

Good Cooperation Between SAS and R for Regulatory Submission

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Objects

- Why to make SAS and R cooperate for submission work
- Illustration:
 - case one: to prove R can make submission ready products
 - Example from SUB Model 5
 - Comparison
 - case two: cooperate SAS with R for Exploratory analysis
 - Exploratory analysis request from EMA
 - Analysis Plan
 - Demo for 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

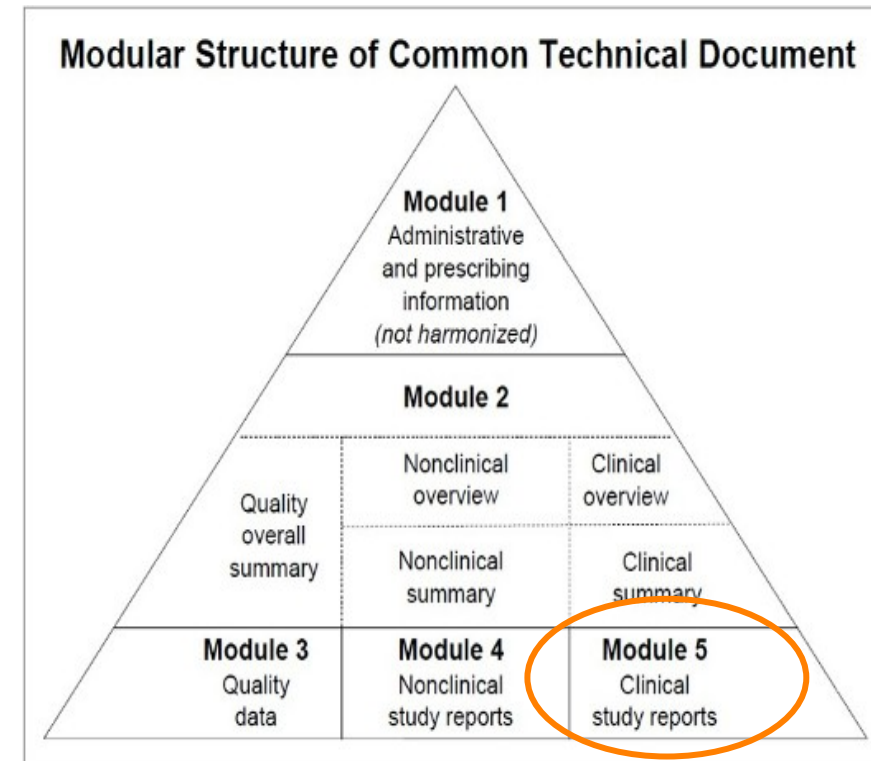


Illustration:

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:

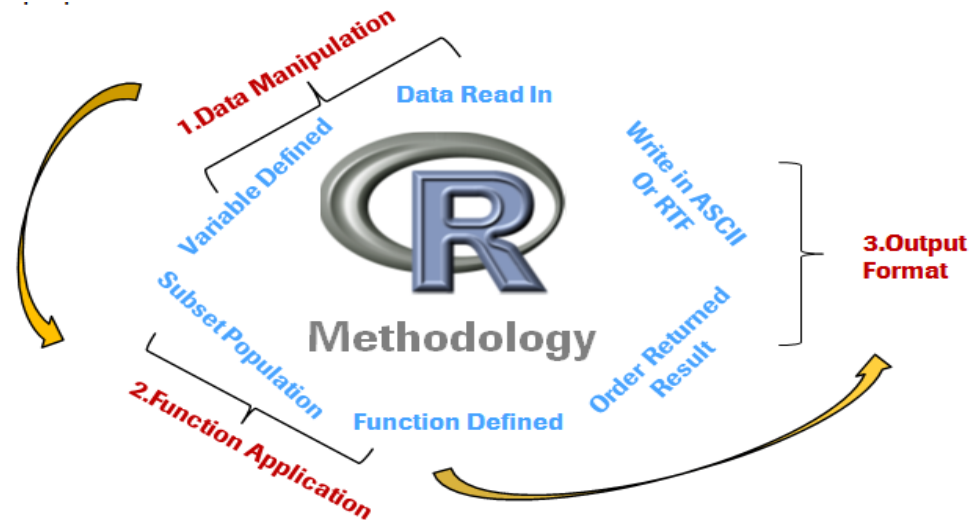


Illustration:

