

A series of horizontal bars of varying lengths and colors (teal, blue, and dark blue) are positioned on the left side of the slide, creating a modern, abstract background element.

RW₀₂ - Addressing industry disruptions in Clinical Trials with Real World Data in lieu of COVID₁₉

Sherrine Eid, Stijn Rogiers, Robert Collins



COVID-19

Impact on Clinical Trials

COVID-19

Impact on Clinical Trials

Companies with affected trials, by size

Number of companies that have reported trial impacts

Small biotech

54 companies

Mid-sized biotech

26

Large biotech or pharma

19

Affected trials, by study phase

Number of affected trials in each phase of development

Phase 1

117 trials

Phase 2

66

Phase 3

56

<https://www.biopharmadive.com/news/coronavirus-clinical-trial-disruption-biotech-pharma/574609/>

COVID-19

Impact on Clinical Trials

“... *Recruitment and enrolment* for most other studies stopped during the early stages of the pandemic...”

“...we must be cognizant that COVID-19 might affect *key study outcomes*.”

These are *crucial considerations for study analysis and interpretation*.

Potential confounding may be addressed by applying sensitivity analyses.

<https://www.nature.com/articles/s41581-020-00336-9>

Synthetic Control Opportunity?

Leveraging Real World Data

Real World Evidence

PHUSE Paper



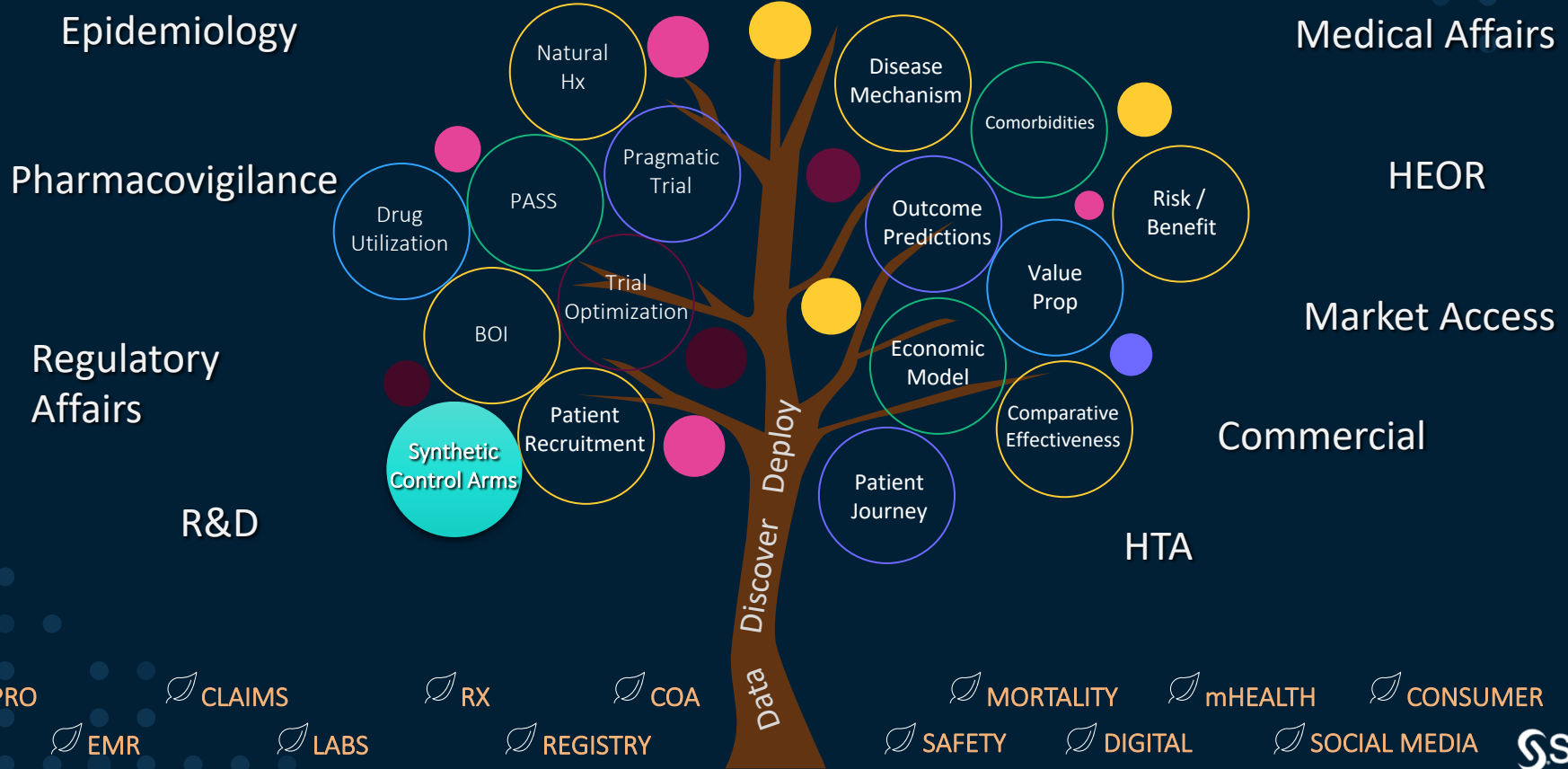
Using RWE may provide advantages in cost, cohort sizes and ethical considerations.

