

Good Cooperation Between SAS and R for Regulatory Submission

Jingyuan Chen

Hoffmann-La Roche

Jingyuan.chen@roche.com



Objective

- Why to make SAS and R cooperate for submission work
- Illustration:
 - Case one: to prove R can make submission ready products
 - Example from eSUB Model 5
 - Comparison
 - Case two: SAS and R can complement each other for Exploratory analysis
 - Exploratory analysis request from EMA
 - Analysis Plan
 - Demo involving R markdown
- Conclusion

Why to make SAS and R cooperate for submission work

- Open source becomes noticeable.
- SAS dominates the work of submission.
- Use the advantages from both, and use the right tool in right situation.
 - How much contribution it can make to this industry?
 - Is R able to make submission ready products ?
 - How much effort it would take to do standard submission?

Illustration:

Case one: use R for eSUB Model 5

- **Background:**

- To prepare e-submission to FDA second post marketing committee for a phase III oncology study with 516 patients.

- **Module 5 : Clinical Study Reports**

- Listing of all clinical studies
- Case report forms
- Study Reports
- Datasets
- Periodic Safety Update Reports
- Literature References

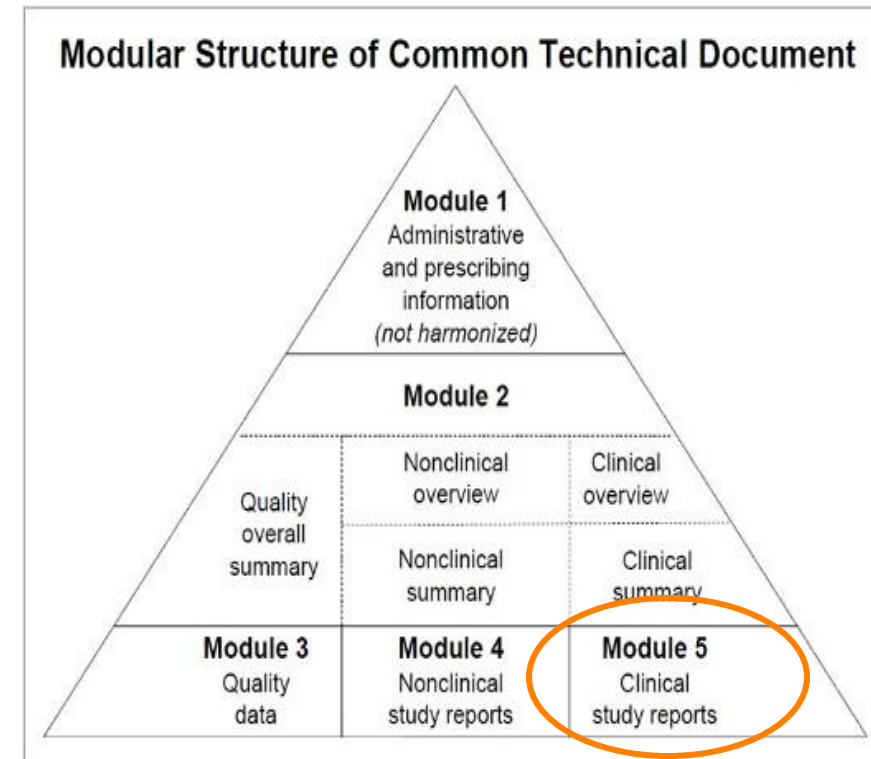


Illustration:

Case one: use R for eSUB Model 5

- **Executing plan**
 - SAS contributed the majority part of Clinical Study Reports (CSR) and Analysis Datasets.
 - Pilot R to generate two types of graphs, one table and one dataset.
 - Working Process for R:

