PharmaSUG 2023 - Paper RW-322

Novel Applications of Real World Data (RWD) in Clinical Trial Feasibility

Sherrine Eid, MPH, Samiul Haque, PhD, and Robert Collins, SAS Institute, Inc.

ABSTRACT

INTRODUCTION: Today Real World Evidence (RWE) derived from Real World Data (RWD) is essential to explore target patient populations (TPP) and more accurately inform robust initial trial hypotheses and expected performance. Applying RWD creates more patient-centric protocols, identifies and reduces operational risk and development costs, while also increasing the likelihood of regulatory approval and patient retention.

METHODS: Three scenarios of conventional and novel methods of informing target patient populations intended for Phase II and III clinical trials were explored and compared on overall population counts, demographic and baseline characteristic distributions, and scientific robustness using SAS Viya and Python. The first scenario (STRINGENT) implements a conventional approach where a subject matter expert defines the study TPP based on expertise and literature. The second scenario (RELAXED) leverages RWD with a subject matter expert to determine the impact of removing an exclusion criterion on the patient count, as well as the scientific robustness of the study. The third scenario (ML+SME) leverages RWD and machine learning algorithms to determine the role and importance of comorbidities in defining the eligibility criteria.

RESULTS: The results showed that relaxing eligibility criteria in the RELAXED scenario increased the population count without compromising the scientific robustness of study outcomes. Although, machine learning algorithms in the ML+SME scenario revealed potentially additional exclusion criteria and smaller counts, it suggested a more precise TPP, which would yield less attrition, greater retention, and more efficient trial operations.

CONCLUSION: RWE is a necessary and critical factor in assessing clinical trial feasibility.

INTRODUCTION

Today Real World Evidence (RWE) derived from Real World Data (RWD) is essential to explore target patient populations (TPP) and more accurately inform robust initial trial hypotheses and expected performance. Applying RWD creates more patient-centric protocols, identifies and reduces operational risk and development costs, while also increasing the likelihood of regulatory approval and patient retention.

METHODS

Three scenarios of conventional and novel methods of informing target patient populations intended for Phase II and III clinical trials were explored and compared on overall population counts, demographic and baseline characteristic distributions, and scientific robustness using SAS® Viya®, SAS® Cohort Builder, R and Python.

Figure 1 illustrates the process to using RWD for clinical trial feasibility.

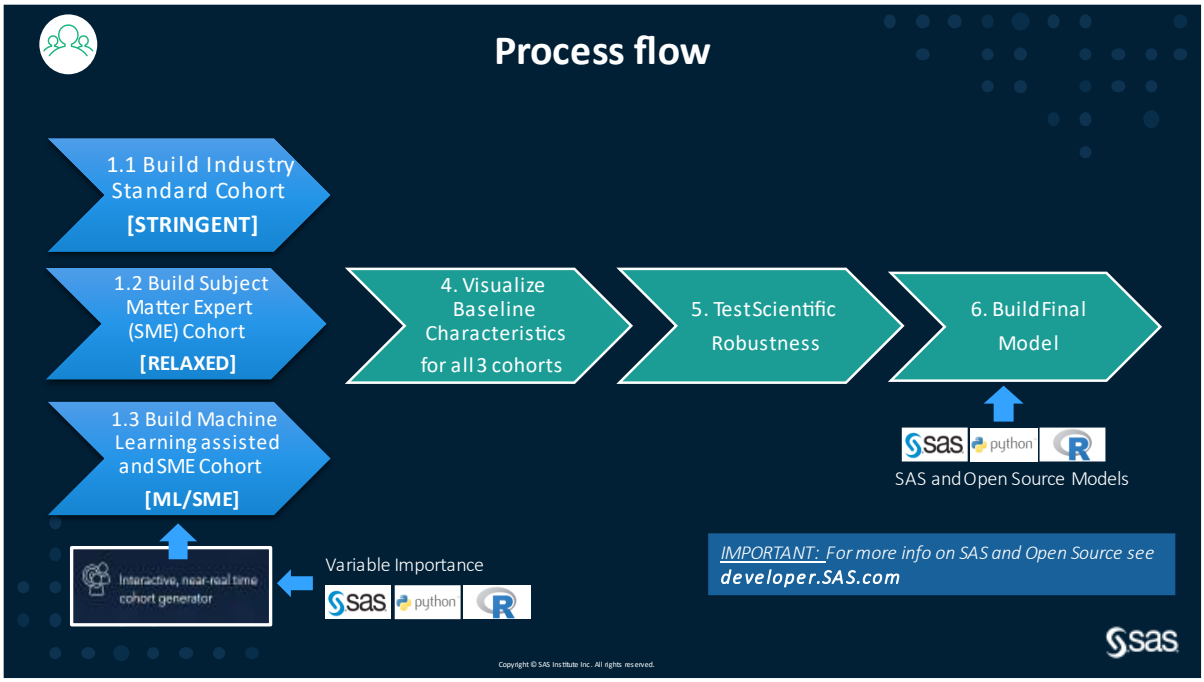
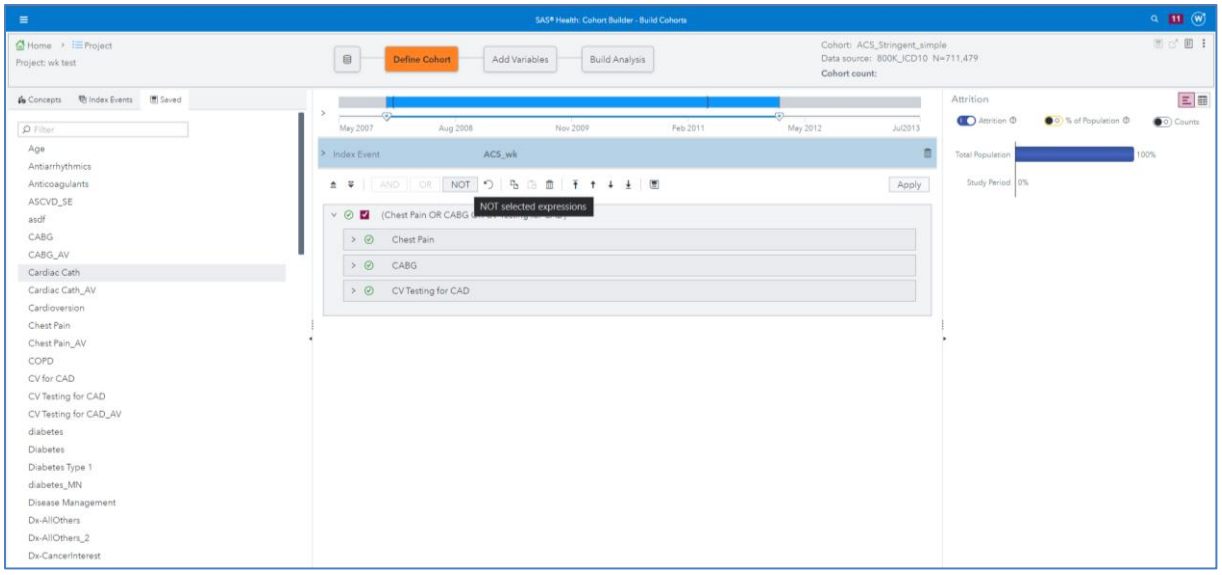