Case one: use R for eSUB Model 5

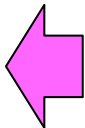
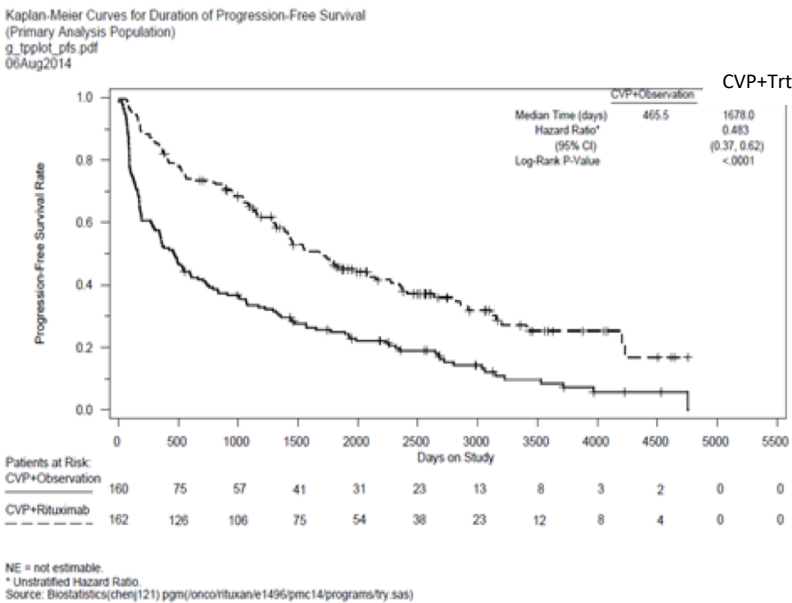
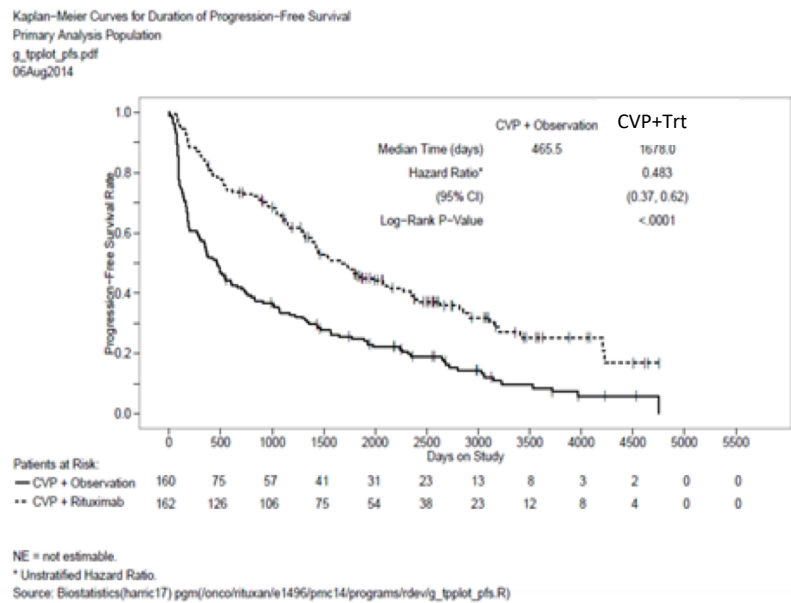
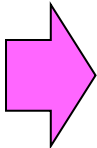
- **Quality Control Process**
 - Double program in traditional way, and applied company standard quality control process .
 - Compare outputs from R and SAS.
 - Use SAS program to compare submission dataset made by R and SAS.

Illustration:

