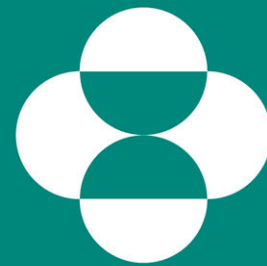


Enhancing PK Data Exploration and Visualization by using a R shiny Application

Paper DV03



MERCK

INVENTING FOR LIFE

26FEB2024

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Agenda

- INTRODUCTION
- PROJECT INITATION
- INTERFACE AND DEMOSTRATION
- CODE BEHIND THE APP
- CONCOULSION

INTRODUCTION



Leverage R shiny' capabilities to create a business-driven application



An interactive web app to assist PK scientists in PKPD analysis data review and exploration without writing programming scripts.



A handy tool to -- Provide quick review of PKPD analysis data by browsing through variables, filtering data, retrieving quick default plotting



A handy tool to -- Conduct data check to examine PKPD data set, download data check reports



A handy tool to -- Plot PKPD data with interactive/dynamic features, and downloadable outputs

PROJECT INITIATION

- Specific challenges faced by PK scientists
 - Unfamiliar with CDISC standard
 - They may need to create their own programming scripts to perform data check
- Engaging stakeholders to define requirements
 - Actively involving stakeholders in discussions to identify essential requirements, ensuring the tool aligns with real-world needs
- Designing key functions and User Interface (UI)

PROJECT INITIATION

Must Have

- Ability to filter dataset, flexibility to select variables
- Ability to present quick/simple summary of variables
- Dynamic data plotting such as PK vs time plot, etc., ability to elect variables to stratify by subgroup,
- Enable data checks with an option to export all the check results to a PDF
- Function to export/download reports (tables and figures)

Nice to Have

- Allow conversion of data types from user selected dataset
- Download R script or even edit within the App
- Upload source data and check the analysis dataset against it
- Independent filter for each functional tabs
- Ability to zoom in/out from the plot, change the coordinates, etc.

INTERFACE AND DEMOISTRATION

DATA

Upload data

Filter data

3 sub tabs:

- Data Summary
- Data Review
- Data Browsing

CHECK

Select check items from ADPC check list

Submit request to generate reports

View the reports

Export reports as PDF

PLOT

Select from two types of plot:

- Correlation plot
- PK over time plot

Select x, y variables, log/linear scale

Select stratification

Define x, y label and title, footnotes

Export plot

DATA

- Upload source datasets in sas or csv format
- A simple summary of uploaded datasets will be displayed on the right side

The screenshot displays the 'PKPD Data Review and Exploration Shiny App' interface. The top navigation bar includes links for Home, Data, Check, Plot, and SDLC. The main interface is divided into two sections: 'Upload' and 'Data Summary'.

Upload Section:

- ADPC:** A file named 'adpc.csv' has been uploaded. The status bar shows 'Upload complete'.
- ADSL:** A file named 'adsl.csv' has been uploaded. The status bar shows 'Upload complete'.
- SDTM:** Three files have been uploaded. The status bar shows 'Upload complete'.

Data Summary Section:

Uploaded Datasets: adpc.csv adsl.csv dm.sas7bdat ex.sas7bdat pc.sas7bdat

	Name	Observations	NumberOfColumns	NumberOfUniqueSubject
1	ADPC	249	86	16
2	ADSL	46	58	46
3	DM	46	26	46
4	EX	16	16	16
5	PC	325	325	16