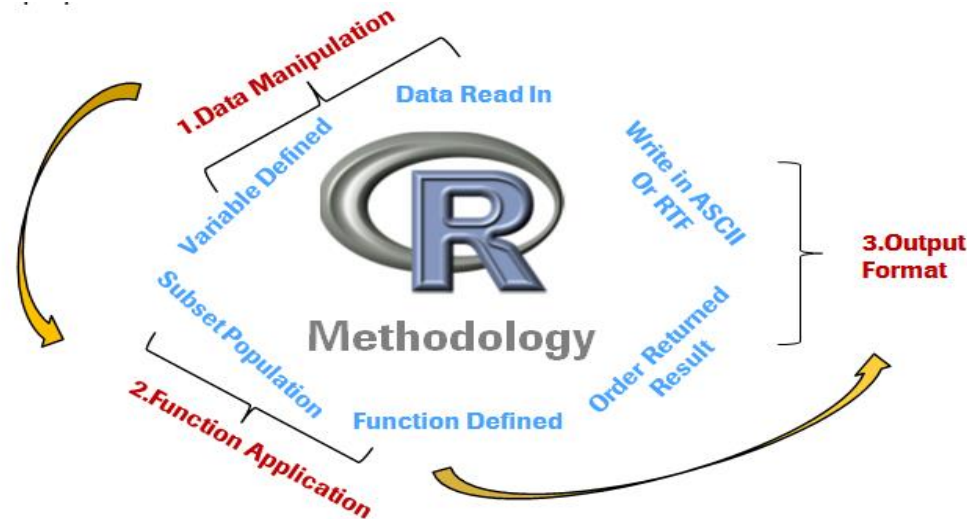


Illustration:

Case one: use R for eSUB Model 5

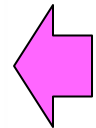
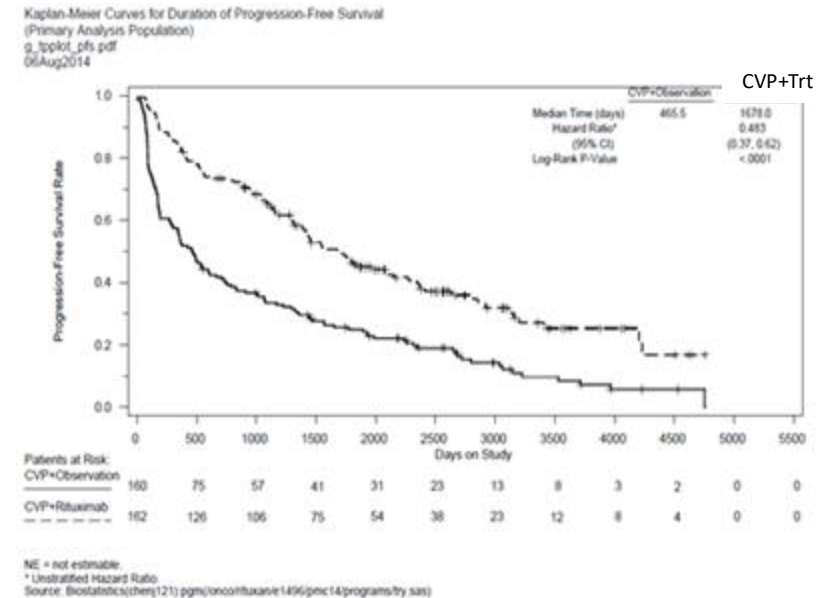
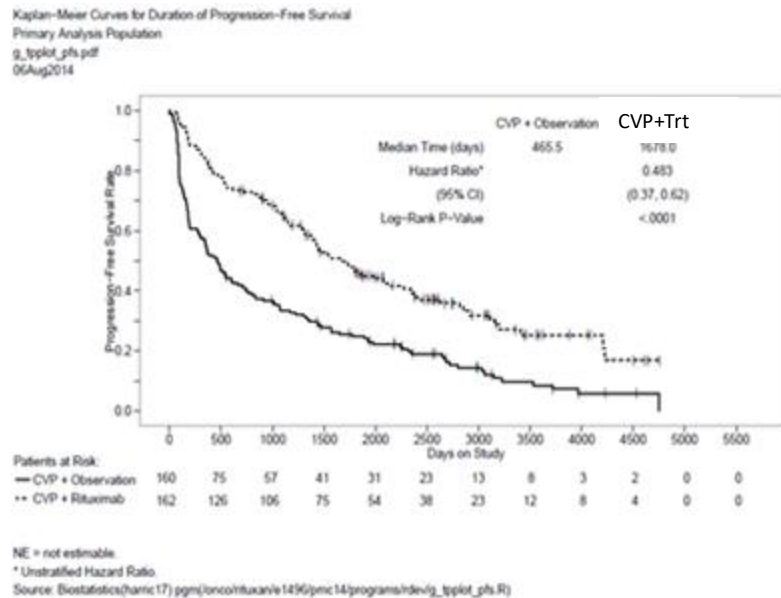
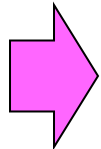
- **Quality Control Process**
 - Double program in traditional way, and applied company standard quality control process .
 - Compare outputs from R and SAS.
 - Use SAS program to compare submission dataset made by R and SAS.