Figure 1 Process Flow of Leveraging Clinical Trial Feasibility

This process yields a multifaceted approach to data-driven clinical operations. Clinical Trial Operations professionals goal is to minimize risk to the patient and risk to the process. These teams are then able to identify opportunities to expand eligibility criteria (RELAXED) versus recruiting a more precise (ML+SME) and fewer potential eligible patients. Both approaches have potential impact on patient recruitment and patient retention, limiting potential protocol amendments. SAS® Viya allows researchers to develop and execute code in SAS, R, Python and other opensource languages).

DEFINE, BUILD AND ANALYZE A COHORT

The first scenario (STRINGENT) implements a conventional approach where a subject matter expert defines the study TPP based on expertise and literature. SAS® Cohort Builder was used to build a TPP using RWD that was registered on the platform. Inclusion and exclusion criteria were defined as concepts using a sophisticated combination of ICD-10 codes, HCPCS Procedure Codes, and ICD-10 Procedure Codes to determine eligibility for clinical trial participation. All Acute Coronary Syndrome patients who had a newly assigned ICD-10 diagnosis code of I24.* were included and any of those initial patients who also had a Coronary Artery Bypass Graft (CABG) or Stress test procedure or a Chest Pain diagnosis (ICD-10= R07.*) were excluded.



Display 1 Defining "Stringent" TTP using SAS® Cohort Builder

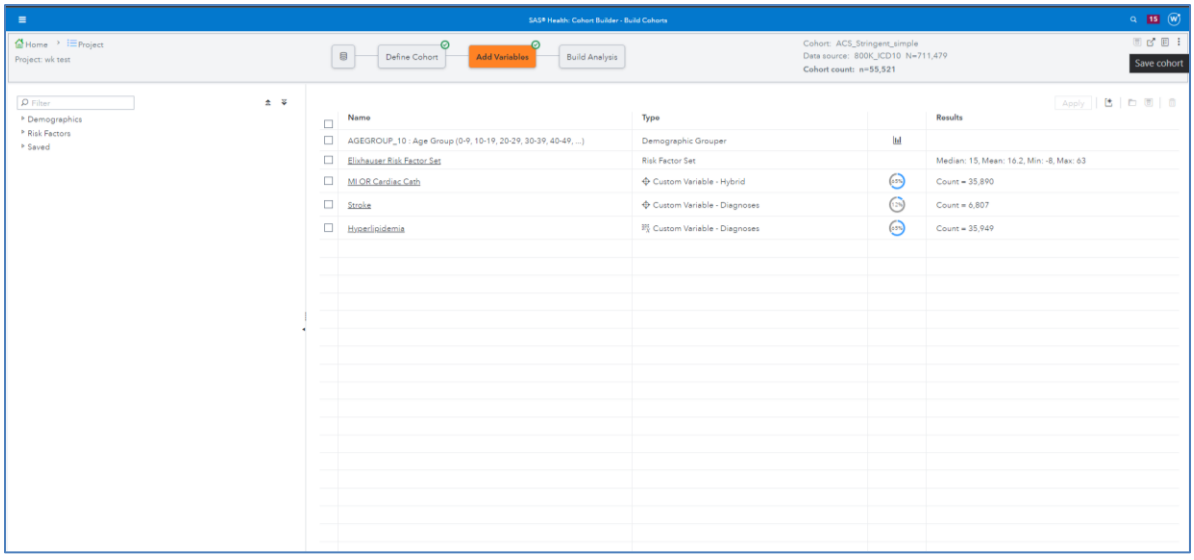
Since this work also tested the scientific robustness of the TTP definition, analysis variables -namely all endpoints and covariates- were also defined and included in this scenario as shown in Display 2.

Covariates included:

1. Ten year age groups
2. Elixhauser Comorbidity Risk Score
3. Hyperlipidemia (ICD-10 E78.5)

Endpoints included:

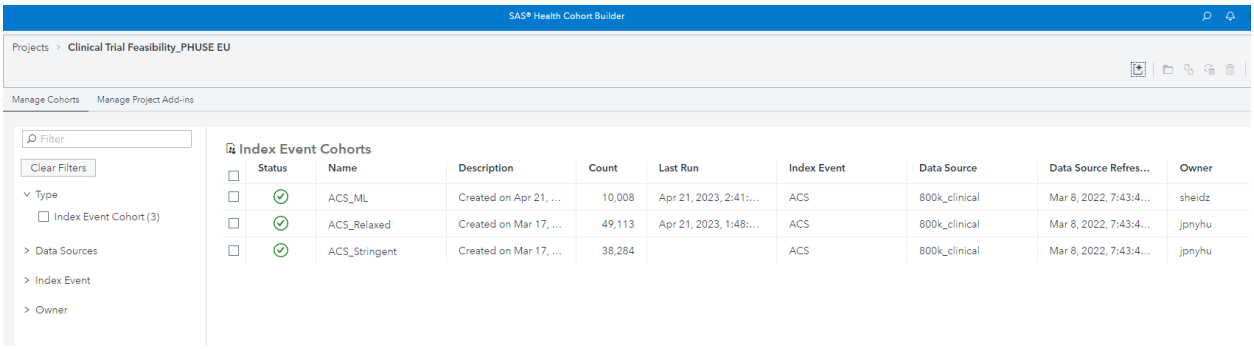
1. Stroke
2. Myocardial Infarction or Cardiac Catheterization