This PHUSE paper attempts to collate all related information such as sources of RWD (Real-World Data), privacy laws and use cases in one document which can act as a reference point for individuals or companies who wish to design, conduct, and submit studies using RWE (Real-World Evidence).

It includes FDA's current direction and guidance as of the date of this publication.

[PHUSE RWE Paper](#)

Real World Evidence



Synthetic Control Arms

Save Time and Money in Clinical Trials

Examples in regulatory decision-making

■ Roche

- European Union coverage requirements for marketing Alecensa (alectinib) in 20 European markets.
- In 2015, Alecensa received accelerated FDA approval as a treatment for a specific form of lung cancer.
- In February 2017 it was conditionally approved in the EU.
- Used a synthetic control arm of 67 patients to provide evidence of relative performance to Ceritinib.
- Advanced coverage of Alecensa by 18 months in 20 European countries.

- **Amgen** accelerated the approval of Blincyto (blinatumomab) for the treatment of a rare form of leukemia.

Synthetic Control Arms - Types

Potential (Pre-COVID) vs. Necessity (Post-COVID)

	External Control Cohort Inception Date	Possible Types of Data Collection	
		Retrospective RWD Collection	Prospective RWD Collection
Contemporaneous External Control	On or after the first patient enrollment in the clinical trial		
Historical External Control	Before the first patient enrollment in the clinical trial		
Hybrid External Control	Varies		

Example

Theoretical Use Case with Synthetic data

Use Case

PARAGLIDE-HF (example)

Novartis

Updated May 4, 2020

NCT03570892 and **NCT03338998**

- **Disease:** Lymphoma and intracerebral hemorrhages
- **Drug:** Kymriah and BAF312
- **Action:** Suspended recruitment

Novartis has temporarily halted recruitment for a Phase 3 study of its CAR-T cancer therapy Kymriah, which is meant to test the drug in some 300 patients with lymphoma. Recruitment was also paused for a Phase 2 trial of BAF312, also known as Mayzent.

NCT04237116

- **Disease:** Non-alcoholic fatty liver disease, plaque psoriasis
- **Drug:** secukinumab
- **Action:** Suspended study

Novartis suspended the "PINPOINT" study of secukinumab in patients with plaque psoriasis alongside fatty liver disease.

PARAGLIDE-HF, **PARACHUTE-HF** and three other trials

- **Disease:** Heart failure, Sjogren's syndrome, Type 1 diabetes and cancer
- **Drug:** Entresto, CFZ333 and a cancer radiotherapeutic
- **Action:** Paused recruitment and, in one study, treatment

Several trials run by Novartis, one of the largest drugmakers worldwide, are now marked as suspended on clinicaltrials.gov, hinting at the widening impact being felt by even the biggest pharmas. Most notable is an 800-patient Phase 3 study of Novartis' heart failure medicine Entresto.

COVID-19 is an emerging, rapidly evolving situation.
Get the latest public health information from CDC: <https://www.coronavirus.gov>.
Get the latest research information from NIH: <https://www.nih.gov/coronavirus>.

NIH U.S. National Library of Medicine
ClinicalTrials.gov

Find Studies ▾ About Studies ▾ Submit Studies ▾ Resources ▾ About Site ▾ PRS Login

Home > Search Results > Study Record Detail Save this study

Changes in NT-proBNP and Outcomes, Safety, and Tolerability in HFpEF Patients With Acute Decompensated Heart Failure (ADHF) Who Have Been Stabilized During Hospitalization and Initiated In-hospital or Within 30 Days Post-discharge (PARAGLIDE-HF)

ClinicalTrials.gov Identifier: NCT03988634

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. **Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our [disclaimer](#) for details.**

Recruitment Status 📌 : Recruiting
First Posted 📌 : June 17, 2019
Last Update Posted 📌 : May 15, 2020
[See Contacts and Locations](#)

Sponsor:
Novartis Pharmaceuticals

Information provided by (Responsible Party):
Novartis (Novartis Pharmaceuticals)

[Study Details](#) [Tabular View](#) [No Results Posted](#) [Disclaimer](#) [How to Read a Study Record](#)

Study Description

Brief Summary:
The purpose of this study is to assess the effect of sacubitril/valsartan (LC2696) vs. valsartan on changes in NT-proBNP and outcomes, safety and tolerability in patients with HFpEF (left ventricular ejection fraction (LVEF) > 40%) who have been stabilized during hospitalization for acute decompensated heart failure and initiated in-hospital or within 30 days post discharge.

