

R Shiny Applications within Ophthalmology

Julia Dedic, Hoffman-La Roche Limited, Mississauga, Canada

ABSTRACT

With the increasing need for faster and more efficient exploratory analysis of clinical trial data, R Shiny provides a framework that does just that. The time consuming task of re-running code to further investigate and report on deliverables is replaced with this interactive web application. This not only makes workflow faster, but it also provides a convenient feature; the ease of access and usage of data and results through a web URL. Through the creation of packages, the R Shiny applications can be streamlined to fit the outputs required for different therapeutic areas. In this paper, the work presented will cover a package created for Ophthalmology. This package will contain reproducible code containing modules to create tables, listings, and graphs for analyzing Ophthalmology studies in a dynamic setting. Within these modules, dynamic filtering options will allow the user to explore the data with specifications predefined.

1. INTRODUCTION

At Roche, introducing more R based programming in everyday tasks as programmers has allowed us to create agile solutions to complex problems caused by the growing complexity of studies. One of these solutions is the use of R Shiny. Why do we need an R Shiny application for our study work? It is a great way for quick data exploration and quality control. Roche has been using R Shiny applications for this purpose. This has allowed us to share insights in a more intuitive, interactive way that enables self-service analysis.

Roche has developed an R package, known as “TEAL”, which is based on R Shiny to create interactive data exploration web applications. This framework provides us with a standard template for data exploration that allows us to have code reproducibility and interactive dynamic filtering. The main three components of every TEAL application are: the encoding panel on the left, filter panel on the right, and the output in the center panel.

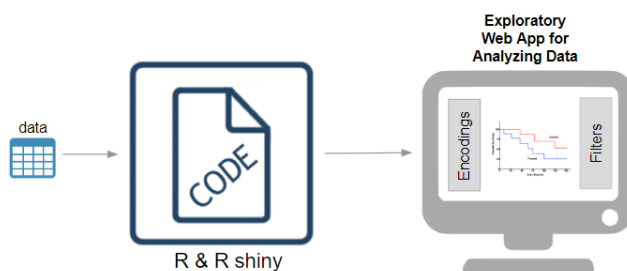


Figure 1: Teal Development Roadmap

The encoding panel on the left allows the user to adjust the output in the center interactively. The filter panel on the right allows the user to subset the data interactively. The TEAL module defines the output in the center. Through the creation of different packages, the applications can be streamline to fit the outputs required for a specific therapeutic area. In this paper, a package designed for Ophthalmology studies is presented. This package will contain a set of modules that will allow the user to dynamically explore the data within predefined specifications. This application uses two dummy BDS ADaM datasets; Subject Level Analysis Dataset (ADSL) and Ophthalmic Examinations Analysis Dataset (ADOE).

2. APPLICATION LAYOUT

2.1 THE MODULES

This application contains four main modules: Data Table, Variable Browser, Demographics and Efficacy. The Data Table module, **Figure 2**, lists all the data available in the dataset. The Variable Browser, **Figure 3**, allows you to visually display one specific variable within a dataset. The demographics table, **Figure 4**, summarizes the demographics variables of interest for your dataset. This may include age, sex, race, and ethnicity of the patients within your study.