DATA

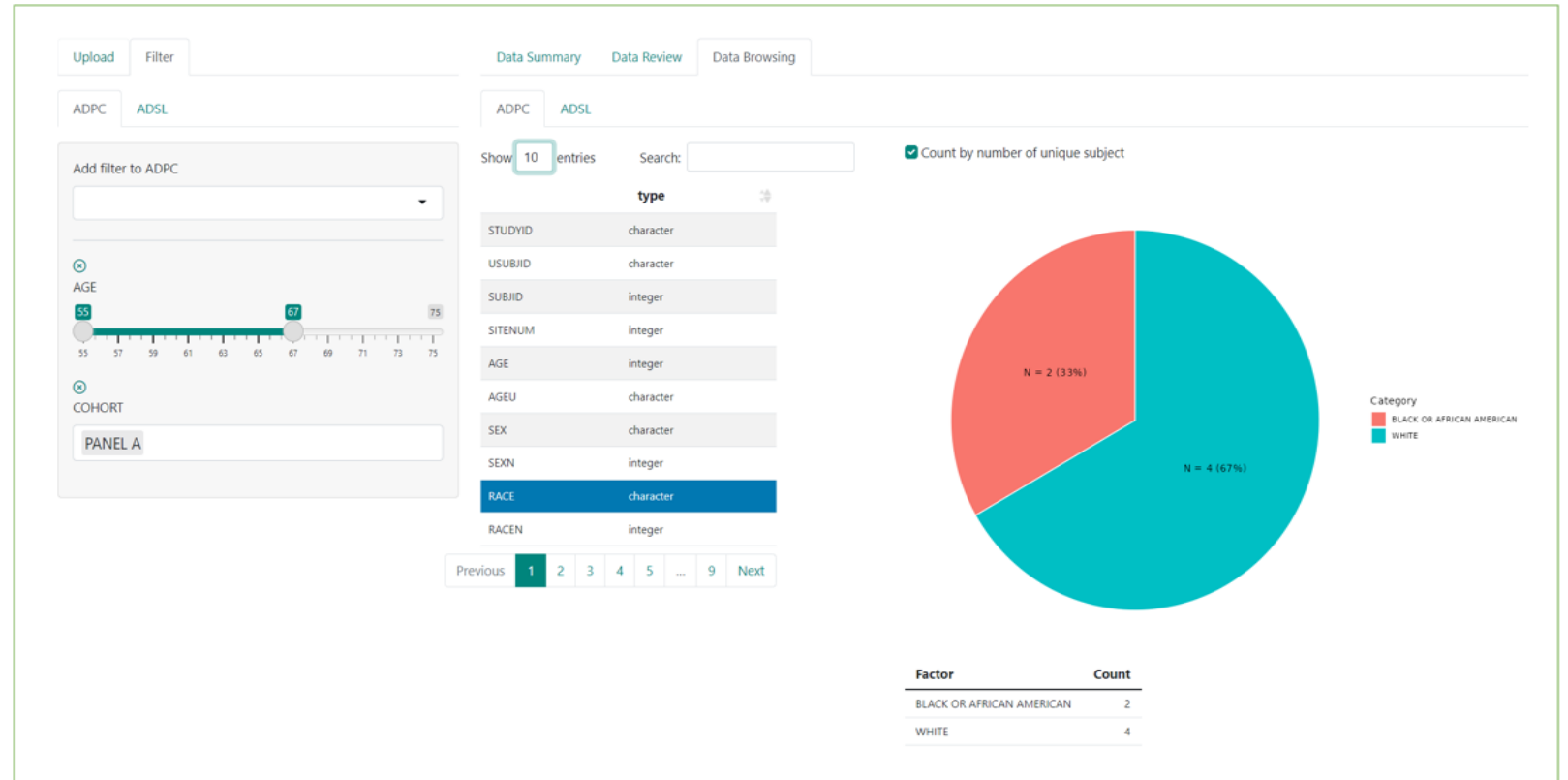
- Review the selected dataset with the functions of selecting variables, adding or removing filters, searching the key words, etc.

The screenshot displays a data analysis interface with two main sections. On the left, the 'Filter' tab is active, showing options for 'ADPC' and 'ADSL'. Under 'ADPC', there is a search bar for 'Add filter to ADPC'. Below this, a slider for 'AGE' is shown with a range from 55 to 75, and a 'COHORT' dropdown menu set to 'PANEL A'. On the right, the 'Data Summary' tab is active, showing a table of data. The table has columns for STUDYID, USUBJID, PCSPEC, PCCAT, PARAM, AVAL, ATPT, TRTA, PCDTC, and SITENUM. The data is filtered to show 25 entries, all of which are for the same study and subject, but with different time points (ATPT) and values (AVAL).