Condition or disease 📌	Intervention/treatment 📌	Phase 📌
Heart Failure With Preserved Ejection Fraction (HFpEF)	Drug: sacubitril/valsartan Drug: valsartan	Phase 3

Disclaimer: For this theoretical use case we used SYNTHETIC patient data.

Use Case

Study Arms and Primary Outcome

Experimental

Patients on Sacubitril/Valsartan

Active Comparator

Patients on Valsartan

Primary Outcome Measures

Proportional change in NT-proBNP from baseline

Disclaimer: For this theoretical use case we used SYNTHETIC patient data.

Use Case

Eligibility Criteria

Inclusion Criteria*

- Patients ≥ 40 years of age, male or female
- Patients with a diagnosis of acute heart failure
- SBP ≥ 100 mmHg
- Patients will have a NT-proBNP local lab value
- Currently on Valsartan

**partial list of eligibility criteria*

Exclusion Criteria*

- Currently taking Entresto™ (sacubitril/valsartan) or any prior use
- Acute coronary syndrome, stroke, transient ischemic attack; cardiac, carotid or other major CV surgery
- COVID-19 diagnosis

Synthea

Real World Data Usage

SYNTHEA™

[HOME](#) [ABOUT](#) [TECHNOLOGY](#) [COLLABORATE](#) [CONTACT](#)

SYNTHEA EMPOWERS DATA-DRIVEN HEALTH IT



Synthea™ is an open-source, synthetic patient generator that models the medical history of synthetic patients. Our mission is to provide high-quality, synthetic, realistic but not real, patient data and associated health records covering every aspect of healthcare. The resulting data is free from cost, privacy, and security restrictions, enabling research with Health IT data that is otherwise legally or practically unavailable.

Disclaimer: For this theoretical use case we used SYNTHETIC patient data.

<https://synthetichealth.github.io/synthea/>

Identify Synthetic Control Arm

Powered by SAS® Health

SAS® Health Solutions

Cohort Builder
Episode Builder
Data Mapper (e.g. OMOP, CDISC)
Fraud Investigation

