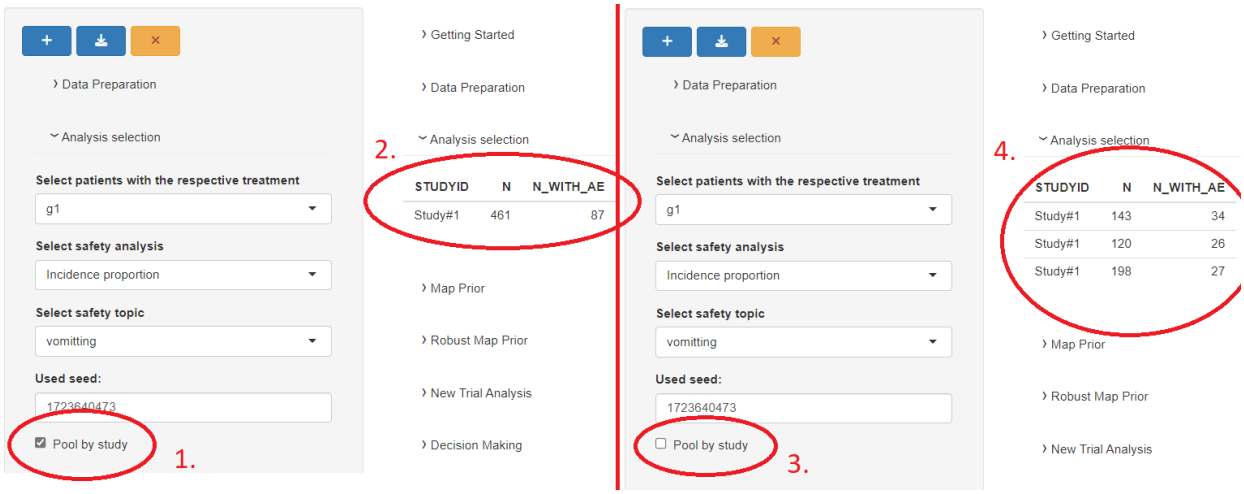
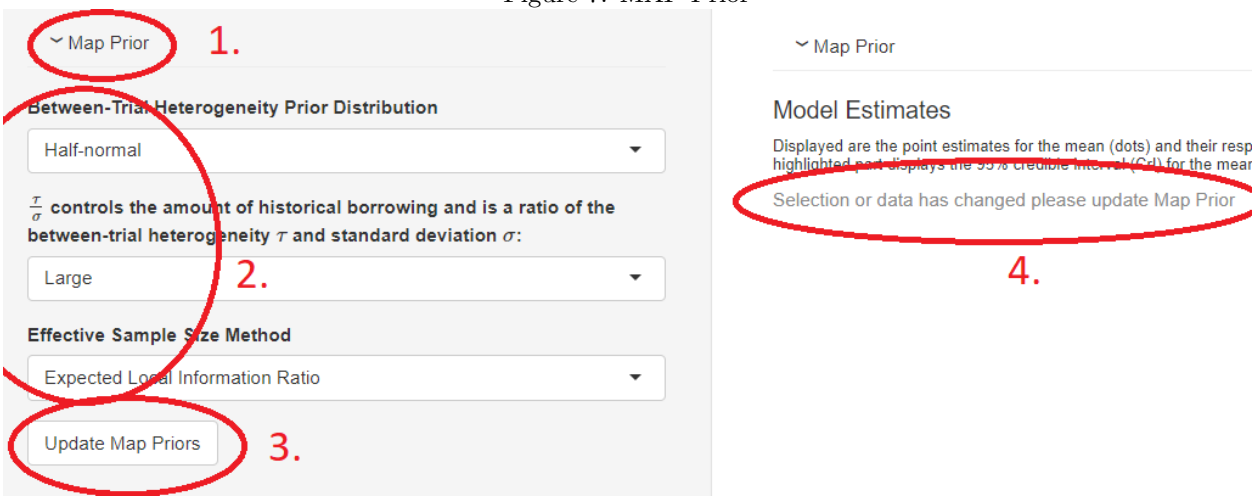


Figure 6: Pool by study

Figure 7: MAP Prior



References

[1] Neuenschwander, B., Capkun-Niggli, G., Branson, M. and Spiegelhalter, D. J. (2010). Summarizing historical information on controls in clinical trials. *Clinical Trials* **7** 5–18.

[2] 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.

[3] Weber, S., Li, Y., Iii, J. W. S., Kakizume, T. and Schmidli, H. (2021). Applying meta-analytic-predictive priors with the *r* bayesian evidence synthesis tools. *Journal of Statistical Software* **100**.

[4] Ghadessi, M., Tang, R., Zhou, J., Liu, R., Wang, C., Toyoizumi, K., Mei, C., Zhang, L., Deng, C. Q. and Beckman, R. A. (2020). A roadmap to using historical controls in clinical trials – by drug information association adaptive design scientific working group(Dia-adswg). *Orphanet Journal of Rare Diseases* **15** 69.