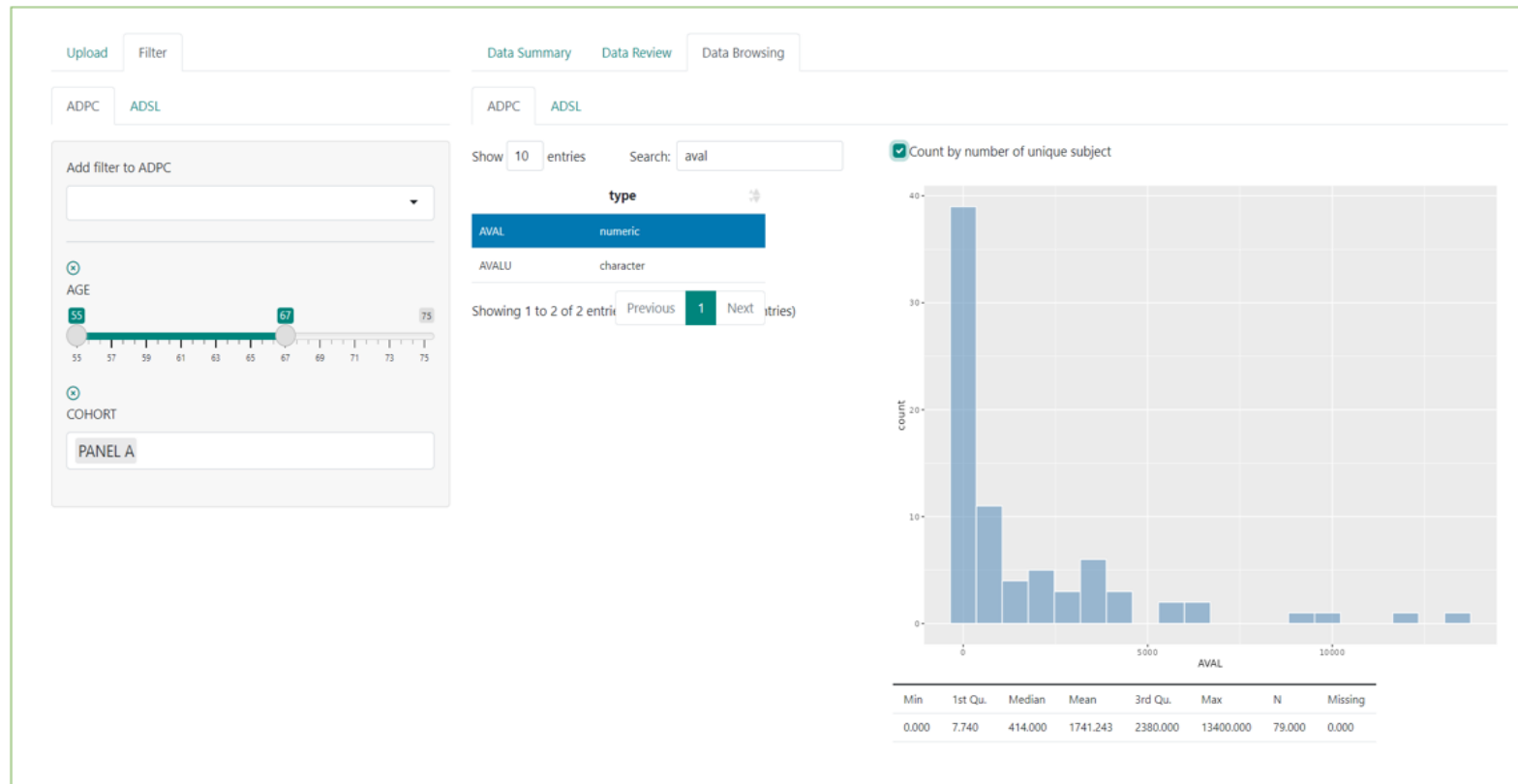
STUDYID	USUBJID	PCSPEC	PCCAT	PARAM	AVAL	ATPT	TRTA	PCDTC	SITENUM
4482-003	4482-003_000100001	PLASMA	ANALYTE	N-HYDROXYCYTIDINE (ug/L)	2.42	PREDOSE	MK-4482 800 mg	2022-10-04T09:02	1
4482-003	4482-003_000100001	PLASMA	ANALYTE	N-HYDROXYCYTIDINE (ug/L)	3640.00	0.5 HR	MK-4482 800 mg	2022-10-04T09:40	1
4482-003	4482-003_000100001	PLASMA	ANALYTE	N-HYDROXYCYTIDINE (ug/L)	6630.00	1.5 HR	MK-4482 800 mg	2022-10-04T10:40	1
4482-003	4482-003_000100001	PLASMA	ANALYTE	N-HYDROXYCYTIDINE (ug/L)	5670.00	2 HR	MK-4482 800 mg	2022-10-04T11:10	1
4482-003	4482-003_000100001	PLASMA	ANALYTE	N-HYDROXYCYTIDINE (ug/L)	2160.00	4 HR	MK-4482 800 mg	2022-10-04T13:09	1
4482-003	4482-003_000100001	PLASMA	ANALYTE	N-HYDROXYCYTIDINE (ug/L)	888.00	6 HR	MK-4482 800 mg	2022-10-04T15:05	1
4482-003	4482-003_000100001	PLASMA	ANALYTE	N-HYDROXYCYTIDINE (ug/L)	267.00	8 HR	MK-4482 800 mg	2022-10-04T17:08	1

DATA

- Select a variable to review the data distribution by generating pie chart or histogram plot with the flexibility to add filters
- Summary statistics will be generated under the plot