SAS® Health Analytic Insight Modules

(aka. SAS® Health App Store)
Payer,
Provider,
Public Health
Life Sciences



SAS® Analytics Platform

Manage Analytical Life Cycle
for continuous innovation

https://www.sas.com/en_us/software/health.html

Prepare Data with Programming Interface

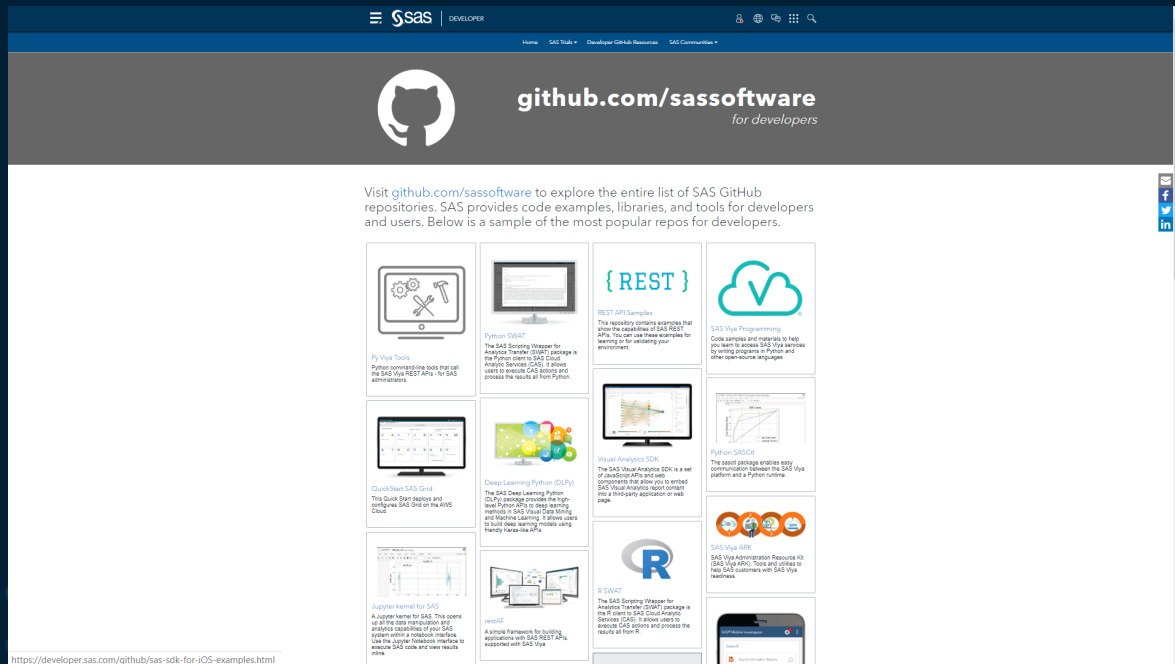
The screenshot displays the SAS Studio environment. The top menu bar includes 'New', 'Options', 'View', 'Open', and 'Save All'. The left sidebar shows a 'Libraries' panel with a tree view containing folders like 'CASUSER', 'FORMATS', 'MAPS', 'MAPSGFK', 'MAPSSAS', 'MODELS', 'OPT', and 'PUBLIC'. The 'PUBLIC' folder is expanded, showing subfolders such as '100K_CONDITIONS', '100K_ENCOUNTERS', '100K_OBSERVATI...', '100K_PATIENTS', 'ACS_COHORT_RE...', 'ACS_COHORT_ST...', 'ENTRESTO', 'SYN100K_ENTRE...', 'SYN100K_MERGED', 'SYNTHEA_100K_N...', 'SYNTHEA_100K...', 'SAMPLES', 'SASHELP', 'SASUSER', and 'WORK'. The main editor window shows a SAS program named 'New_Synthea_Prep.sas'. The code includes comments about a request from Sherrine, flags for CHF, COVID, Entresto, MI, CABG, BP, Stroke, and ACS, and continuous variables. It connects to a public CASLIB, creates a LIBNAME, and defines a macro for calculating age. The program ends with a PROC SQL statement to create a table 'opt.&name' from 'public.&source'.

```
1  options mprint mlogic;
2  options obs=MAX;
3
4  /*
5   Request from Sherrine:
6   Flags: CHF, COVID, Entresto (Valsartan), MI or CABG, BP (>=100mmHg), Stroke, ACS
7   Continuous variables: Age at CHF-Dx, NT-proBNP, NT-proBNP date,
8   */
9
10 /* Connect to Public CASLIB */
11 options cashost="CPOC-Viya-CAS" casport=5570;
12 cas;
13 caslib _ALL_ assign;
14
15 cas casauto sessopts=(caslib="Public");
16
17 /* Create LIBNAME on /opt/sas/RCTarballs/100k */;
18 libname opt "/opt/sas/RCTarballs/100k";
19
20 /* Q&D macro to calculate age */
21 %macro age(date, birth);
22   floor ((intck("month", &birth., &date.) - (day(&date.) < day(&birth.))) / 12)
23 %mend age;
24
25 /* Package up the code we're going to reuse across tables... */
26 %macro getdates(name, source, codes);
27   proc sql;
28     create table opt.&name. as
29     select distinct patient, min(start) as first_&name. format=date9.
30     from public.&source.
31
```

File: /home/robcol/sasuser.viya/New_Synthea_Prep.sas Line 10 Column 31 UTF-8 Recover (19) Submission (0)

SAS & Open Source

Powered by SAS® Health

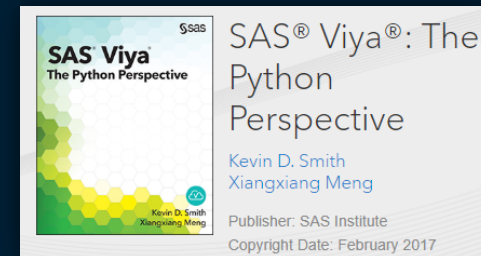


The screenshot shows the SAS Developer GitHub page. At the top, there's a navigation bar with 'SAS' and 'DEVELOPER' links. Below it, a banner for 'github.com/sassoftware for developers' features the GitHub logo. The main content area lists several popular repositories:

- Py Viya Tools**: Python connecting tools that get the SAS Viya REST APIs for SAS administrators.
- QuickStart SAS Grid**: This Quick Start helps you get up and running with SAS on the AWS Cloud.
- Jupyter kernel for SAS**: A Jupyter kernel for SAS. This opens up all of the data manipulation and analytics capabilities of your SAS system with a notebook interface. Use the Jupyter Notebook interface to explore SAS code and view results more.
- REST API Samples**: The repository contains examples that show the capabilities of SAS REST APIs. You can use these examples for learning or for validating your environment.
- SAS Viya Programming**: Code samples and materials to help you learn to access SAS Viya services by writing programs in Python and other open-source languages.
- Visual Analytics SDK**: The SAS Visual Analytics SDK is a set of JavaScript APIs and web components that allow you to embed SAS Visual Analytics report content into a third-party application or web page.
- Python SASOL**: The easiest package enables easy communication between the SAS Viya platform and a Python console.
- SAS Viya ARK**: SAS Viya Administrator Desktop Kit (SAS Viya ARK). Tools and utilities to help SAS customers with SAS Viya readiness.
- R SASOL**: The SAS Scripting Wrapper for Analytics Interface (SASOL) package is the R client to SAS Cloud Analytics Service (SAS CAS). It allows users to execute SAS scripts and process the results in R form.
- REST API Samples**: The repository contains examples that show the capabilities of SAS REST APIs. You can use these examples for learning or for validating your environment.