Ophthalmology Data Exploration App

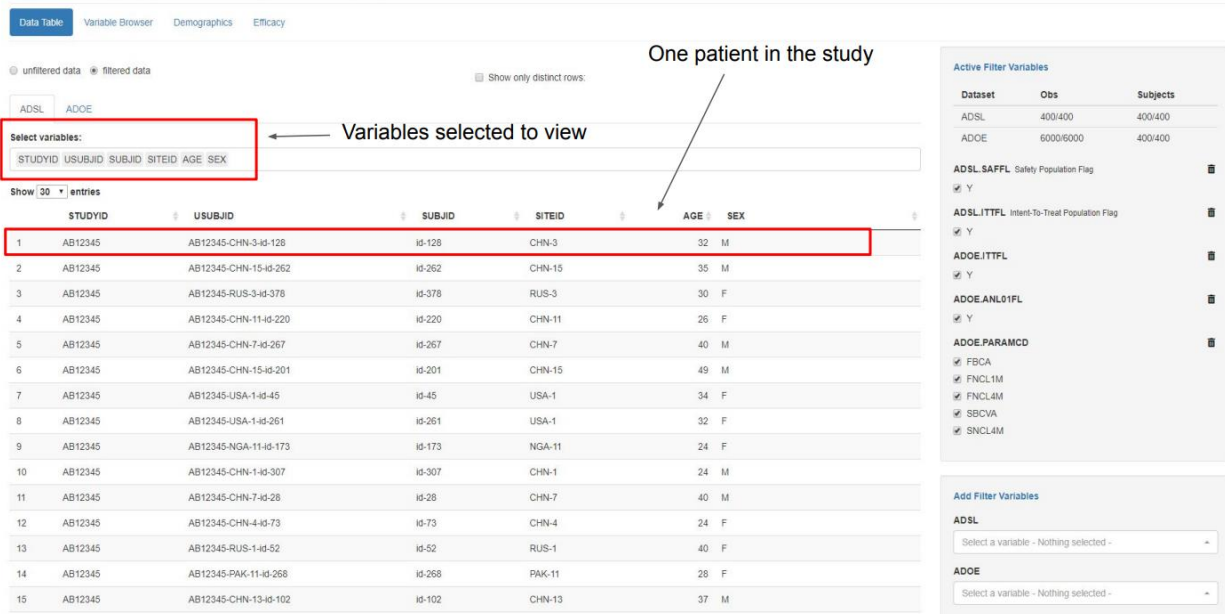


Figure 2: Data Table Module

Ophthalmology Data Exploration App

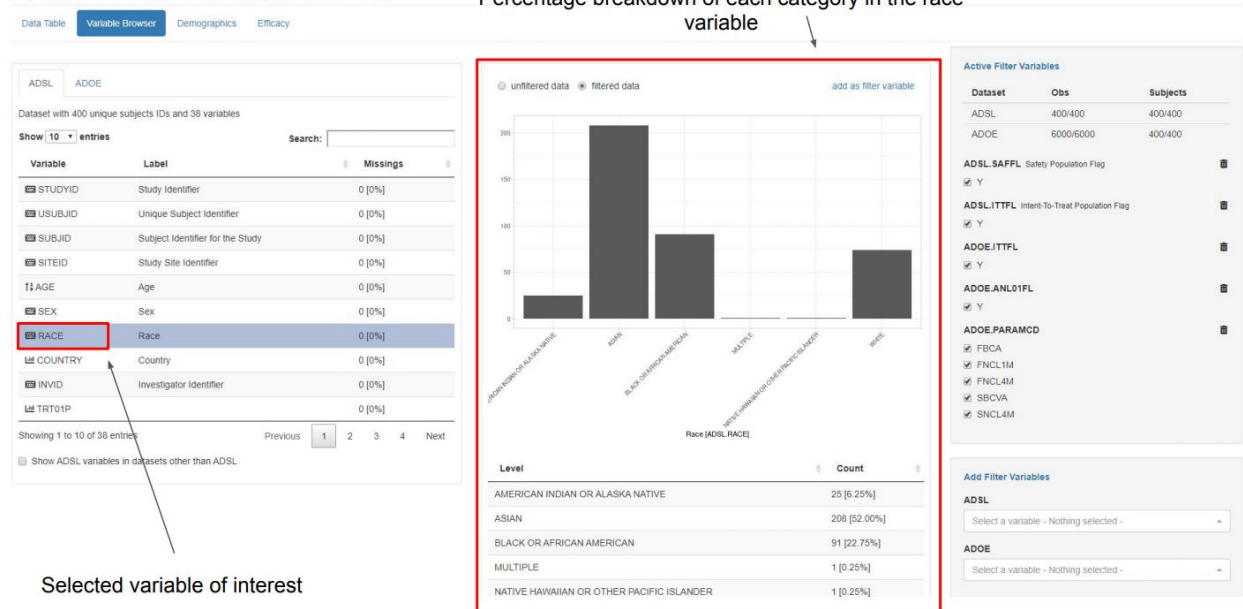


Figure 3: Variable Browser Module

Ophthalmology Data Exploration App

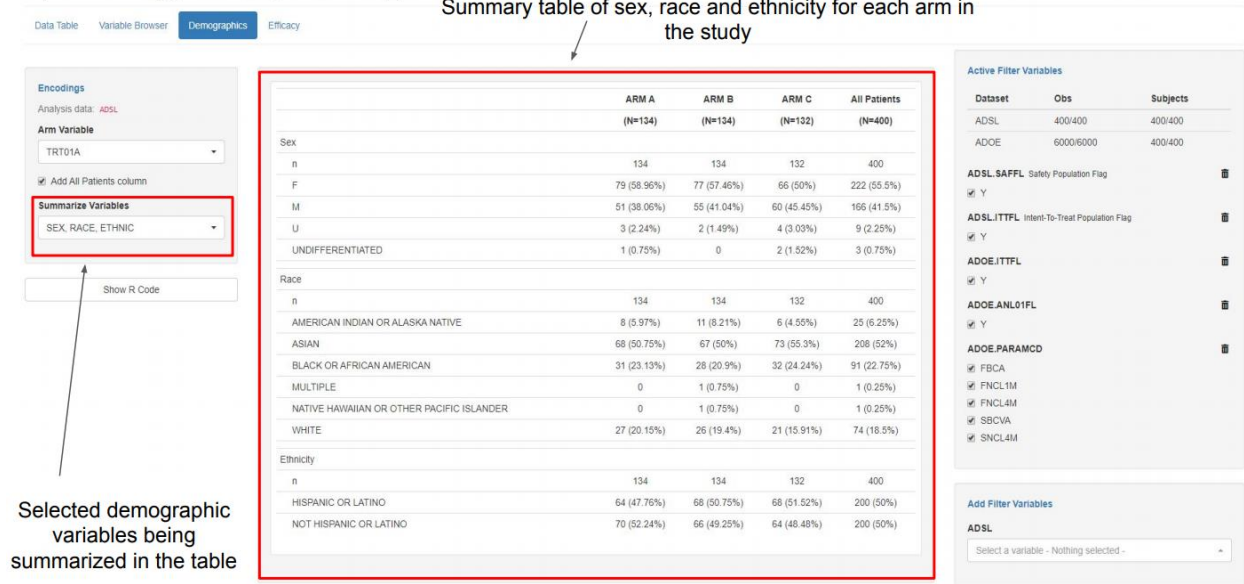


Figure 4: Demographic Table Module

Within the Efficacy module, there are five tabs displaying different analyses. There is a summary table, summary plot, spaghetti plot, ancova table and a mixed model repeated measures table. The summary table, **Figure 5**, gives a summary of the mean, standard deviation, median, and minimum and maximum for a variable of interest at each visit time point for the patients in the study.