Case one: use R for eSUB Model 5

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

Made
By
R



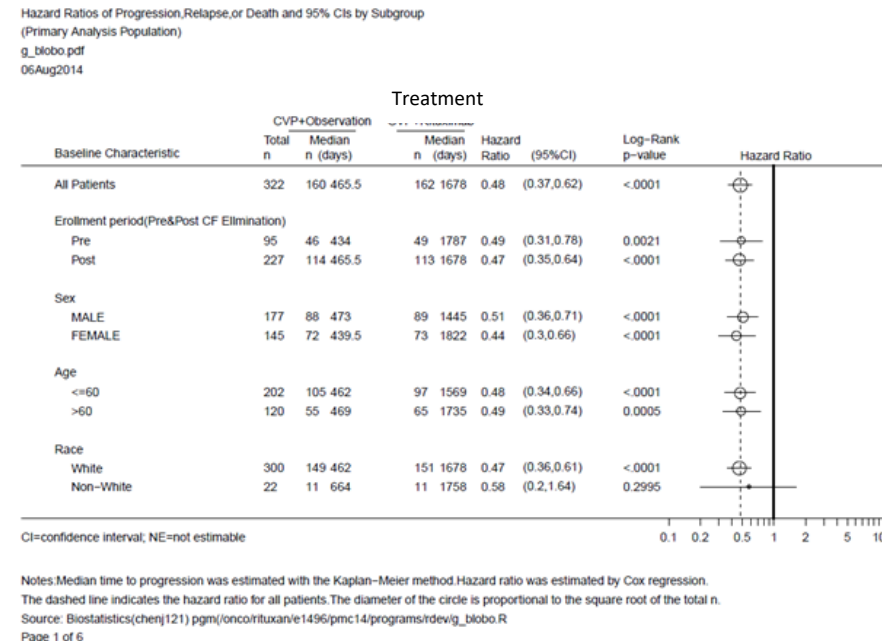
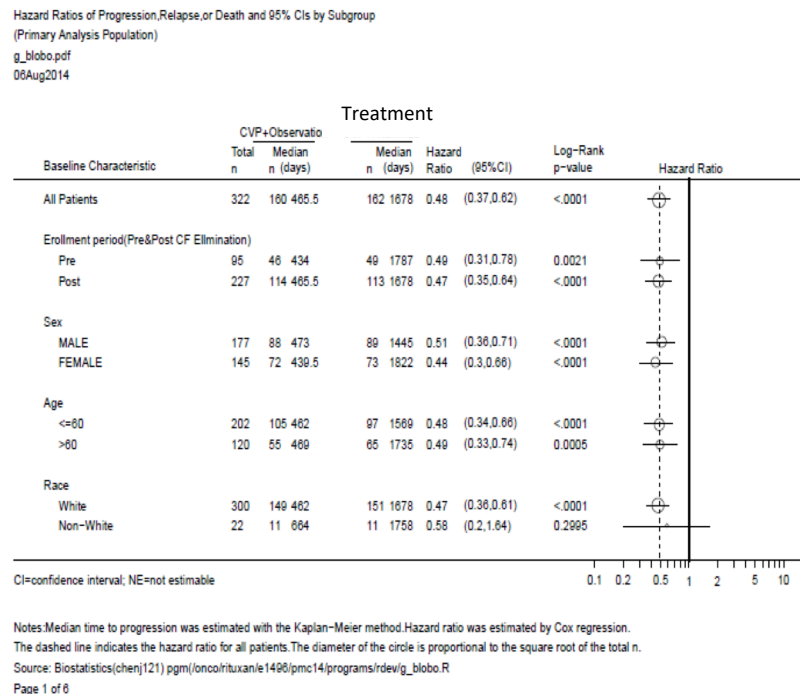
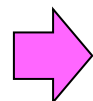
Made
By
SAS

Illustration:

Case one: use R for eSUB Model 5

- Outputs comparison between SAS and R:
- Forest Plot

Made
By
R



Made
By
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
(PPrimary 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

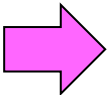


Made by R

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)