At the bottom left, the URL <https://developer.sas.com/github/sas-sdk-for-ios-examples.html> is visible.

<https://developer.sas.com/home.html>

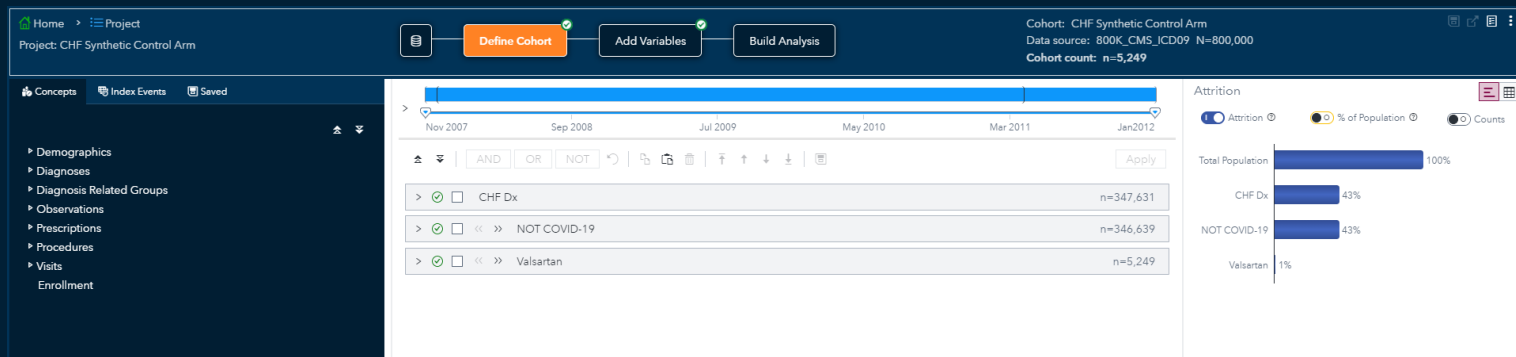


[SAS Viya®: The Python Perspective](#)



[SAS Viya®: The R Perspective](#)

Define Synthetic Control Arm*



Home > Project
Project: CHF Synthetic Control Arm

Define Cohort Add Variables Build Analysis

Cohort: CHF Synthetic Control Arm
Data source: 800K_CMS_ICD09 N=800,000
Cohort count: n=5,249

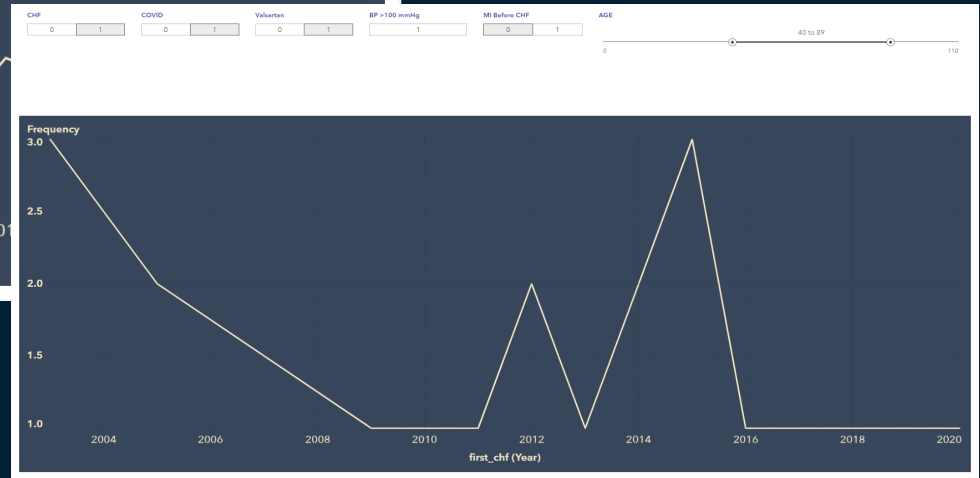
Filter

Demographics
Risk Factors
Saved

Name	Type	Results
AGEGROUP_5 : Age Group (0-17, 18-39, 40-54, 55-64, 65+)	Demographic Grouper	
MI	Custom Variable - Diagnoses	Count = 3168
Gender	Custom Variable - Demographics	Count = 5249
NTproBNP	Custom Variable - Hybrid	Count = 1574