Ophthalmology Data Exploration App

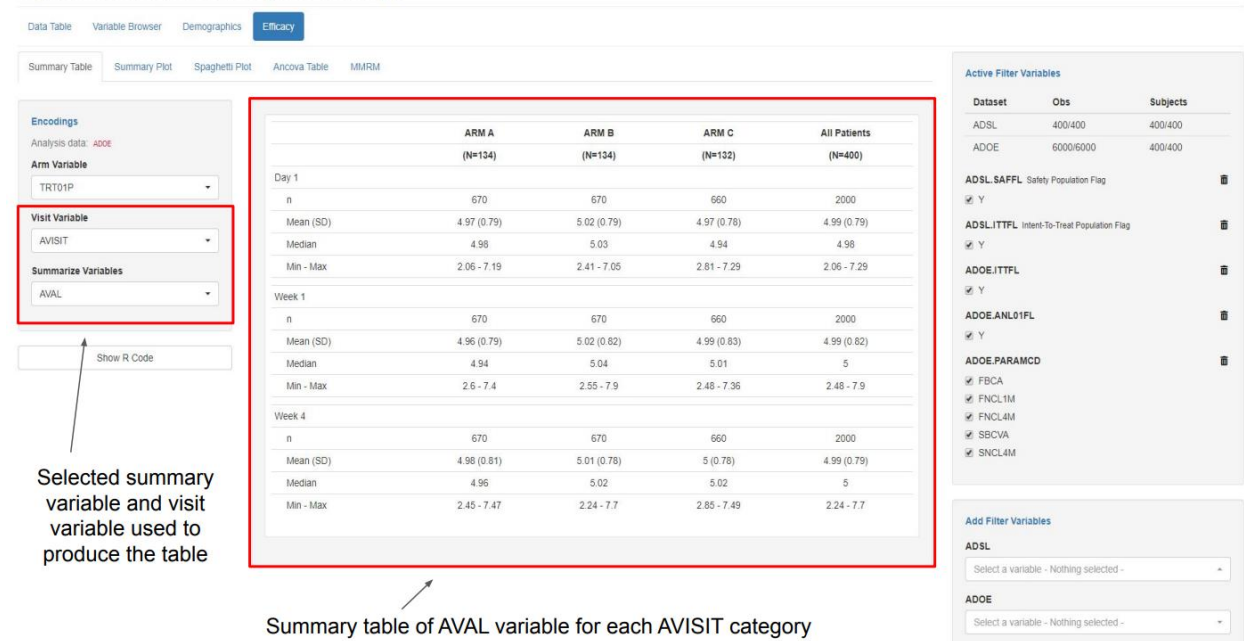


Figure 5: Summary Table Module

In Ophthalmology studies, the variable of interest could be, for example, AVAL or CHG and this would be summarized across the visit variable (AVISIT or AVISTN).

The summary plot, **Figure 6**, allows the user to graphically view the mean number of patients at each visit for the summary variable of interest. It also provides a 95% confidence interval for the mean at each visit. The plot displays this for each arm using different colours. Underneath the plot, there is a table that lists the number of subjects at each visit for each arm.