Display 2 Building Covariates and Endpoints to Test the Scientific Robustness

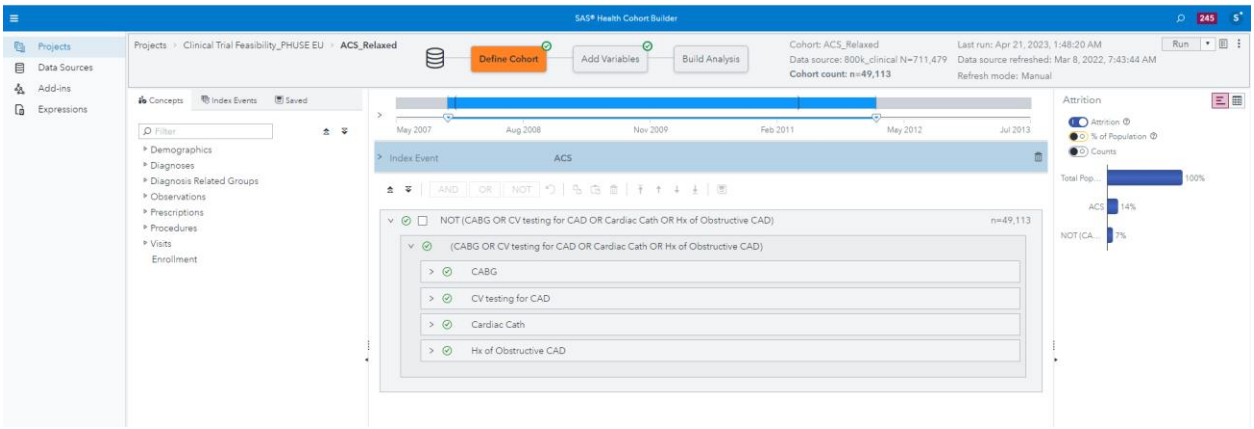
Display 3 illustrates the three TPP and their respective patient count. Notice that the RELAXED yielded more than 10,000 more patients than the STRINGENT TPP. However, the ML+SME TPP yielded a notably smaller patient

count.



Display 3 Building Three Separate TPP Scenarios

Display 4 shows how the second scenario (RELAXED) leverages RWD with a subject matter expert to determine the impact of removing an exclusion criterion -chest pain (ICD-10= R07.9)- on the patient count, as well as the scientific robustness of the study. Display 4 shows the second cohort with RELAXED criteria. Note that the N with RELAXED is greater than the patients who meet the STRINGENT eligibility in the near future.



Display 4 TTP with Relaxed Criteria

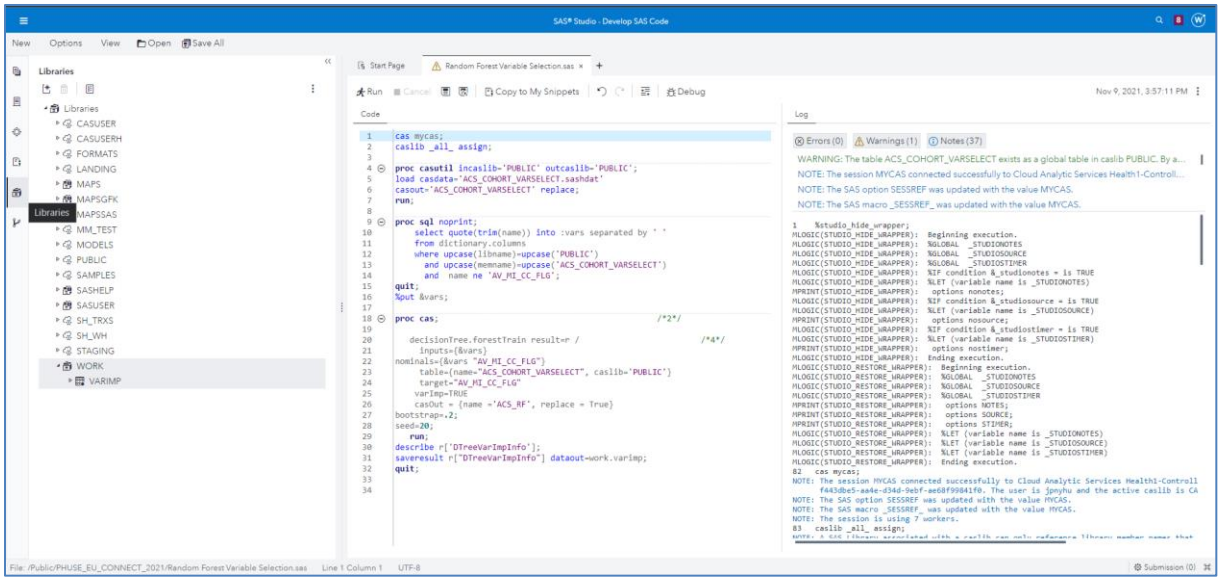
The third scenario (ML+SME) leverages RWD and machine learning algorithms to determine the role and importance of comorbidities in defining the eligibility criteria.

IDENTIFY VARIABLE IMPORTANCE WITH MACHINE LEARNING

A data-driven approach to select the eligibility criteria related to the outcome of interest by the support of machine learning analyses and SME and how will that impact the cohort is a novel approach to determine potential confounding or precision variables.

USE ML IN SAS

Leveraging SAS® Studio, CAS Actions for a Random Forest model were executed to determine potentially new eligibility criteria.



Display 5 SAS(R) Code of Random Forest Model to Determine Variables of Importance

USE ML IN R

The variable importance (ranking) can be observed in the Console by entering “results$DTreeVarImpInfo” to see CAS data frame object using R as seen in Display 6.

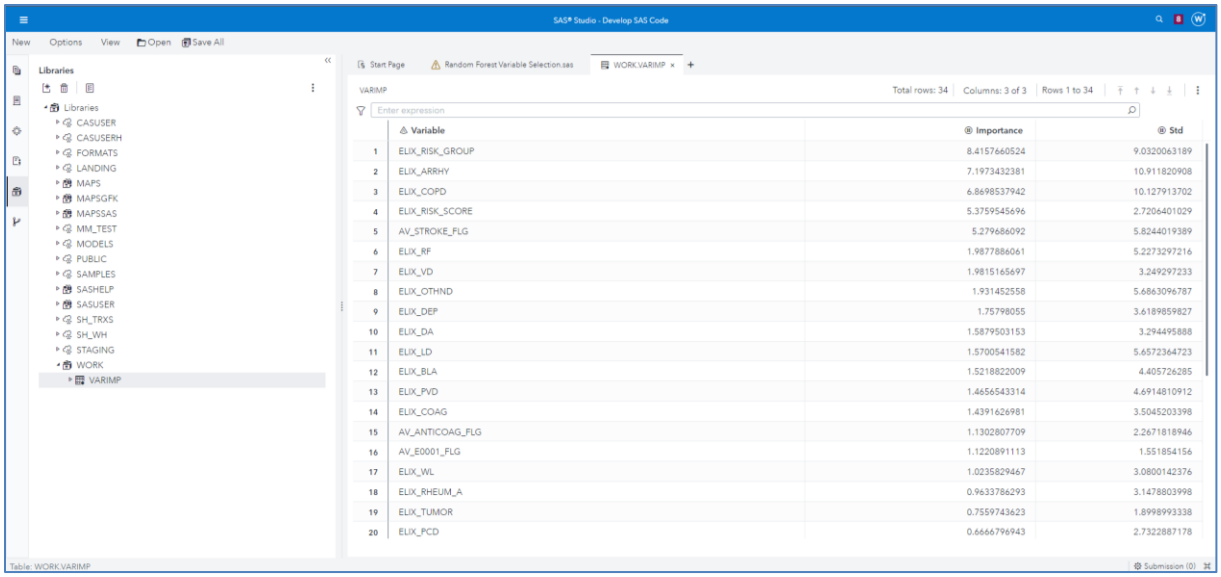
```
library(swat)
#library(getPass)
library(tidyr)

Sys.setenv(CAS_CLIENT_SSL_CA_LIST="/opt/sas/viya/config/etc/SASSecurityCertificateFramework/cacerts/
session<-CAS("Health1-Controller.azure.com",5570,username="***",password="***")