*Prior to Age and MI eligibility criteria applied

Identify Non-COVID Patients



Enroll Control Arm

CHF

☐ 0 ☒ 1

COVID

☐ 0 ☐ 1

Valsartan

☐ 0 ☒ 1

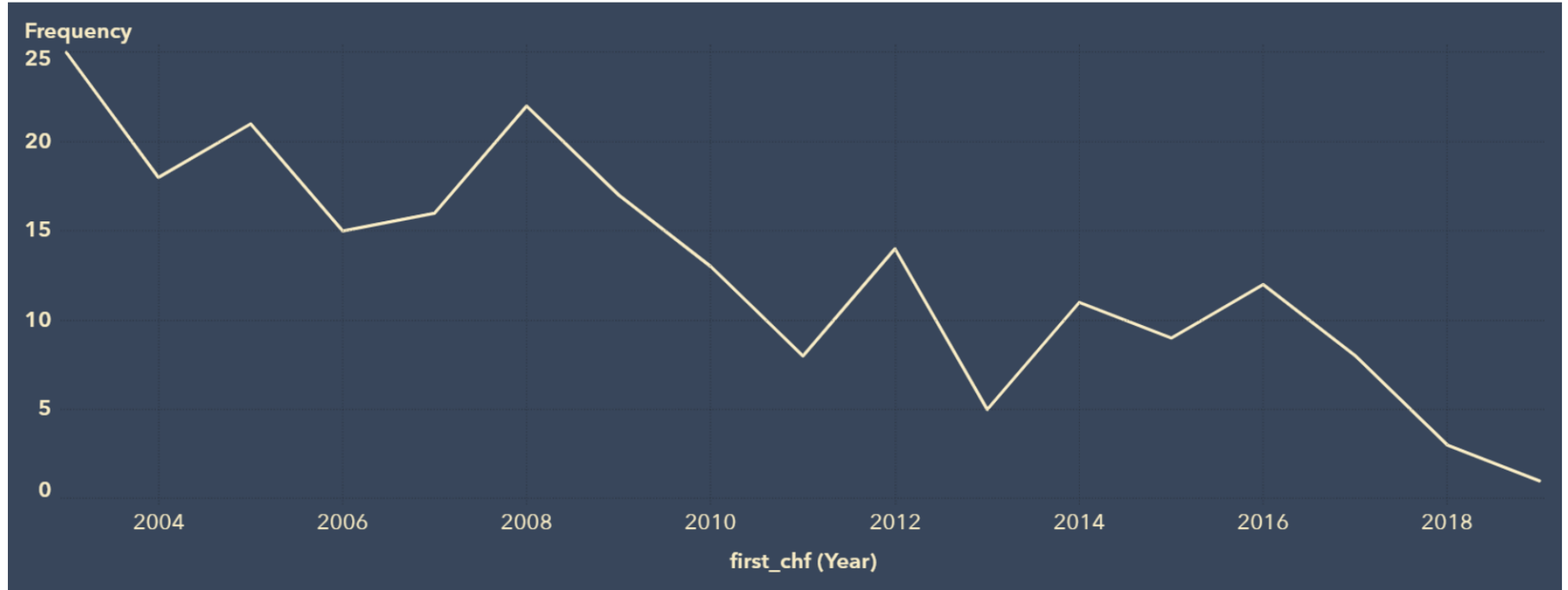
BP >100 mmHg

☐ 1

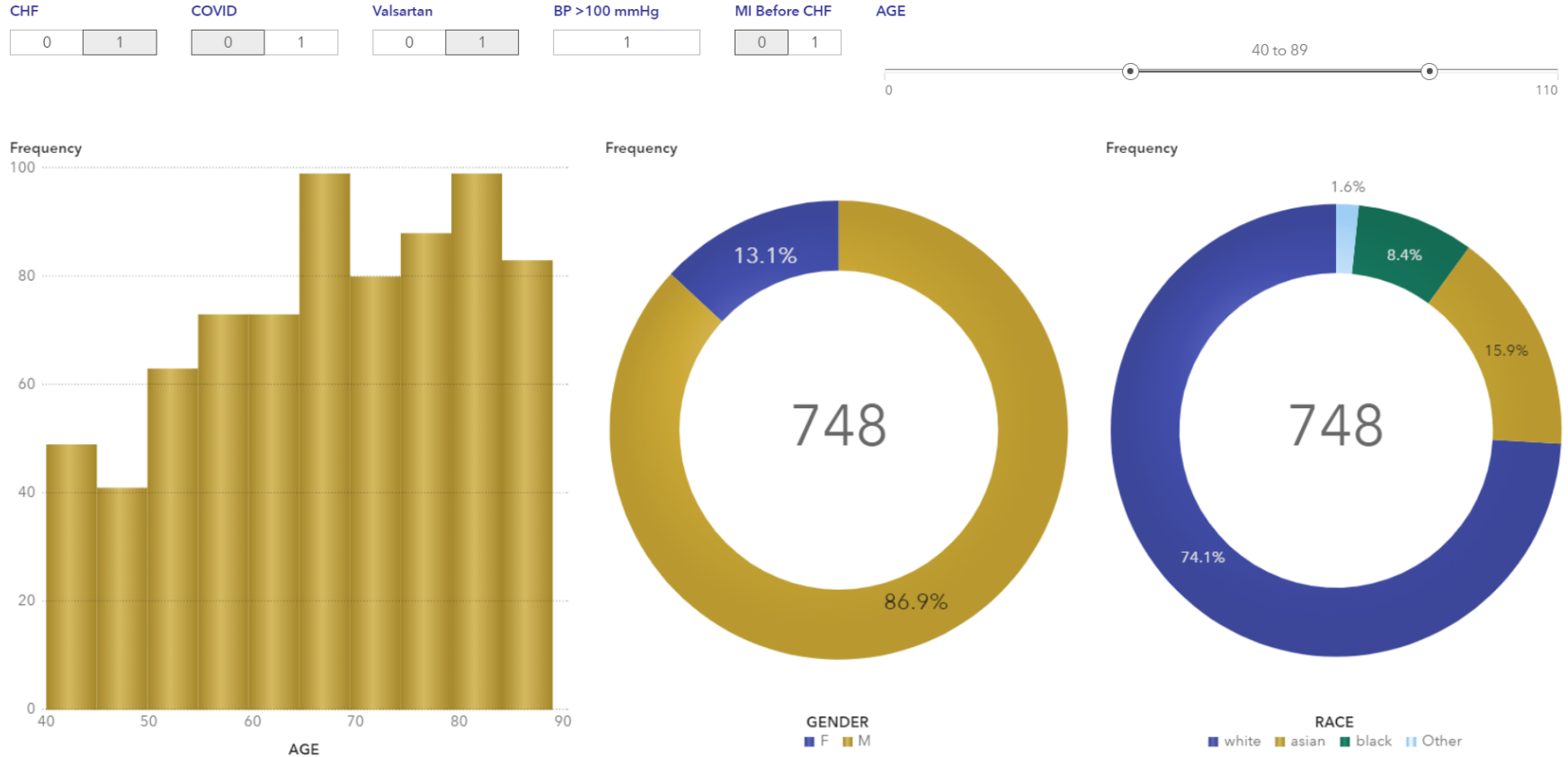
MI Before CHF

☒ 0 ☐ 1

AGE

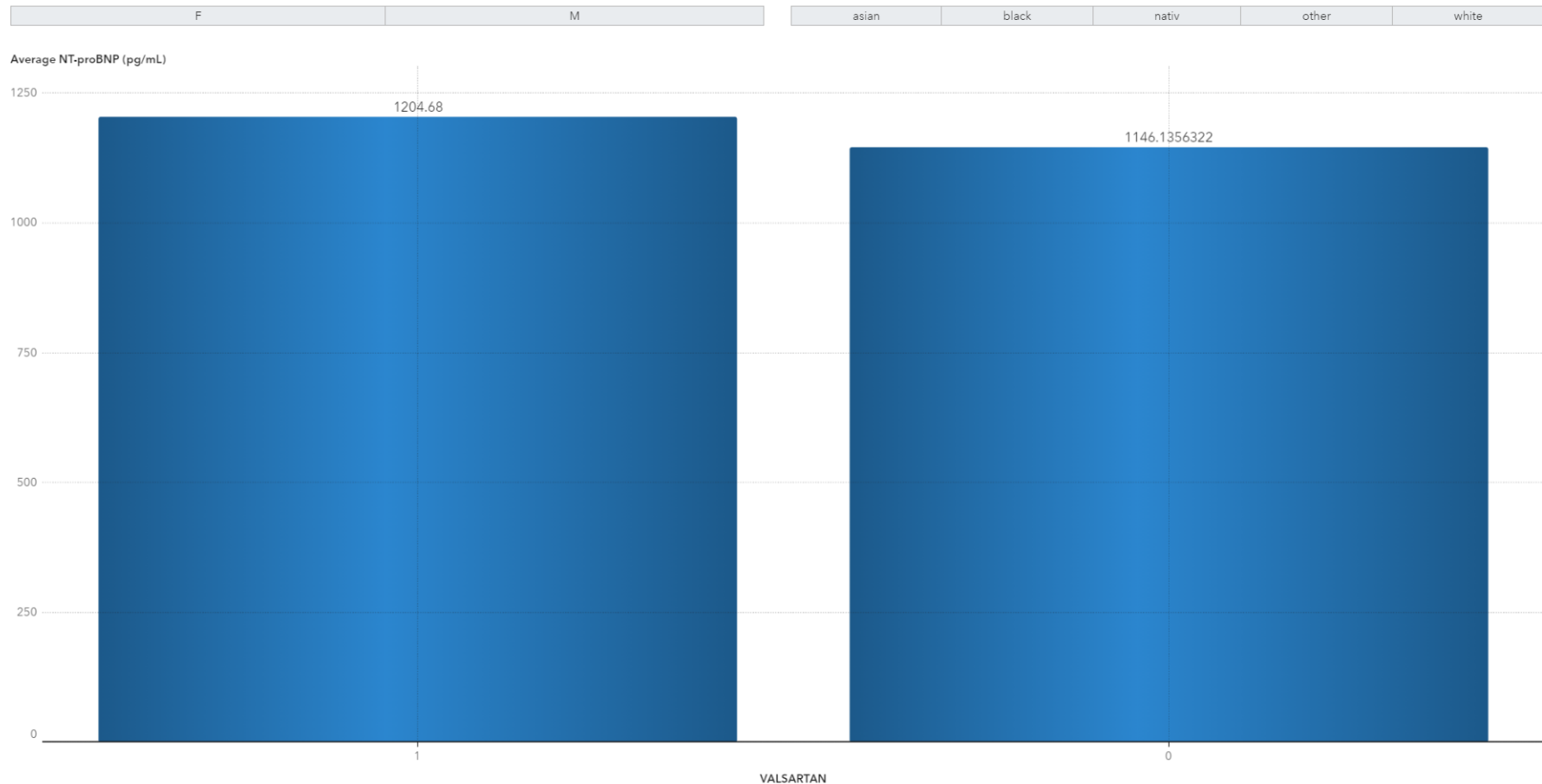


Report Baseline Data*



*Age and MI eligibility criteria applied

Test Primary Endpoint: NT-proBNP Levels



Logistic Regression **flag_mi** (event=1) KS (Youden') **0.7326** Observations Used **195**