Illustration:

Case one: use R for eSUB Model 5

- Outputs comparison between SAS and R:
- Kaplan Meier Plot

Created
using R

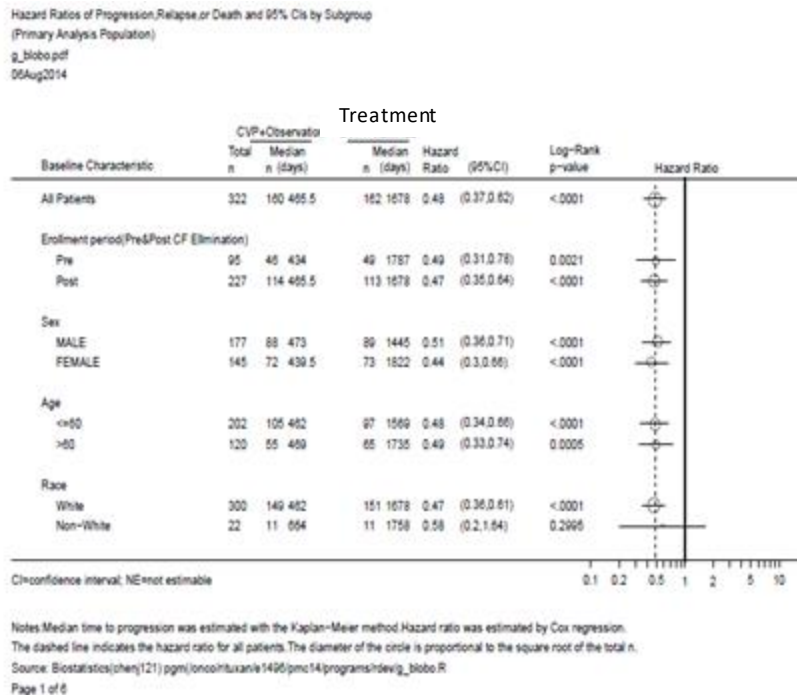


Created
using
SAS

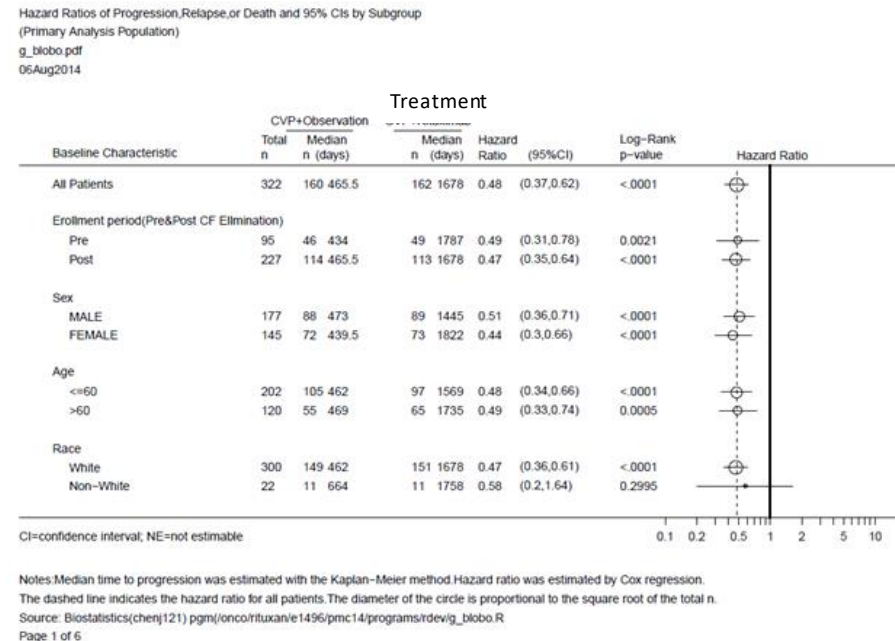
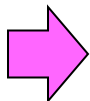
Illustration:

Case one: use R for eSUB Model 5

- Outputs comparison between SAS and R:
 - Forest Plot



Created
using R



Created
using
SAS



Illustration:

Case one: use R for eSUB Model 5

- Outputs comparison between SAS and R:

➤ Survival Table

```
Log-Rank Test for Equality and Hazard Ratios of Progression, Relapse, or Death  
(Primary Analysis Population)  
t_surv_test1.out  
06AUG2014
```

CVP + Observation versus CVP + Treatment	Log-Rank Test	Hazard Ratio	Cox Regression 95% CI	p-value[]
No stratification	<0.0001	0.483	(0.375,0.624)	<0.0001
Stratified by residual disease (minimal vs. gross) and histology (follicular vs. other)	<0.0001	0.481	(0.372,0.622)	<0.0001



Created using R

Note: Censoring time based upon date last known to be in remission/SD or date of last contact if date last known to be in remission/SD is missing.
[] The p-value is from PROC PHREG Wald Test using Efron's method for handling ties.

Source:Biostatistics(chenj121) pgm(/onco/rituxan/e1496/pmc14/programs/t_surv-test)

```
Log-Rank Test for Equality and Hazard Ratios of Progression, Relapse, or Death  
(Primary Analysis Population)  
t_surv-test1.out  
06AUG2014
```

Treatment	Log-Rank Test	Cox Regression		
		Hazard Ratio	95% CI	p-value[*]
CVP + Observation versus CVP + Rituximab				
No stratification	<.0001	0.483	(0.375, 0.624)	<.0001
Stratified by residual disease (minimal vs. gross) and histology (follicular vs. other)	<.0001	0.481	(0.372, 0.622)	<.0001

Created using
SAS

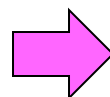


Illustration:

Case one: use R for eSUB Model 5

- Outputs comparison between SAS and R:
 - Laboratory Analysis Dataset
 - Output data set is in .xpt format (SAS version 5)
 - Used 'Proc compare' in SAS to compare the data produced by R and SAS

Illustration:

Case one: use R for eSUB Model 5

- Program Efficiency Comparison between SAS and R

	R	SAS
Condition Calculation	Loop Take long time	If .. then in data step Easy and fast
Change Data Structure (wide format to long format)	'reshape' function Easy and fast	Transpose Take some time
Select 'last' record	'order' and 'aggregate' function Two lines of code	Sort and last in steps Two data steps
Date format	'as.Date' function	Input function
Format and Label	'SASformat' and 'label' function	Format and label in data step
Xpt file	'write.xport' function One line code, but take long	Libname xport and proc copy Two steps

Illustration:

Case two: cooperate SAS with R for Exploratory analysis

- **Background:**

- Trend observed towards an increased risk of early death for subjects treated with anti-PD-1/PD-L1
- European Medicines Agency (EMA) requested to conduct exploratory analyses aiming to identify factors that could predict the likelihood of not benefiting from immunotherapy.
- Complex issue and no established predictive factors have been identified so far.
 - Include different products, indications, lines of treatment, biomarkers and diagnostic assays
 - Different cut-offs used for study inclusion or as stratification factors.

Illustration:

Case two: cooperate SAS with R for Exploratory analysis

- Analysis Plan

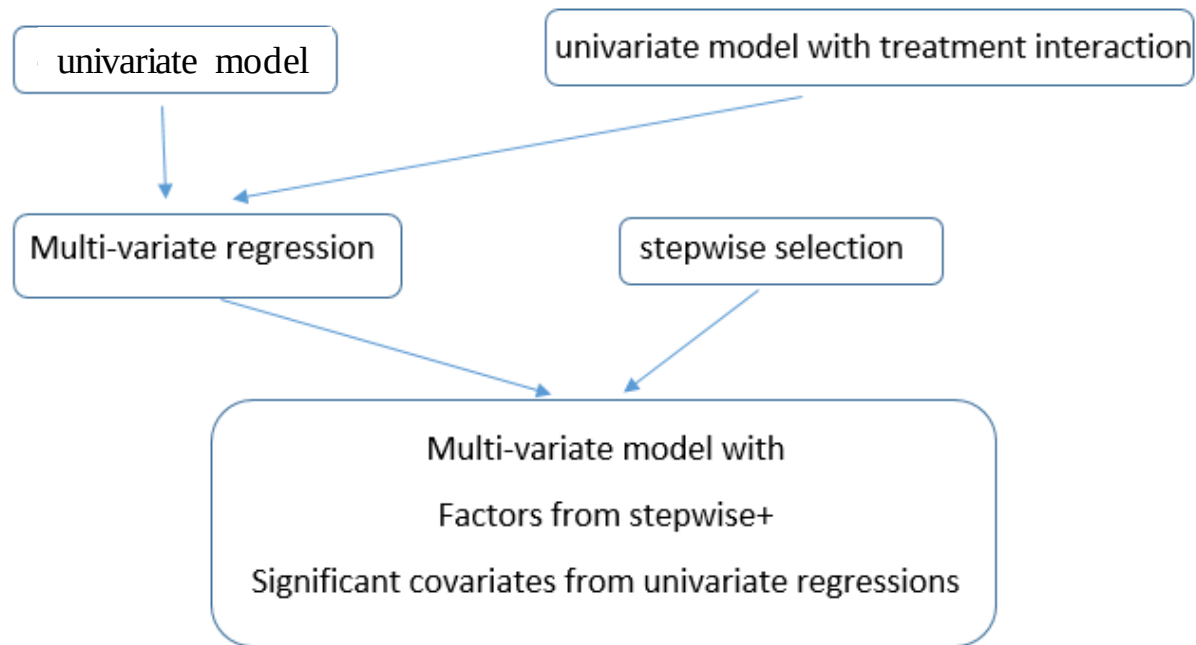
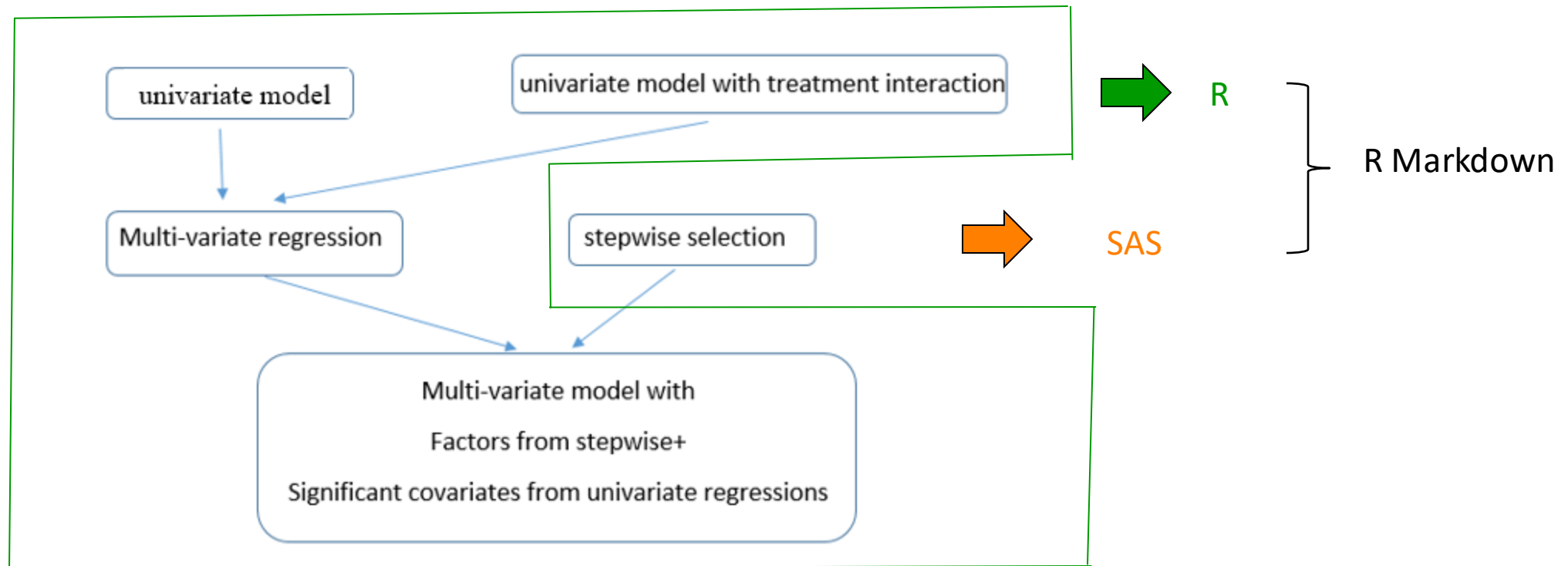