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

Figure 8: Idle Icon

Figure 9: Forrest Plot - Incidence Proportions

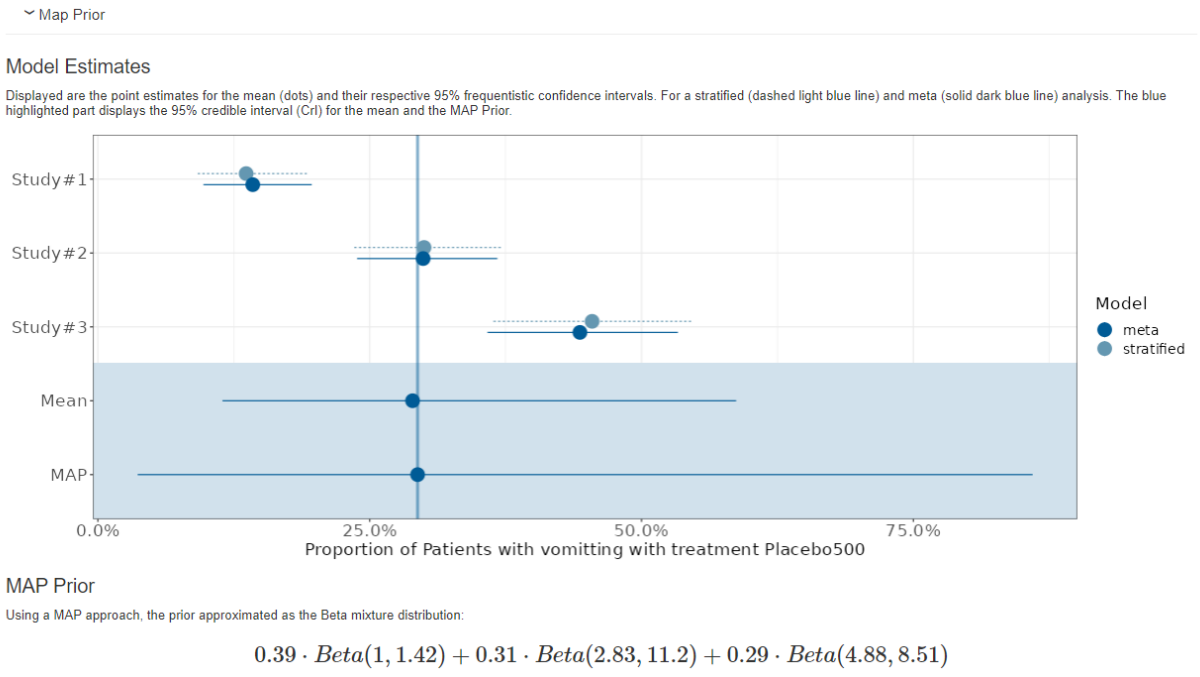
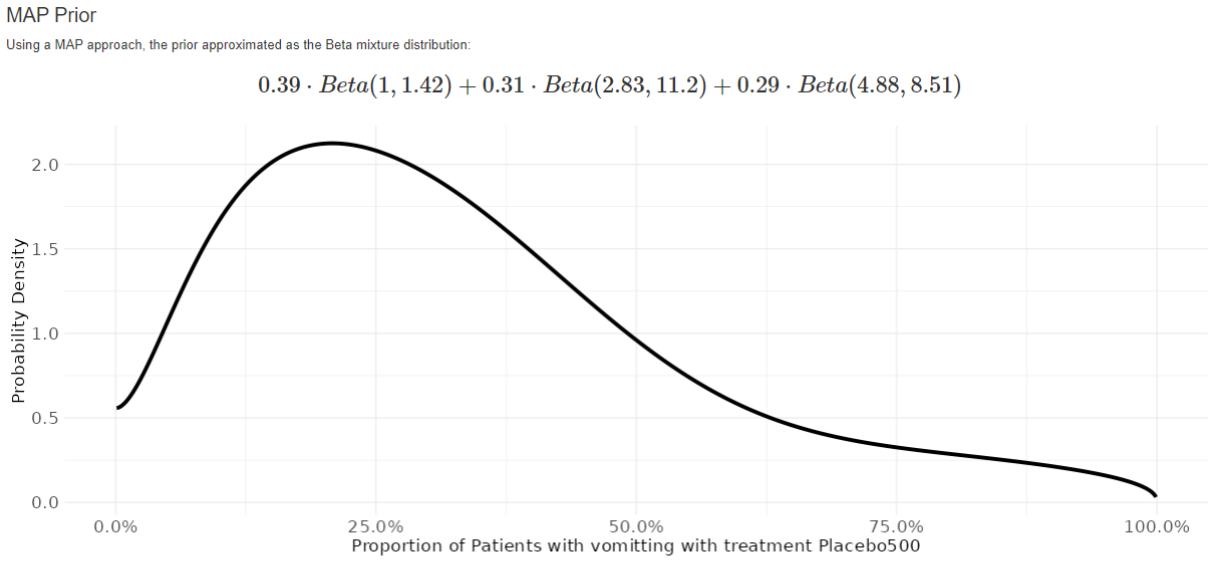


Figure 10: MAP Prior summary - Incidence Proportions



	Mean	SD	Median	95% CrI	ESS
MAP Prior	33.29%	21.03%	29.41%	(3.66%, 85.97%)	3.91