```

Display 6 R SWAT Package to Determine Variables of Importance

USE ML IN PYTHON

The variable importance (ranking) can be observed in Jupyter Notebook using Python code to execute a Random Forest Model using SWAT as shown in Display 7.

Display 7 Python SWAT Package to Determine Variables of Importance

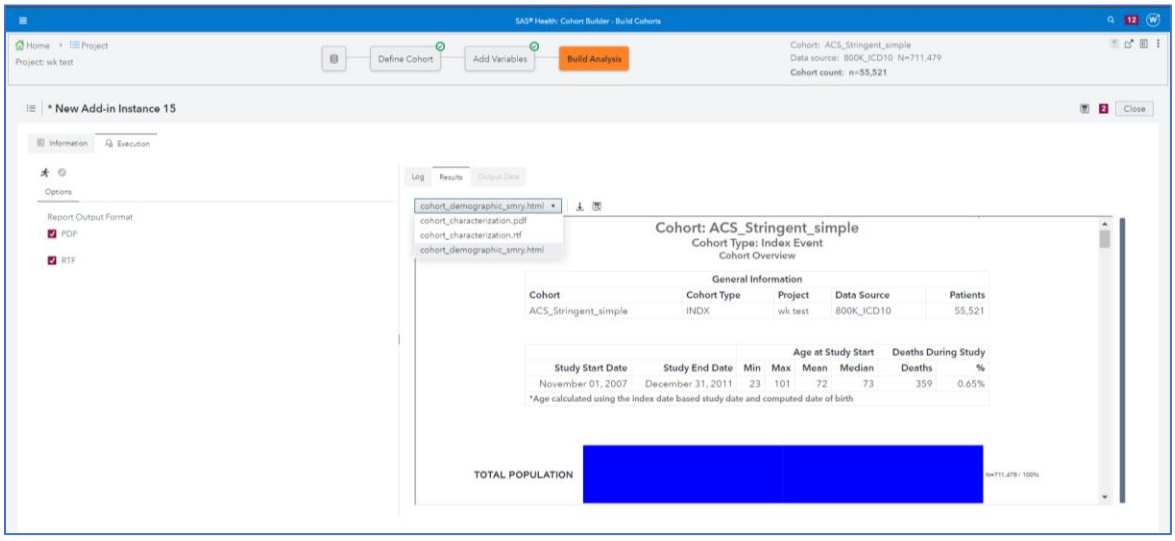


	Variable	Importance	Std
1	ELIX_RISK_GROUP	8.4157660524	9.0320063189
2	ELIX_ARRHY	7.1973432381	10.911820908
3	ELIX_COPD	6.8698537942	10.127913702
4	ELIX_RISK_SCORE	5.3759545696	2.7206401029
5	AV_STROKE_FLG	5.279686092	5.8244019389
6	ELIX_RF	1.9877886061	5.2273297216
7	ELIX_VD	1.9815165697	3.249297233
8	ELIX_OTHND	1.931452558	5.6863096787
9	ELIX_DEP	1.75798055	3.6189859827
10	ELIX_DA	1.5879503153	3.294495888
11	ELIX_LD	1.5700541582	5.6572364723
12	ELIX_BLA	1.5218822009	4.405726285
13	ELIX_PVD	1.4656543314	4.6914810912
14	ELIX_COAG	1.4391626981	3.5045203398
15	AV_ANTICOAG_FLG	1.1302807709	2.2671818946
16	AV_E0001_FLG	1.1220891113	1.551854156
17	ELIX_WL	1.0235829467	3.0800142376
18	ELIX_RHEUM_A	0.9633786293	3.1478803998
19	ELIX_TUMOR	0.7559743623	1.8998993338
20	ELIX_PCD	0.6666796943	2.7322887178

Display 8 Variable of Importance Output from ML Models

VISUALIZE AND INTERPRET FINDINGS

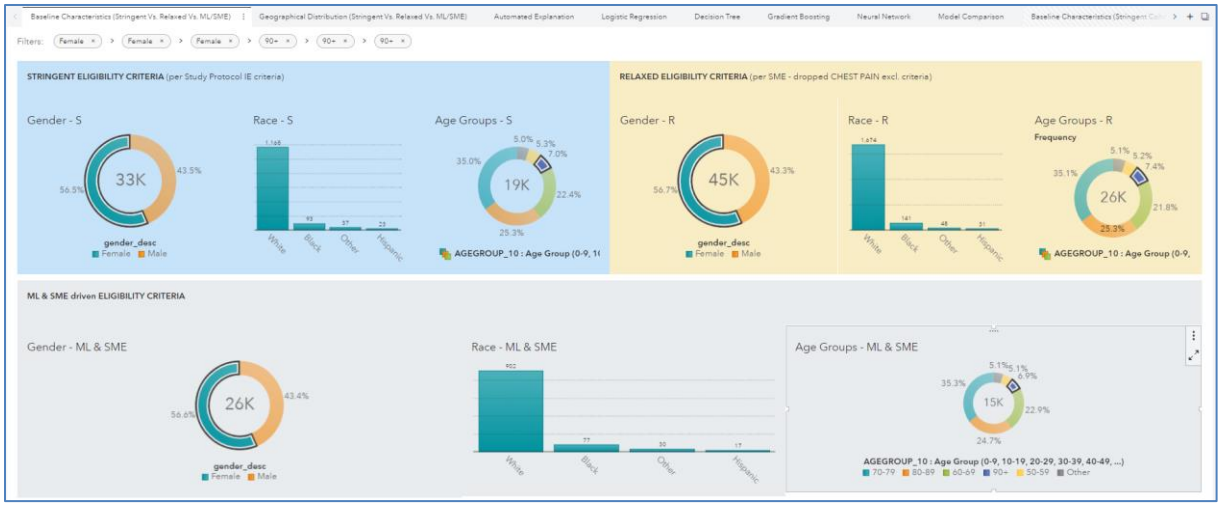
Once each TPP is built in SAS® Cohort Builder, Cohort Characterization reports were executed on each one to assess demographic and geographic distribution between them. Display 9 illustrates the Cohort Characterization report for the STRINGENT TPP.