DATA



CHECK

- Allow user to select from the list of checks, run and download the report as PDF

PKPD Data Review and Exploration Shiny App

Home Data Check Plot SDLC

Select Sections

☐ Select All/None

Contents

- ☐ 1.1
- ☐ 2.1
- ☐ 2.2
- ☐ 3.1
- ☐ 3.2
- ☐ 4.1
- ☐ 4.2
- ☐ 4.3
- ☐ 5
- ☐ 6
- ☐ 7
- ☐ 8.1
- ☐ 8.2
- ☐ 8.3
- ☐ 9.1
- ☐ 9.2
- ☐ 10

Submit

ADPC Checklist

Note: Before proceeding with the checklist, ensure that ADPC, ADSL, SDTM.DM, SDTM.EX, and SDTM.PC have been uploaded successfully.

Export to PDF

Download Report

[1.1 Check counts of subjects and records of ADPC with source data](#)

[2.1 Check parameters and subject counts](#)

[2.2 Check subject and record counts by PERIOD, PARAM, TRTP, DAY and ATPTN](#)

[3.1 Check treatment from ADSL](#)

[3.2 Check treatment and actual dose from ADPC](#)

[4.1 Check date/time variables](#)

[4.2 Check displayed covariates](#)

[4.3 Check analysis value out of 5-95 percentile range by nominal timepoint](#)

[5 Check time deviation of the actual PK sample against the planned](#)

The threshold of difference is 10%

[6 Check PK sample time against Dose time](#)

a) PK or Dose time missing. Check if it is data issue.
b) PK sample time issue if ever-1st-predose sample after dose time (ADTM>LDSDTM).
c) PK sample time issue if non-ever-1st predose sample before dose time (ADTM<LDSDTM).
d) Issue of Relative sample time to 1st dose in a period (PARELTM) if not 0 at start of a period (at ATPTN=0).

[7 Check demographic information that unexpectedly changed within a subject](#)

[8.1 Check variables that are not populated at all](#)

[8.2 Check AVAL, ADTM, or LDSDTM and Display missing value record counts if any](#)

[8.3 Check other variables and Display missing value record counts if any](#)

[9.1 Embedded BLoQ: Postdose PK \(AVAL\) dips to 0 and move up again](#)

[9.2 First predose PK missing](#)

[10 Check if PK time sequence is consistent with scheduled time](#)

Select Checks

CHECK

Checklist report in PDF

ADPC Checklist

1. Check counts of subjects and records of ADPC with source data

1.1 Total number of ADPC subjects/records should be the same as source data.

Domain	Subject_counts	Record_counts
ADSL	16	
ADPC	16	249
PC	16	322

2. Check Study Design

2.1 Eyeball check parameters and subject counts.

PARAMN	PARAMCD	PARAM	Subject_counts
1	NHC	N-HYDROXYCYTIDINE (ug/L)	16

2.2 Eyeball check subject and record counts by PERIOD, PARAM, TRTP, DAY and ATPTN.

The list is too long, only display counts by PARAM, TRTP and PERIOD, not including DAY & ATPTN columns.

PARAMN	PARAMCD	TRTP	PERIOD	Subject_count	Record_counts
1	NHC	MK-4482 800 mg	1	16	249

3. Check actual dose DOSEA

3.1 Treatment from ADSL. Subject counts (Frequency) is calculated by the group of columns displayed.

Subject_TRT_Chg should be populated if discrepancies between the planned and the actual treatment.

ARM	ACTARM	TRT01A	Subject_TRT_Chg	Frequency
MK-4482 (MOV) 800 mg	MK-4482 (MOV) 800 mg	MK-4482 800 mg		16

3.2 Check treatment and actual dose (DOSEA) from ADPC.

If actual and planned treatment are not the same, the subject will display in TRTA_not_match_TRTP column. For other possible issues, eyeball check. e.g. actual dose (DOSEA) against dose level in TRTP and TRTA if available. This check will not be applicable for study with dose by weight and should be excluded.