Ophthalmology Data Exploration App

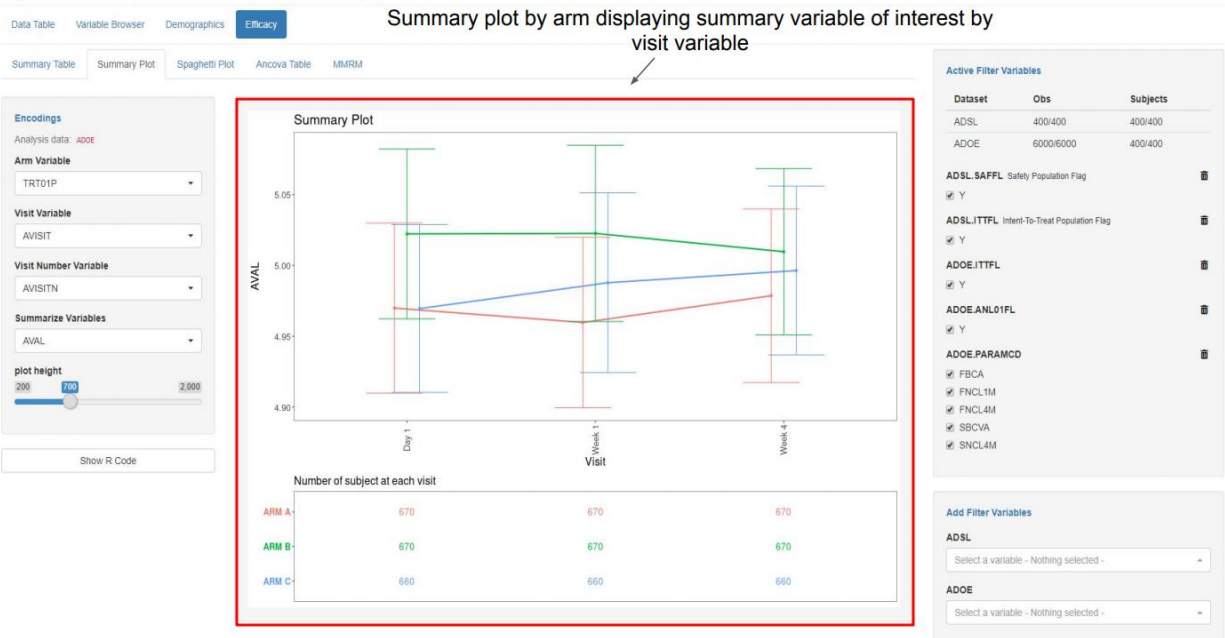


Figure 6: Summary Plot Module

The spaghetti plot, **Figure 7**, displays the summary variable values for each patient at each visit. There is also a brushing feature which allows the user to click over a certain point on the plot which then populates a table with the corresponding subject ID, visit number and summary variable value for that brushed point.



Figure 7: Spaghetti Plot Module

The Analysis of Variance (ANCOVA) table, **Figure 8**, displays the number of patients, the mean (in standard deviations), the standard deviation, the median, and the minimum and maximum of the summary variable at each visit. It also displays the change from baseline analysis at each time point using both the unadjusted analysis and ANCOVA analysis. At the top of the table, the number of patients included in the ANCOVA analysis is indicated for each arm.

Change from baseline (unadjusted and ANCOVA adjusted) at Day 1

	ARM A (N=8)	ARM B (N=11)	ARM C (N=6)
Number of Patients Included in ANCOVA Analysis			
	25	25	25
Baseline			
n	69	75	81
Mean (SD)	-0.01 (0.12)	0 (0.12)	0.01 (0.1)
Median	-0.02	0.02	0
Min - Max	-0.21 - 0.27	-0.37 - 0.25	-0.22 - 0.26
Day 1			
Value at Timepoint			
n	16	25	34
Mean (SD)	0 (0.09)	-0.02 (0.14)	0 (0.11)
Median	0	0	-0.02
Min - Max	-0.16 - 0.12	-0.37 - 0.25	-0.21 - 0.23
Change from Baseline at Timepoint			
Unadjusted Analysis			
n	16	25	34
Mean (SD)	0 (0.09)	-0.02 (0.14)	0 (0.11)
Median	0	0	-0.02
Min - Max	-0.16 - 0.12	-0.37 - 0.25	-0.21 - 0.23
95% CI for Mean	(-0.05, 0.05)	(-0.07, 0.04)	(-0.04, 0.03)
Difference in Means (vs ARM A)		-0.01	0
95% CI		(-0.06, 0.07)	(-0.06, 0.06)
ANCOVA Analysis			
Adjusted Mean (SE)	-0.01 (0.02)	-0.01 (0.01)	-0.03 (0.01)
95% CI	(0, 0)	(0, 0)	(-0.1, 0)
Difference in Adjusted Means (vs ARM A)		0	0
95% CI		(0, 0)	(-0.1, 0)
Week 1			
Value at Timepoint			
n	31	20	24

The Mixed Model Repeated Measures (MMRM) table, **Figure 9**, is similar to the ANCOVA table except it uses the MMRM for the change from baseline analysis instead of ANCOVA. The MMRM model provides an alternative method to dealing with missing data. It is shown to be a more efficient and reliable method for primary efficacy analysis as it lowers bias and type 1 error while increasing power.^[1]