Display 9 Cohort Characterization Report

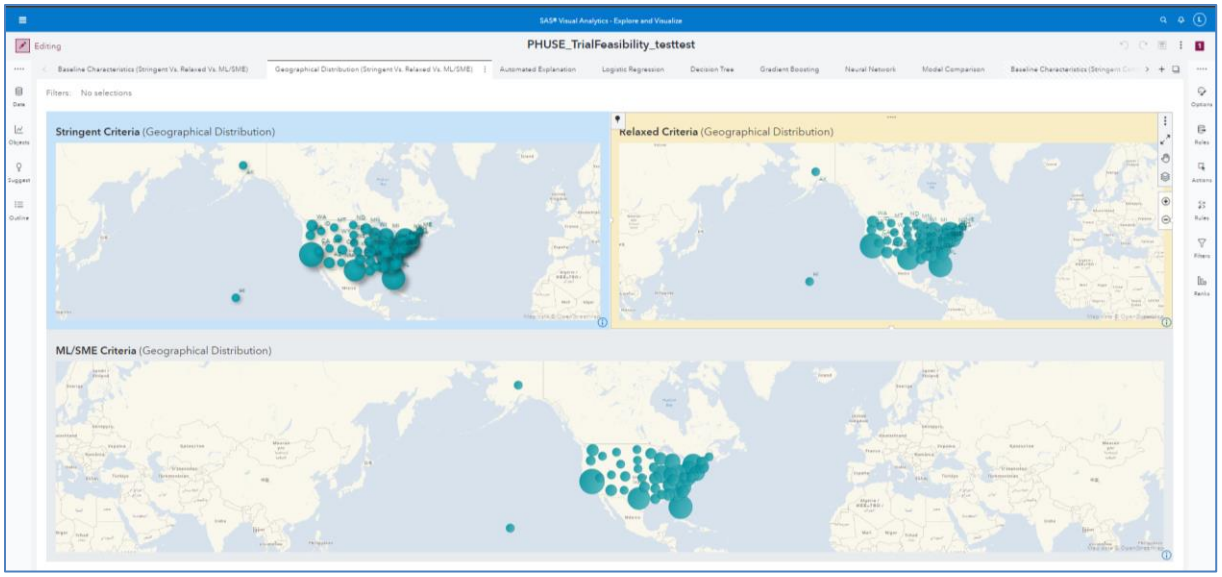
COMPARE BASELINE DATA

Once each cohort was built, baseline demographic characteristics were visualized and compared. Descriptively, if the cohorts were not comparable, this would indicate a potential bias and potentially introduce yet more error. Display 10 illustrates the visual analysis of the three cohorts and demonstrates no major demographic differences between them.



Display 10 Comparing Baseline Characteristics of Each Cohort

Display 11 demonstrates the ease with which clinical operations teams can identify potential sites for patient recruitment based on the geographic distribution of the patients.



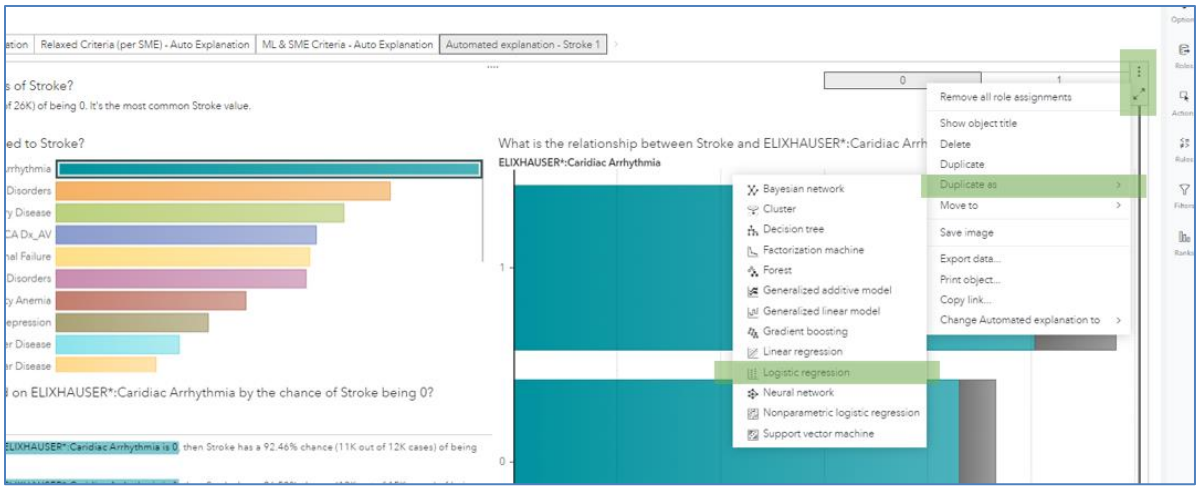
Display 11 Comparing Geographic Distribution of Each Cohort

TEST SCIENTIFIC ROBUSTNESS

The risk of removing stringent exclusion criteria such as “chest pain” is that noise has now been introduced to the analysis. This inherently increases bias and, subsequently, increases error. Thus, introducing noise requires the team to assess the impact to the scientific robustness of the study. There is a chance that the noise could compromise the scientific robustness of the study, yielding it obsolete despite the larger pool of patients that could potentially enroll in the study.