4. Check outliers.

4.1 Eyeball check date/time variables.

Check_Date	Min	Max
ADT	2022-08-01	2023-02-04
LSDT	2022-08-01	2023-02-01

4.2 Check displayed covariates.

Variable	Mean	Median	Range	Quantile_5_95	n_lt_Q5	n_gt_Q95
AGE	61.56	59.50	55-75	55-75	0	1
BMIBL	30.94	30.85	22.9-34.8	22.9-34.8	1	1
HEIGHTBL	170.18	169.25	155-188	155-188	1	1
WEIGHTBL	89.91	89.60	60.6-123	60.6-123	1	1

4.3 Check AVAL. Only displayed concentration counts when any out of 5-95 percentile range by nominal timepoint.

USUBJID	PERIOD	PCSPEC	PARAMCD	TRTA	DAY	ATPTN	AVAL	Q5	Q95
4482-003_000400013	1	URINE	NHC	MK-4482 800 mg	1	0	121,000	0	62,400

5. Check time deviation of the actual PK sample against the planned.

By comparing time from the last dose (LARELTM) with sample collection nominal time (ATPTN). Look for deviations beyond 10 %, which is specified by input parameter: pct4PKdeviation= (default value is 10). Recommended for Phase I study and not to other phases. Exclude if this check is not applicable.

Result
- No findings -

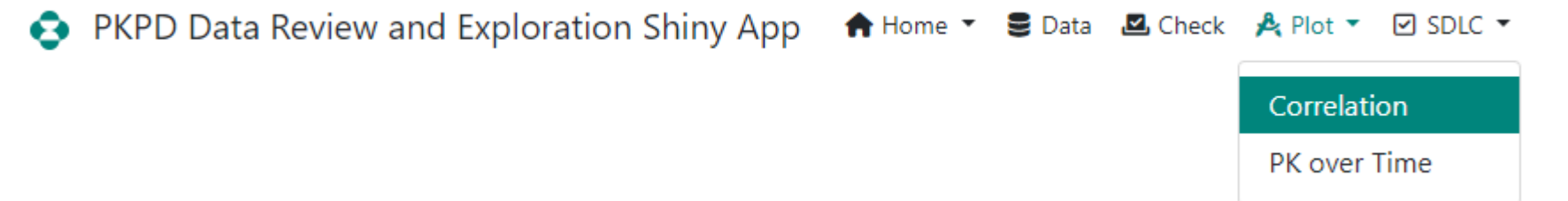
6. Check PK sample time against Dose time.

Exceptions checked:

- a) PK or Dose time missing. Check if it is data issue.
- b) PK sample time issue if ever-1st-predose sample after dose time (ADTM>LSDTM).
- c) PK sample time issue if non-ever-1st predose sample before dose time (ADTM<LSDTM).