Made by SAS



```
Log-Rank Test for Equality and Hazard Ratios of Progression, Relapse, or Death
(PPrimary 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

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

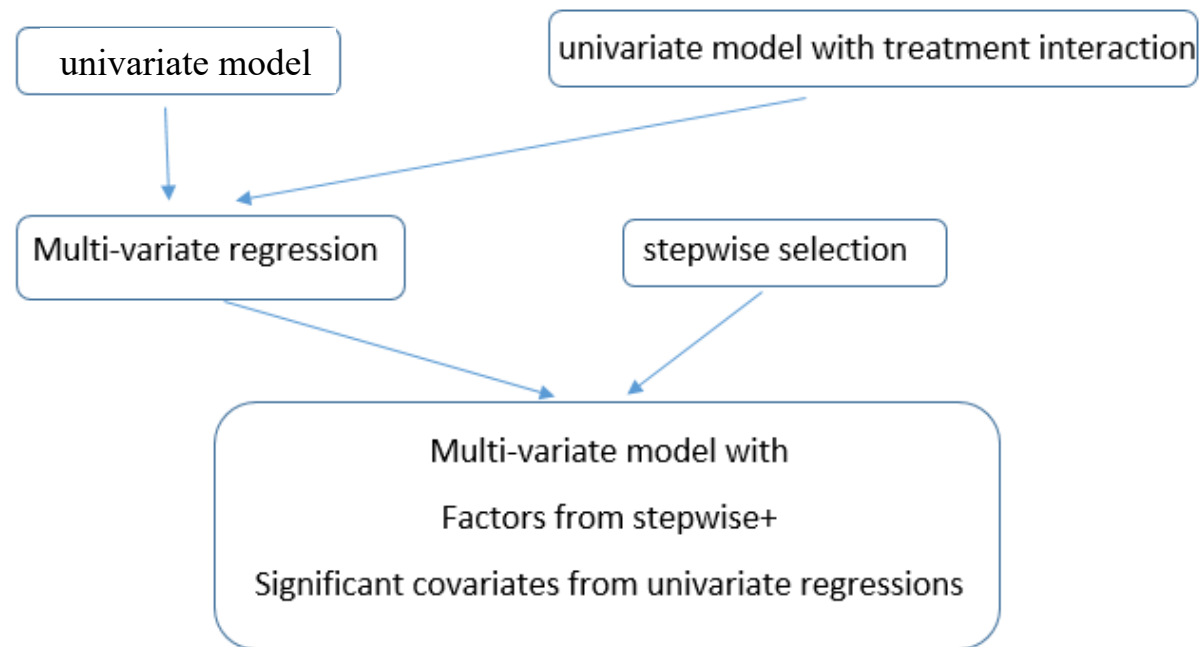
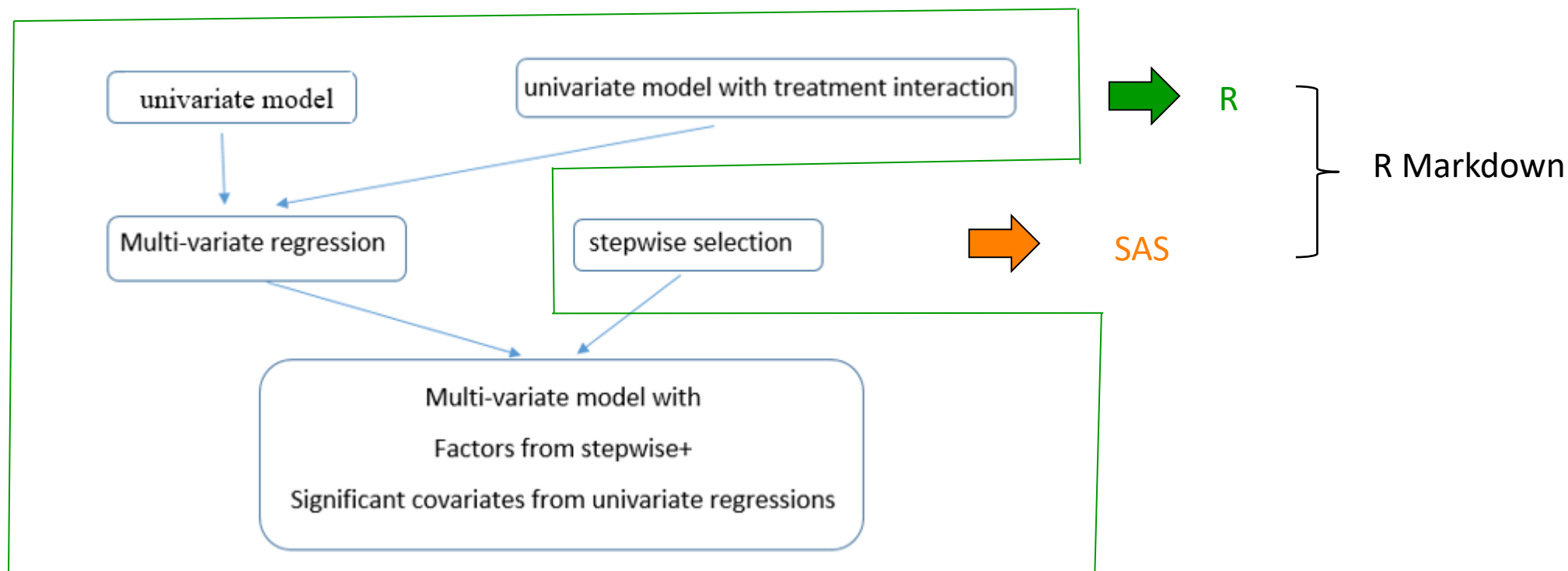


Illustration:

Case two: cooperate SAS with R for Exploratory analysis

- Analysis Execution



The screenshot shows the RStudio interface with the following components:

- Console:** Displays the output of the R script. It shows a warning about the logi variable, the results of the chr variable, and the creation of the demo.html file. The output file is demo.knit.md.
- Source Editor:** Shows the R code used for the analysis. The code includes library loading (tidyverse, knitr, kableExtra, survival, papeR, stringr), path setting, and data reading from the SAICE database. It also shows the creation of new variables (ldh, ldh_hu1n) and the generation of the HTML report.
- Environment Pane:** Shows the current working directory and the files created. The files listed are cox_v2.pdf, cox_v2.Rmd, and cox_v2.R.



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***