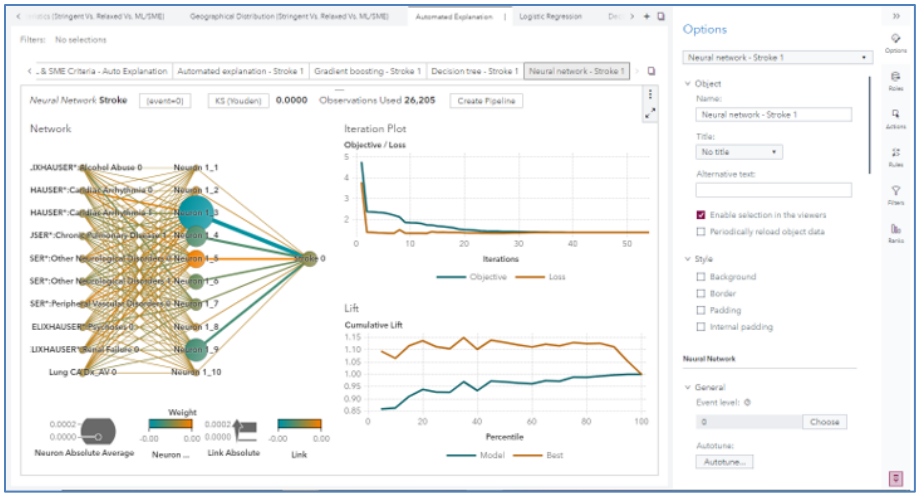
Display 12 illustrates the first step in exploring this impact. The statistical analysis plan may have called for an “industry standard” predictive analytic such as a logistic regression to test the adjusted likelihood of the primary or secondary endpoint -stroke or MI or Cardiac Catherization. SAS®’ Automated explanation allows quick and robust machine learning and natural language generation (NLG) ‘out of the box’ to determine which factors (variables) are most important in predicting the outcome “MI or Cardiac Cath”.

SAS® Viya eases the burden of exploratory analyses by allowing researchers to duplicate a logistic regression as another predictive or machine learning analytic with the same target variable and parameters with auto hypertuning as shown in Display 13 and Display 14.



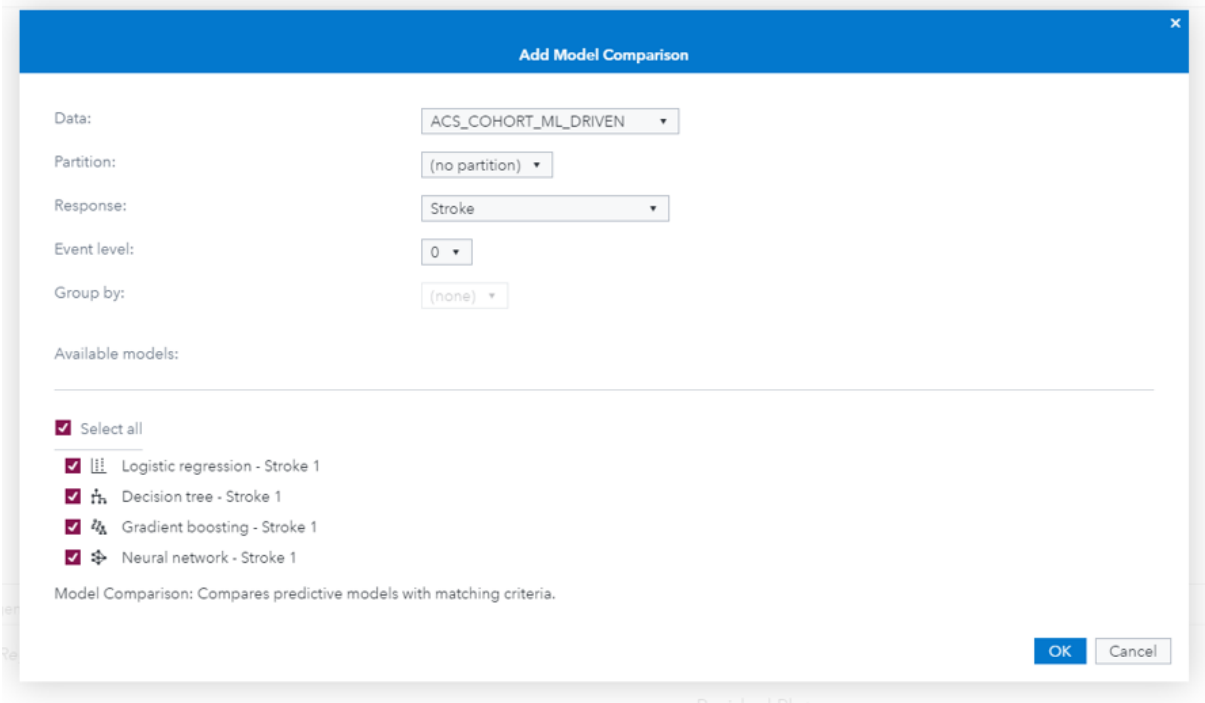
Display 12 Exploratory Impact Analysis Using Automated Explanation

Display 13 Duplicated Automated Explanation as a Logistic Regression



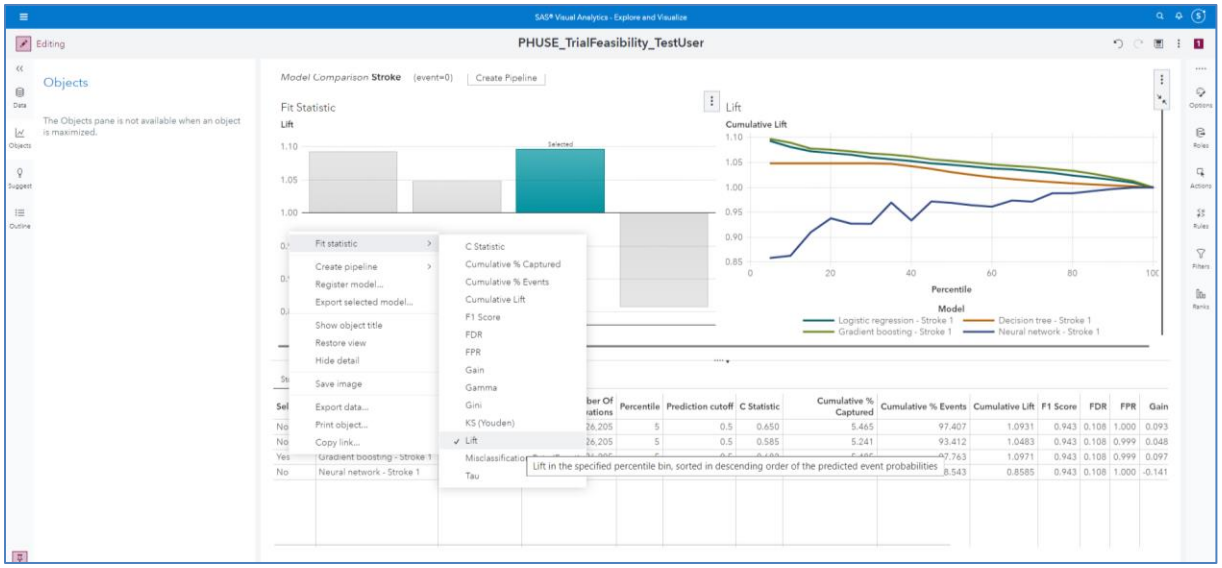
Display 14 Duplicated Logistic Regression as a Neural Network

Once we were able to explore various predictive and ML analyses to assess the scientific robustness of the study with RELAXED or ML+SME criteria defining the TPP, all the models were compared to identify the best fit model based on the fit statistic of choice. Display 15 illustrates the ease with which the models were compared.