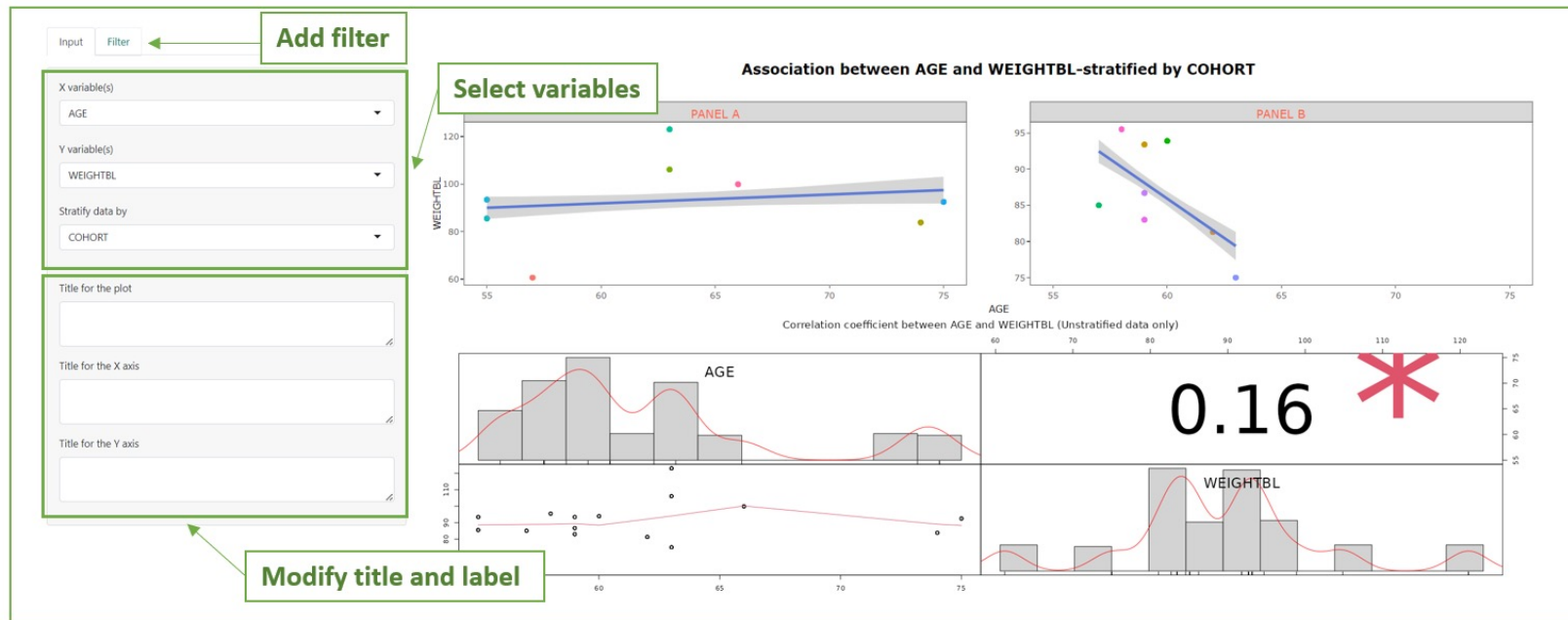
PLOT

- After navigate to plot tab, user can select plot type from a dropdown list. Currently we only include two types, and we will add more in the future to meet the analysis need.



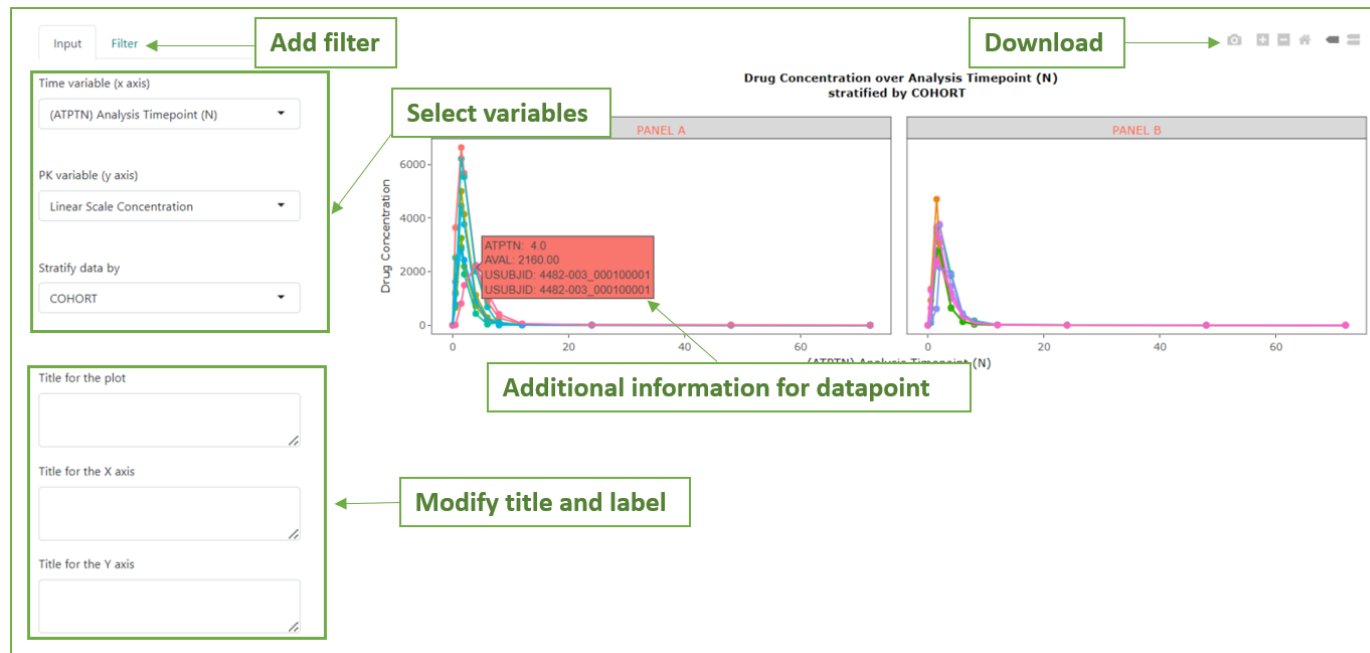
PLOT

- Generate customized correlation plot by selecting the x and y inputs, adding filters and using strata variable
- Modify title and label and download the plot for future use.



