User Manual of R Shiny Web Application "Safety Monitoring"
http://rshiny.gilead.com/dev/safety_monitoring/

Version 1.0
Date 12/07/2017

Oncology Statistics Group
Wei Deng (Wei.Deng@gilead.com)
Xiaomin Lu (Xiaomin.Lu@gilead.com)
Ying Fan (Ying.Fan@gilead.com)

Analytical Solutions Group
Feiyang Niu (Feiyang.Niu@gilead.com)
Shuo Wang (Shuo.Wang@gilead.com)
Qinghua Song (Qinghua.Song@gilead.com)

Description

This R Shiny web application was developed as a tool for safety signal detection in the clinical safety database.

Statistical methods implemented in this tool include the following:
- o Fisher's Exact test
- o Odds Ratio and Relative Risk
- o Exposure-Adjusted Incidence Rate (EAIR)
- o Time-to-Event Analysis
- o Double False Discovery Rate (DFDR)
- o Bayesian Hierarchical Mixture Model (BHMM)

The outputs of this tool include one table and two graphical outputs. The table summarized the above statistics following the hierarchical structure of data specified by the user. The two graphical outputs are a volcano plot, and a dot plot combined with a forest plot.

User Direction

Step 1. Prepare datasets

A total of four files are required to run the tool:

- o ADSL data

- o ADSL naming file

- o ADAE data

- o ADAE naming file

- ADSL data:

  - o required data format: SAS

  - o required columns

    1. USUBJID: subject ID

2. TRT01A: treatment group

3. TRTSDT, TRTEDT: treatment start and end dates.

- Note:

1. <mark>For the SAS dataset, both columns need to be in numeric date format</mark>
2. <mark>Only entries for TRTEDT are allowed to contain missing value, TRTSDT can not be missing</mark>

4. SAFFL: Y/N, or you can leave the entire column blank

- ADAE data:
  - required data format: SAS
  - required columns

1. USUBJID: subject ID

2. TRT01A: treatment group

3. ASTDT, AENDT: AE onset and end dates.

- Note:

1. <mark>For the SAS dataset, both columns need to be in numeric date format</mark>
2. <mark>Only entries for AENDT are allowed to contain missing value, ASTDT can not be missing</mark>

4. AEBODSYS: SOC term

5. AEDECOD: PT term

6. AETOXGRN: toxicity grade (numeric)

7. AESER: Flag for SAE

8. AEHLGT, AEHLT: high level group term, high level term

- Note:

1. <mark>If they're not available in the dataset, you still need to manually create these two columns with the content left blank in order to ensure that the tool will run smoothly. As long as you choose SOC and PT terms as your grouping factors for calculation, it won't affect your results.</mark>

9. TRTEMFL: Y/N, or you can leave the entire column blank

- ADSL naming file and ADAE naming file:
  - If your data use different column names from those placed in the template ADSL and ADAE naming files, you could update the naming files for the tool to recognize variables in your data. Below is an example of modifying ADSL naming file to match the column names in your data. Same procedures apply to ADAE naming file.

1. Download the template naming file by clicking "Need template?" from

     , and save the excel file on your computer.

2. Open the file and change the default column name to the corresponding column name in your dataset. For example, if your treatment column is named as "Treatment" instead of "TRT01A", do the following:

Name	Description
USUBJID	Subject ID
TRT01A	Actual treatment received
TRTSDT	First dose date of study drug
TRTEDT	Last dose date of study drug

→

Name	Description
USUBJID	Subject ID
Treatment	Actual treatment received
TRTSDT	First dose date of study drug
TRTEDT	Last dose date of study drug

3. Save the edited file on your computer and use it for uploading to the tool.

Step 2. Upload datasets

- Click Browse... to import ADSL data and its naming file.
- The tool will show you a message for successful uploading of the data and a preview of the dataset only after you have uploaded both the data and the naming file.