Illustration:

Case two: cooperate SAS with R for Exploratory analysis

- Analysis Execution



File Edit Code View Plots Session Build Debug Profile Tools Help

chenj121
Sessions
statsspa_515
R 3.5.3

Console Terminal R Markdown Jobs

```

.../programs/demo.rmd
$ warning: logi FALSE
$ results: chr "asis"

output file: demo.knit.md

/usr/lib/rstudio-server/bin/pandoc/pandoc +RTS -K512m -RTS demo.utf
8.md --to html4 --from markdown+autolink_bare_uris+tex_math_single_b
ackslash+smart --output demo.html --email-obfuscation none --self-co
ntained --standalone --section-divs --template /home/bceuser/chenj12
1/R/x86_64-pc-linux-gnu-library/3.5/rmarkdown/rmd/h/default.html --n
o-highlight --variable highlightjs=1 --variable 'theme:bootstrap' --
include-in-header /tmp/Rtmp1iBT0n/rmarkdown-stre287466aec2.html --ma
thjax --variable 'mathjax-url:https://mathjax.rstudio.com/latest/Mat
hJax.js?config=TeX-AMS-MML_HTMLorMML' --lua-filter /home/bceuser/che
nj121/R/x86_64-pc-linux-gnu-library/3.5/rmarkdown/rmd/latex-div.lua
Now removing local cache ...
Nothing to remove ...
Bye bye...

Output created: demo.html

```

Environment History Connections Git

Import Dataset

Global Environment

Environment is empty

demo.R
Source on Save
Run
Source

```

1 library(tidyverse)
2 library(knitr)
3 library(kableExtra)
4 library("survival")
5 library(papeR)
6 library(stringr)
7
8
9
10
11 options(scipen=999)
12 SAICE::initialize_connection(entimice_env = "PROD")
13 path<-'root/clinical_studies/R05541267/share/pool_SAGO_2019/qa/outdata_vad/'
14 ATE = SAICE::read_entimice(paste0(path, "ate.sas7bdat"))
15 ASL = SAICE::read_entimice(paste0(path, "aslada.sas7bdat"))
16 alb = SAICE::read_entimice(paste0(path, "alb_211.sas7bdat"))
17
18 SAICE::close_connection()
19 #alb<-read_bce('/opt/BIOSTAT/prod/cdt3840p/s29294h/libraries/alb.sas7bdat')
20
21
22 #select analysis data
23 asl<-ASL[ASL$STUDYID=='G029294',]
24 ate<-ATE[ATE$STUDYID=='G029294',]
25
26 #derive new variables
27 ldh<-alb[alb$PARAMCD=='LDH' & alb$ABLFL=='Y',]
28 ldh$ldhuln<-ifelse(ldh$AVAL >= 1.5*ldh$LBSTNRHI,"__Baseline LDH >= 1.5ULN","__Baseline LDH < 1.5ULN")
29 ldh<-ldh[c("USUBJID", "ldhuln")]
30
31

```

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New Folder Upload Delete Rename More

Home
R
statsspa_515
programs

Name	Size	Modified
cox_v2.pdf	95.1 KB	May 31, 2019, 2:32 PM
cox_v2.Rmd	17.9 KB	May 31, 2019, 2:26 PM
cox_v2.R	0.7 KB	May 31, 2019, 10:34 AM



Conclusion:

- R is capable to make submission standard products.
- Making the advantages from open source and SAS can speed up submission activities.
- Learning the features from different tools and using the right tool in the right situation
- Connect to new concepts, advanced theories, mature skills, and provide smarter analysis.

Acknowledgement

- Laura Harris
- Will Harris
- Aditi Qamra

***Doing now what patients need
next***