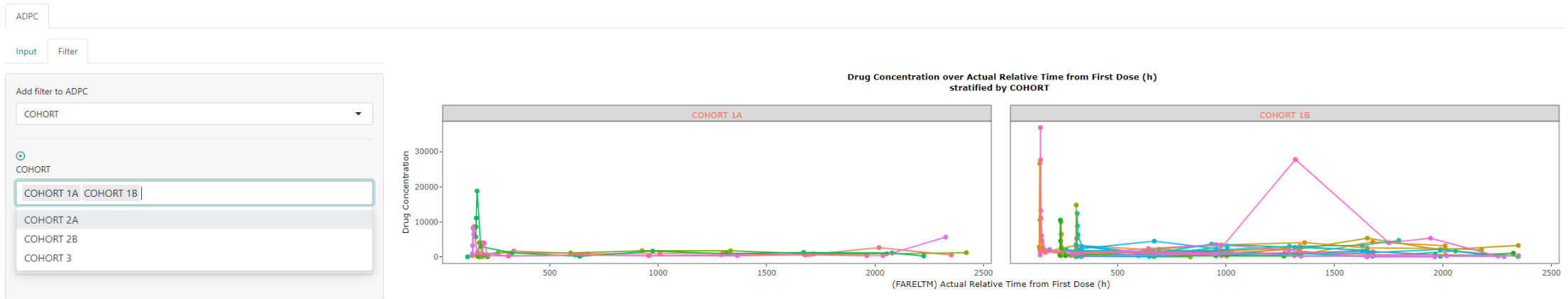
PLOT

- PK concentration vs time plots
- A list of time variables could be selected as x-axis including ATPTN, ADY, ADTM,FARELTM, LARELTM, etc.



PLOT

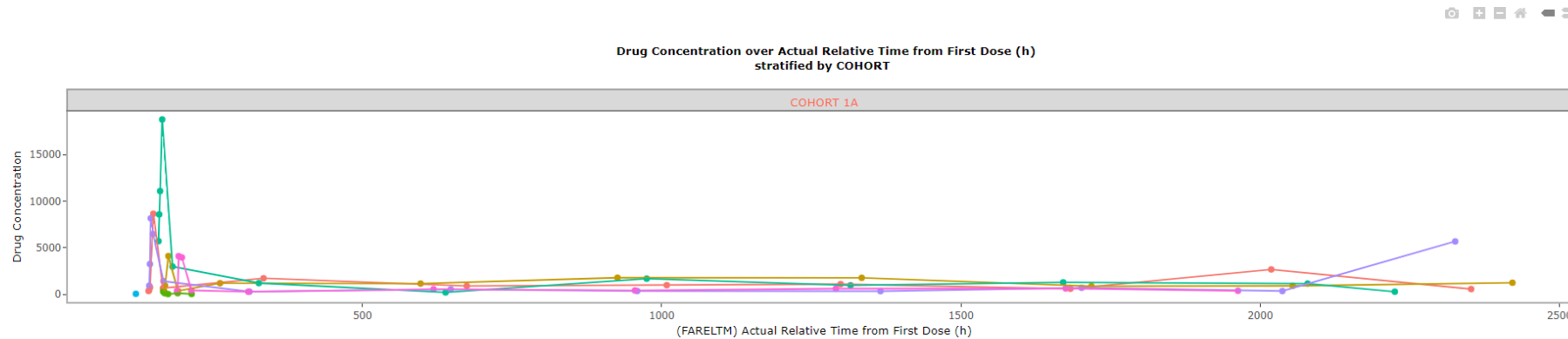
- Find extreme values
- Select subgroups and compare