ADSL data

The file is successfully imported: adsl_ex.sas7bdat
The file is successfully imported: adsl_naming_example.xlsx

Show 10 ▾ entries   Search: [   ]

	USUBJID	SAFFL	TRT01A	TRTSDT	TRTEDT
1	GS-US-000-0000-0000-0001	N	Screen Failure		
2	GS-US-000-0000-0000-0002	Y	Treatment	2012-12-06	2013-12-03
3	GS-US-000-0000-0000-0003	Y	Treatment	2013-07-30	2014-02-24
4	GS-US-000-0000-0000-0004	Y	Treatment	2013-06-12	2013-08-07
5	GS-US-000-0000-0000-0005	Y	Treatment	2012-10-23	2013-10-03
6	GS-US-000-0000-0000-0006	Y	Placebo	2013-07-09	2013-11-26
7	GS-US-000-0000-0000-0007	Y	Treatment	2012-08-14	2013-12-10
8	GS-US-000-0000-0000-0008	Y	Placebo	2013-02-01	2013-03-25
9	GS-US-000-0000-0000-0009	Y	Placebo	2013-07-10	2013-11-18
10	GS-US-000-0000-0000-0010	N	Screen Failure		

- Follow the same procedure for uploading ADAE and its naming file.

The file is successfully imported: adae_ex.sas7bdat
The file is successfully imported: adae_naming_example.xlsx

Show 10 entries   Search: [   ]

	USUBJID	AEDECOD	AEHLGT	AEHLT	AEBODSYS	ASTDT	AENDT	AETOXGRN	TRTEMFL	AESER	TRT01A
1	GS-US-000-0000-0000-0146	AE166	HLGT97	HLT276	SOC19	2013-10-04		1	Y	N	Placebo
2	GS-US-000-0000-0000-0146	AE471	HLGT105	HLT275	SOC24	2013-10-23	2013-10-24	2	Y	N	Placebo
3	GS-US-000-0000-0000-0146	AE428	HLGT62	HLT278	SOC7	2013-08-08	2013-08-31	2	Y	N	Placebo
4	GS-US-000-0000-0000-0146	AE428	HLGT62	HLT278	SOC7	2013-08-28	2013-08-28	2	Y	N	Placebo
5	GS-US-000-0000-0000-0146	AE477	HLGT24	HLT67	SOC19	2013-08-08	2014-01-02	1	Y	N	Placebo
6	GS-US-000-0000-0000-0146	AE252	HLGT137	HLT203	SOC17	2013-09-01		2	Y	N	Placebo
7	GS-US-000-0000-0000-0263	AE438	HLGT62	HLT278	SOC7	2013-11-05	2013-11-05	1	Y	N	Treatment
8	GS-US-000-0000-0000-0263	AE452	HLGT140	HLT46	SOC15	2013-06-29	2013-06-29	1	Y	N	Treatment
9	GS-US-000-0000-0000-0263	AE158	HLGT78	HLT8	SOC9	2013-07-20	2013-07-27	2	Y	N	Treatment
10	GS-US-000-0000-0000-0263	AE158	HLGT78	HLT8	SOC9	2013-09-25	2013-10-23	2	Y	N	Treatment

- Click ☑ TEAE above the data preview panels to select TEAE from ADAE dataset.

- Once all four datasets are successfully uploaded, [Merge ADSL & ADAE] button will show up. Click the button to merge data.
  - Note:
    - If you choose TEAE after you have merged the datasets, you will need to click the merge button [Merge ADSL & ADAE] again to refresh the merged datasets, since TEAE filter only applies to ADAE dataset.

- Once datasets are merged, you could click [⬇ Download merged data] button to download merged data in excel format.

- To set the snapshot date to a specific date, choose the date from **Snapshot Date** [2017-11-13]

- To further subset the data, click [Filter merged data] button and choose the variable to use from the dropdown menu **Variable 1** [Choose ▾]

Step 3. Analyze data

- Click [Safety analysis] on the top of the window to switch to data analysis panel. An input parameter panel will show up on the left.