Display 15 Comparing Models to Determine the Best Fit Model

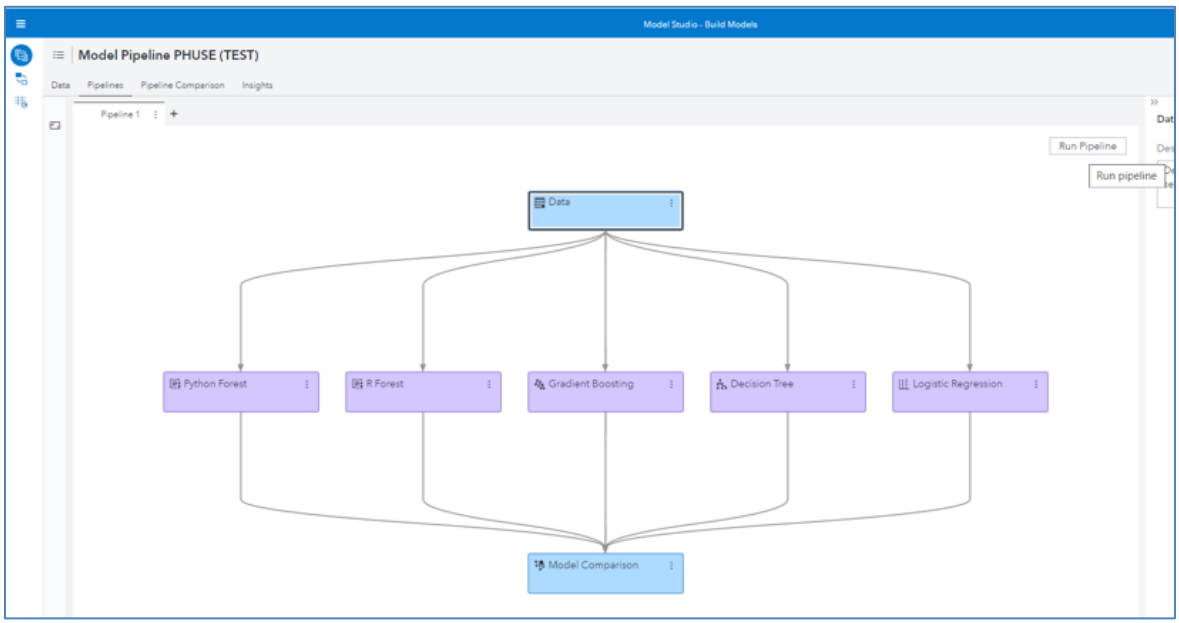
Display 16 demonstrates the interface through which an appropriate fit statistic is selected.



Display 16 Determine the Best Fit Statistic

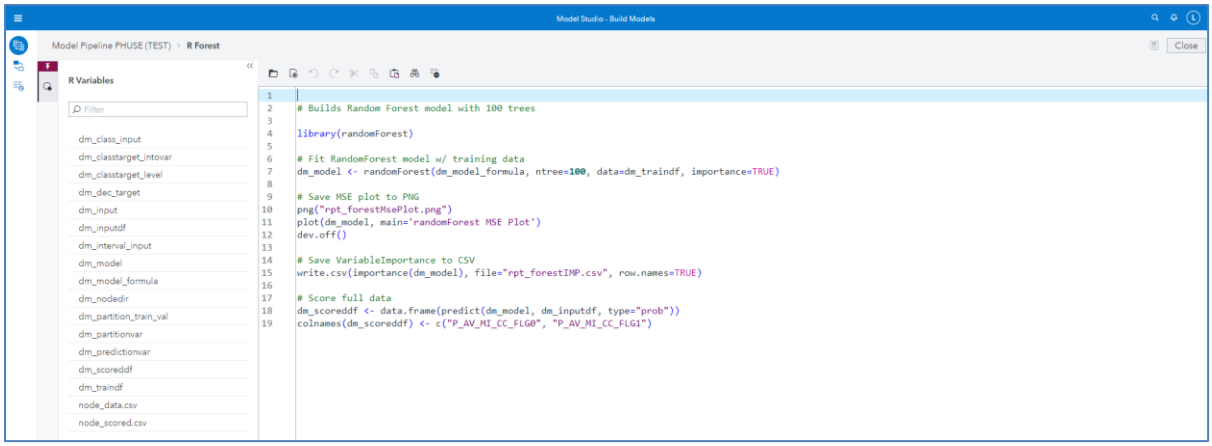
BUILD FINAL MODELS AND INTEGRATE

Once the best fit models were identified, a model pipeline was built to be repeated deployed as needed. Display 17 shows the model pipeline developed for this work. It includes all data that were used in executing the models, all of the models tested, including the R Random Forest Model, and the Model Comparison results. Each node is interactive and allows users to navigate to the appropriate interface or step within each to further edit or execute.



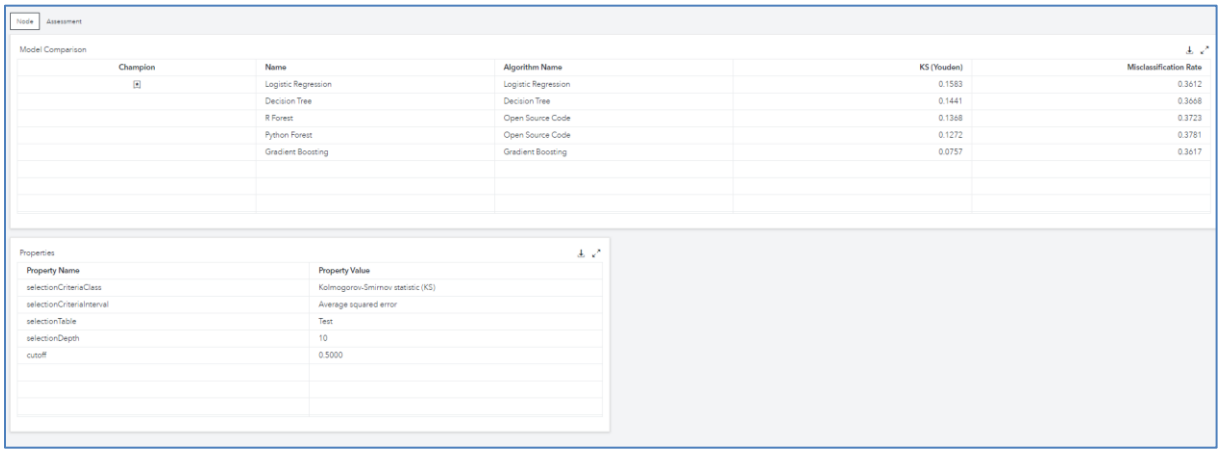
Display 17 Model Pipeline

Display 18 demonstrates what users will find when the R Random Forest model node is clicked and entered. R Studio is opened and shows the code to edit or modify.