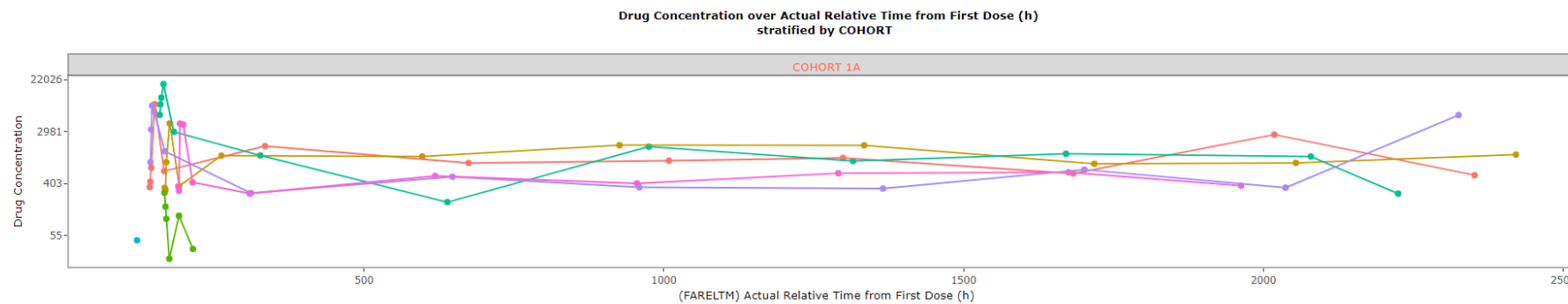
PLOT

- Create plot in linear scale or log scale

Linear

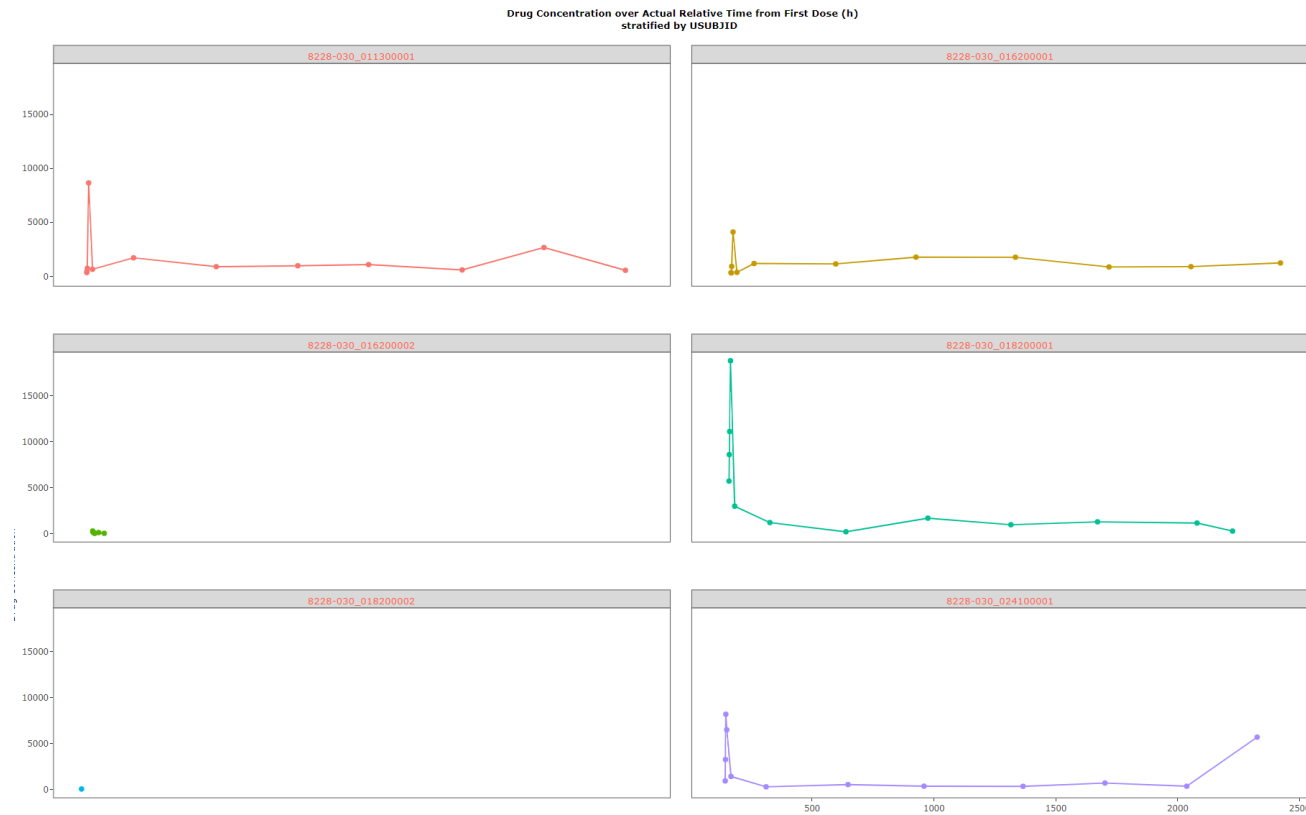


Log



PLOT

- Check by subject



CODE BEHIND THE APP

- Dynamic UI with Shiny
 - Retrieve information from data uploading
 - Write the UI part on the server side to make sure the UI will be rendered correctly with the input datasets
 - Add independent filtering functions for each section Dynamic UI with Shiny
- Use plotly for data visualization
 - Create interactive visualization for each data point
 - Easily add useful functions including zoom in/out, download, etc.
 - Highly customized with ggplot2
- Refer to the paper for sample code

CONCLUSION

- Conclusion
 - Demonstrated the application's capabilities in PK data exploration and visualization
 - Leverage R Shiny's interactive features to improve the PK data review process for PK scientists
- Next Step
 - Add more features to include ADA and nmpk datasets for analysis
 - Enable user to download R code
 - Release to public

THANK YOU!

Q&A



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