- Choose your treatment and control groups under "Treatment mapping" section.

  Treatment mapping
  Control   [Placebo ▾]
  Treatment [Treatment ▾]

- Choose the high level and low level AE grouping factors from "AE structure" section.

  AE structure
  High level [SOC ▾]
  Low level   [PT ▾]

- Define the follow-up days.

  > Exposure for no AE occurrence is defined as:
  > First dose date to
  >
  > Last dose date plus   [30]   Days

- Define the confidence level for estimates of odds ratio, relative risk, risk difference, EAIR, and hazard ratio.

  > Confidence level   [0.95]

- Define the time point to be used in Landmark KM estimate.

  > Landmark KM time point (year)   [   ]

  - Note:
    - By default, this field is left blank, and the time point is computed from the data.
    - If the user enters a specific time point, then the entered value will be used instead.

- Define DFDR p value threshold. The value selected here is the cutoff value used to control the false discovery rate.

  > DFDR p value threshold   [0.1]

- Check 'Apply Rule of 4 to DFDR' to include the low level AE terms into DFDR calculation only if at least 4 subjects from either arm experienced that AE.

- To include results from Bayesian Hierarchical Mixture Model, select the corresponding model type(s) under 'BHMM models', and set log of relative risk cutoff, number of draw (number of samples drawn from posterior distribution), and number of burn in (number of pre-convergence samples to be discarded).

  > **BHMM models**
  >
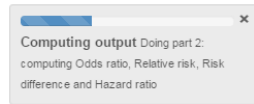 > ☑ Add BHMM Poisson model
  >
  > ☑ Add BHMM Logistic model
  >
  > BHMM log of relative risk cutoff (usually   [0]
  > a positive number)
  >
  > # of Draw   [10000]
  >
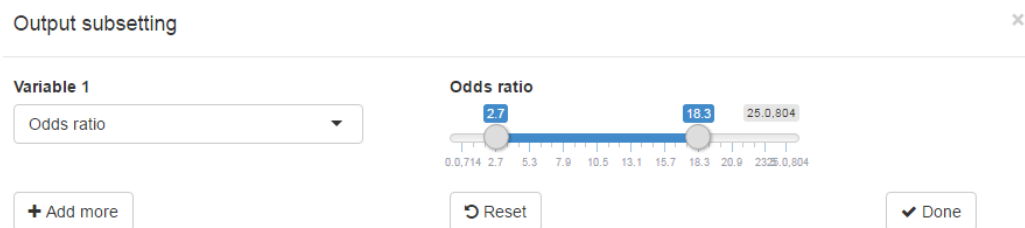 > # of Burn in   [5000]

  - Note: It normally takes a few minutes for the Bayesian models to run.

- Once all the parameters are set, click [Compute output] to run the analyses. In the lower right corner, a progress bar will pop up to show you the computation status.

Computing output Doing part 2:
computing Odds ratio, Relative risk, Risk
difference and Hazard ratio

Step 4: Obtain analysis results

- Output table
  - o Once computation is completed, you can view the results under 'Output table' panel. Click
    Filter output table in the upper right corner to select the variable and value for further filtering of
   results.

Output subsetting

Variable 1   Odds ratio
Odds ratio   2.7   18.3   25.0,804

                                    0.0,714 2.7 5.3 7.9 10.5 13.1 15.7 18.3 20.9 2325.0,804

+ Add more   ⟳ Reset   ✔ Done

 - o Click ⬇ Download output to save the results in excel format.

- Volcano plot

  - o Click Volcano plot to go to the volcano plot panel.
  - o By default, the volcano plot presents odds ratio vs. Fisher's exact t test p value. To use
    different measurements for x- or y-axis, go to the parameter panel on the left and change the
    variables from the following dropdown menu. Options for x-axis are odds ratio, relative risk,
    risk difference, and hazard ratio. Options for y-axis are Fisher's exact t test p value, EAIR test
    p-value, log-rank test p-value, and landmark KM test p-value.