Change in baseline (unadjusted and MMRM adjusted) at Day 1

Encodings
Analysis data: ADOE
Arm Variable: TRT01P
Visit Variable: AVISIT
Summarize Variables: CHG
Covariate Variables: STRAT1

Show R Code

	ARM A	ARM B	ARM C
Number of Patients Included in MMRM Analysis			
	139	140	121
Baseline			
n	1230	1225	1145
Mean (SD)	50.4 (8.44)	50.22 (8.33)	50.61 (8.52)
Median	50.41	50.29	50.13
Min - Max	25.82 - 74.52	26.04 - 74.52	25.62 - 74.52
Day 1			
Value at Timepoint			
n	400	375	425
Mean (SD)	-0.01 (0.12)	-0.01 (0.12)	-0.01 (0.12)
Median	-0.02	0	-0.01
Min - Max	-0.34 - 0.32	-0.37 - 0.32	-0.37 - 0.33
Change from Baseline at Timepoint			
Unadjusted Analysis			
n	400	375	425
Mean (SD)	-0.01 (0.12)	-0.01 (0.12)	-0.01 (0.12)
Median	-0.02	0	-0.01
Min - Max	-0.34 - 0.32	-0.37 - 0.32	-0.37 - 0.33
80% CI	(-0.017, 0.002)	(-0.013, 0.003)	(-0.013, 0.002)
Difference in Means (SE) (vs. ARM A)		0.004 (0.006)	0.004 (0.006)
95% CI		(-0.013, 0.021)	(-0.013, 0.02)
MMRM Analysis			
Adjusted Mean (SE)	50.267 (0.664)	49.635 (0.664)	48.886 (0.668)
95% CI	(48.965, 51.57)	(48.333, 50.936)	(47.575, 50.197)
Difference in Adjusted Means (SE) (vs. A: Drug X)		-0.632 (0.940)	-1.381 (0.942)
95% CI		(-2.476, 1.212)	(-3.229, 0.487)
Relative Reduction (%)		-1.3%	-2.7%
Test for Treatment Difference			
p-value (MMRM)		0.5014	0.1429
p-value (t-test)		0.6397	0.6669

Active Filter Variables

Dataset: Obs: Subjects

ADSL: 400/400: 400/400

ADOE: 3600/6000: 400/400

ADSL.SAFFL: Safety Population Flag

ADSL.ITTFL: Intent-To-Treat Population Flag

ADOE.ITTFL

ADOE.AN.O1FL

ADOE.PARAM.CD

FBCA

FNC.L1M

SBCVA

SNC.L4M

Add Filter Variables

ADSL

Select a variable - Nothing selected -

ADOE

Select a variable - Nothing selected -

3.1 ENCODING AND FILTERING PANEL

The screenshot displays the "Ophthalmology Data Exploration App". At the top, there are navigation tabs: "Data Table", "Variable Browser", "Demographics", and "Efficacy", with "Efficacy" being the active tab. Below these are sub-tabs: "Summary Table", "Summary Plot", "Spaghetti Plot", "Arcova Table", and "MMRM", with "Summary Table" selected.

A red box highlights the "Encoding" panel on the left. It contains the following elements:

- Encodings**: Analysis data: ADCE
- Arm Variable**: TRT01P (selected from a dropdown)
- Visit Variable**: AVISIT (selected from a dropdown)
- Summarize Variables**: AVAL (selected from a dropdown, indicated by a checkmark icon)
- Buttons: "Select All" and "Deselect All"
- Listed variables: AVAL and CHG

An arrow points from the text "Encoding panel where the summary variable selected is AVAL" to the highlighted encoding panel.

The main area shows a "Summary Table" with columns for different groups: ASM A (N=134), ARM B (N=134), ASM C (N=132), and All Patients (N=400). The rows represent statistical measures across four time points: Day 1, Week 1, Week 4, and Week 8. Each row includes counts (n) and mean values with standard deviations (SD).