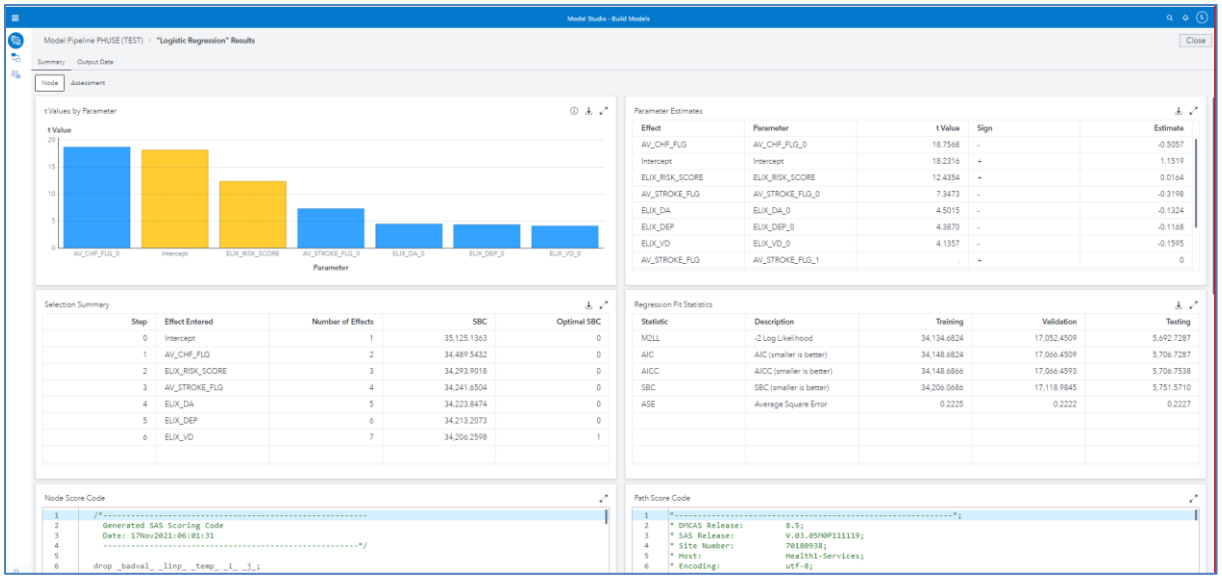


Display 18 R Random Forest Node Exploration

The model comparison yielded that the Logistic Regression was the best fit model for these data shown in Display 19. Researchers can dive more deeply into this node to understand the magnitude of impact and specific parameter estimates as seen in Display 20.

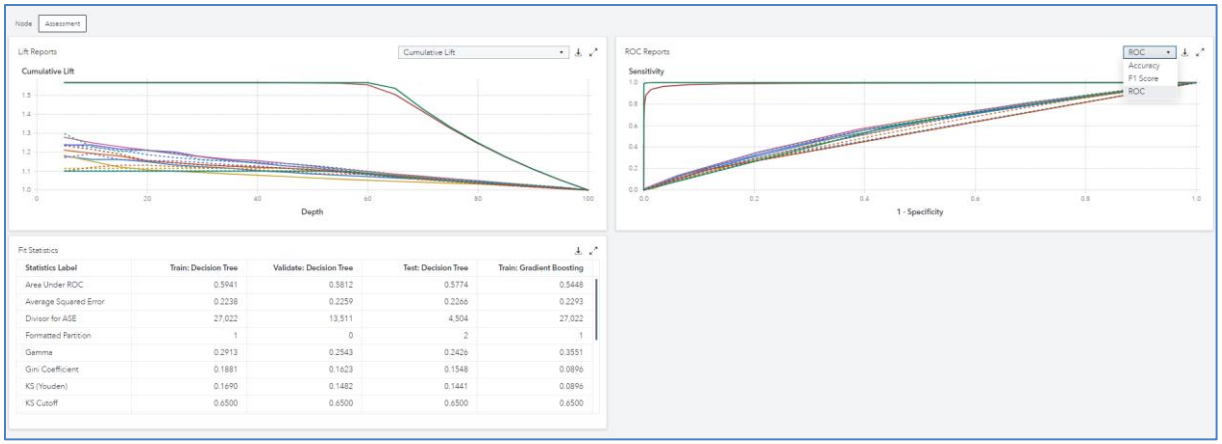


Display 19 Model Comparison Details



Display 20 Logistic Regression Details

Display 21 shows the model comparison assessment of various fit statistics and their respective parameters.



Display 21 Model Comparison Fit Statistics Assessment

RESULTS

The results showed that relaxing eligibility criteria in the RELAXED scenario increased the population count without compromising the scientific robustness of study outcomes. Although, machine learning algorithms in the ML+SME scenario revealed potentially additional exclusion criteria and smaller counts, it suggested a more precise TPP, which would yield less attrition, greater retention, and more efficient trial operations.

CONCLUSION

This body of work reflects the growing importance of the role that RWD and RWE play in clinical trials. Although no scientific robustness was compromised, it seemed that the age-old quandary of quantity (RELAXED) versus quality (ML+SME) presents itself in clinical trial operations. There is no doubt that using RWD is critical to clinical trial operations to reduce risk to patients and to the process. For example, using RWD, clinical operations teams are better able to assess probability of success after determining

the best TPP based on real patients. Not only are patient counts and demographic and geographic distributions assessed, but also scientific robustness and statistical methods assessments are easily and routinely executed based on the data and the therapeutic area. The authors expect only more utility of RWD in clinical trial operations focusing on feasibility, probability of success, patient counts, diversity, equity and inclusion planning and execution and assessment of scientific robustness as noise is introduced. This new information will mitigate risk to patients and processes, lower cost and expedite precise clinical trials.

CONTACT INFORMATION

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

Sherrine Eid
SAS Institute, Inc
Sherrine.Eid@sas.com