X-axis: measurements
Odds ratio   ▼

Y-axis: p value option
Fisher exact test p value   ▼

  - o To view detailed information for the data point of interest, hover your mouse over that data
    point and a small panel will appear to display the critical information.

SOC: SOC14
PT: AE509
Odds ratio: 11.3
Fisher exact test p
value: 0.031
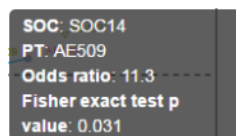
  - o Modify plot title and labels, edit footnotes, and change cutoff values for x- and y-axis using
    the widgets on the right side of the plot.
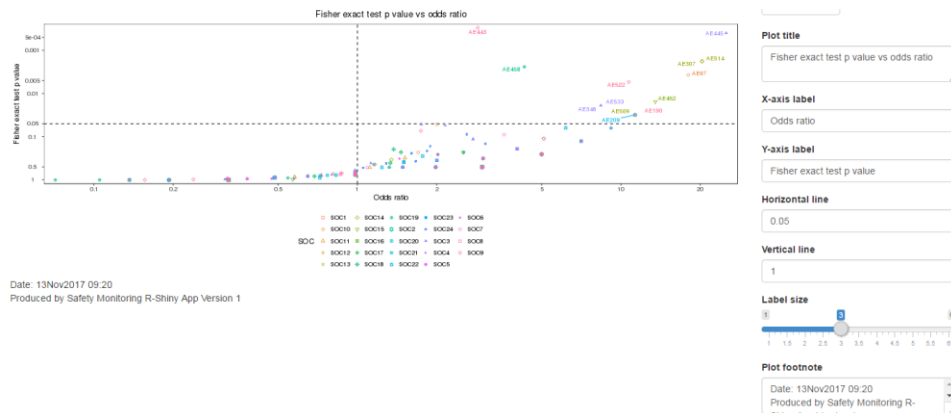
- o Click [Download plot] to save the plot. It can be saved in pdf, jpg, pgn, or ps format. Adjust the height, width, and resolution of the plot according to your need.

- Dot plot

  - o Click [Dotplot] to switch to dot plot panel.
  - o By default, the left panel will show the proportions of different AE events in treatment and placebo arm, respectively. The right panel will present the odds ratio of the AE events in the two arms and the confidence intervals for the estimates. AE events are sorted by descending order of odds ratio.

    - ▪ Note:

      The confidence level is dependent on the pre-specified number used in

      [Confidence level 0.9] . To use a different number, you will need to change the value and go to 'Output table' panel to redo the calculation by clicking 'Compute output'. Changing the value without redoing the calculation only changes the label
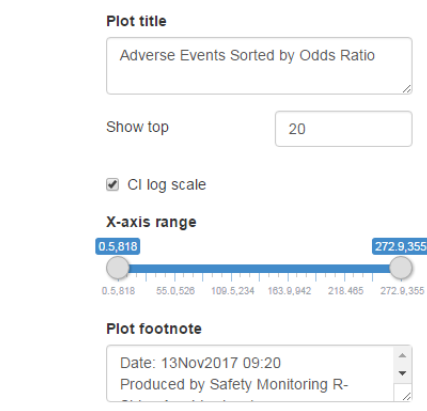
      [Odds ratio with 90% CI] without changing the values displayed on the plot.

  - o To sort AEs by a different measurement other than odds ratio, click

    [X-axis: measurements Odds ratio] at the bottom of the parameter panel and choose from the dropdown menu. In addition to odds ratio, you will have relative risk, risk difference, or hazard ratio as your options.

  - o Use the widgets on the right side of the plot to adjust the plot to your needs.

Plot title

Adverse Events Sorted by Odds Ratio

Show top   20

☑ CI log scale

X-axis range

0.5,818   272.9,355

0.5,818   55.0,526   109.5,234   163.9,942   218.465   272.9,355

Plot footnote

Date: 13Nov2017 09:20
Produced by Safety Monitoring R-

o   Click   Download plot   to save the plot.