	ASM A (N=134)	ARM B (N=134)	ASM C (N=132)	All Patients (N=400)
Day 1				
n	400	375	425	1200
Mean (SD)	4.94 (0.78)	5 (0.78)	4.98 (0.79)	4.97 (0.78)
Median	4.92	5.04	4.95	4.97
Min - Max	2.06 - 6.94	2.67 - 7.05	2.81 - 7.29	2.06 - 7.29
Week 1				
n	405	440	355	1200
Mean (SD)	4.95 (0.79)	5 (0.84)	4.98 (0.84)	4.98 (0.82)
Median	4.97	5.04	5.01	4.99
Min - Max	2.9 - 7.4	2.55 - 7.9	2.48 - 7.23	2.48 - 7.9
Week 4				
n	425	410	365	1200
Mean (SD)	5.04 (0.8)	4.98 (0.79)	5.03 (0.8)	5.02 (0.8)
Median	5.02	5.01	5.03	5.02
Min - Max	2.81 - 7.32	2.24 - 7.7	2.85 - 7.37	2.24 - 7.7

On the right side, there are two panels for filter variables:

- Active Filter Variables**: Shows a list of variables like Dataset, Obs, Subjects, ADSL, etc., with their respective counts.
- Add Filter Variables**: A section for selecting additional variables to filter the data.

Figure 10: Encoding Panel on Summary Table Module

The screenshot displays the "Ophthalmology Data Exploration App" interface. At the top, there are navigation tabs: "Data Table", "Variable Browser", "Demographics", and "Efficacy". The "Summary Table" tab is active, showing a table with columns for "Day 1", "Week 1", and "Week 4", each subdivided by "ARM A (N=15)", "ARM B (N=14)", "ARM C (N=25)", and "All Patients (N=54)". The table lists statistics such as n, Mean (SD), Median, and Min-Max for variables like TRT01P, AVISIT, and AVAL.

To the left of the table is a sidebar with sections for "Encodings", "Analysis data: ADOE", "Arm Variable" (set to TRT01P), "Visit Variable" (set to AVISIT), and "Summarize Variables" (set to AVAL). Below this is a "Show R Code" button.

To the right of the table is a "Filtering panel" titled "Active Filter Variables". It shows filters for "ADSL.SAFFL Safety Population Flag" (set to Y), "ADSL.ITFL Inten-To-Treat Population Flag" (set to Y), "ADSLAGE Age" (range 20-69), and "ADSL.COUNTRY Country" (USA, JPN). Below the filtering panel is a section for "Add Filter Variables" with dropdowns for "ADSL" and "ADOE".

An arrow points from the text "Filtering panel where age and country have been filtered" to the "ADSLAGE Age" and "ADSL.COUNTRY Country" filter settings.

Figure 11: Filtering Panel selection on Summary Table Module

3.2 SHOW R CODE BUTTON

The **Show R Code** button is displayed under the encoding panel of each module. Once clicked, the user sees a pop-up page with the code used to create the current displayed output. This code can be copied using the “copy to clipboard” button. With this copied code, the user can paste it into an R script and produce the static output. This allows for code reproducibility.

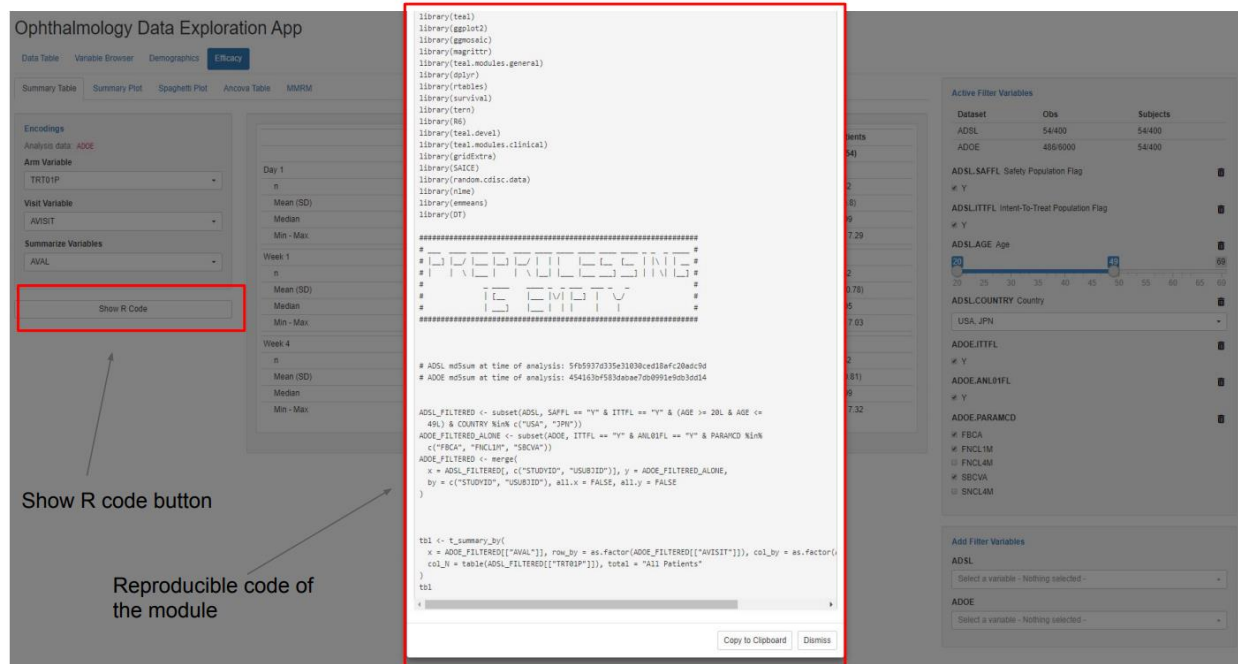


Figure 12: Show R Code Button

4. ADVANTAGES FOR OPHTHALMOLOGY

Some of the advantage of an R shiny application are as follows:

- Provides an agile solutions to problems caused by the growing complexity of studies
- Efficient (automated)
- Easy setup to create tables, listings and graphs (TLGs)
- Tailor for study-specific needs
- Platform-independent
- Transparent analysis environment

Ophthalmology studies can have hundreds of parameters recorded per patient in its Ophthalmology assessment and imaging data. Having the ability to quickly filter out different parameters of interest is a huge advantage. This allows the user to select the parameters of interest within the encoding and filtering panel which then prepopulates the desired output. The user no longer needs to reproduce a static output each time they want to view an output involving new parameters. This provides a great agile solution for quality control and data exploration within Ophthalmology studies.

5. CONCLUSION

With the ability to tailor visualizations through the creation of R packages, R shiny applications can provide a great framework for agile solutions to complex study work needs. In particular, Ophthalmology studies can greatly benefit from these applications due to their large datasets. With hundreds of parameters recorded per patient, the ability to quickly filter and subset the data is done very efficiently within the applications. The above application shows how many TLGs for Ophthalmology studies can be easily produced to fit the needs of the study. Quality control and

exploratory data analysis can become much more efficient since the user no longer needs to reproduce a static output by writing code but rather select the filtering option they are interested in within the application.

6. ACKNOWLEDGMENTS

I would like to acknowledge the NEST - internal scientific software development group at Hoffman-La Roche for the development and guidance of this application. As well, I would like to give a special thank you to Wenyi Liu for all of her guidance and Wes Tarlton for this opportunity.

7. REFERENCES

[1] Mallinckrodt, Craig H., et al. "Recommendations for the Primary Analysis of Continuous Endpoints in Longitudinal Clinical Trials." *Drug Information Journal*, vol. 42, no. 4, 2008, pp. 303–319.

8. CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

Julia Dedic
Hoffman-La Roche Limited
7070 Mississauga Road
Mississauga, ON L5N 5M8 Canada
julia.dedic@roche.com