Fit Summary

AGE
GENDER
VALSARTAN
RACE
VALUE_N

Residual Plot

Residual

Predicted Probability

Confusion Matrix

Observed

0 1

0 1

flag_mi

0 1

Decision Tree

VALSARTAN

Variable Importance

VALSARTAN
AGE
GENDER
RACE
VALUE_N

Importance

Confusion Matrix

Observed

0 1

0 1

flag_mi

0 1

Gradient Boosting **flag_mi** (event=1) KS (Youden') **0.9942** Observations Used **195**

Variable Importance

VALSARTAN
AGE
VALUE_N
RACE
GENDER

Importance

Iteration Performance

Misclassification

Gradient Boosting **flag_mi** (event=1) KS (Youden) **0.9942** Observations Used **195**

Neural Network **flag_mi** (event=1) KS (Youden) **0.7652** Observations Used **195**

Variable Importance

VALSARTAN
AGE
VALUE_N
RACE
GENDER

Iteration Plot
Misclassification Rate

Number of Trees

Network

Iteration Plot
Objective / Loss

Iterations

Objective Loss

Confusion Matrix
Observed

0 1

0 1

Predicted

Confusion Matrix
Observed

0 1

0 1

Predicted

Neural Network

Neuron Absolute Average

Weight

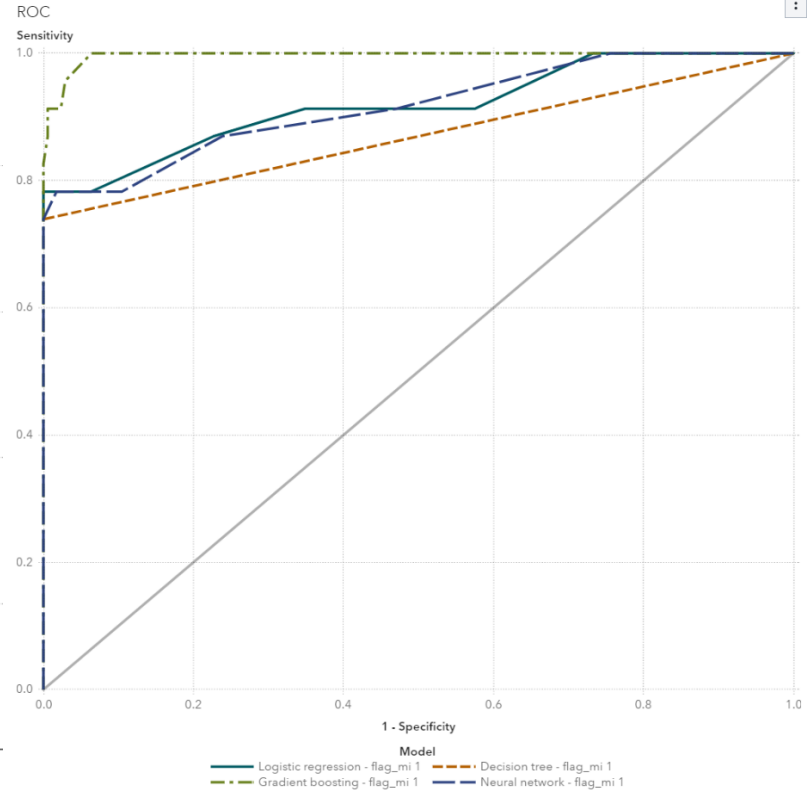
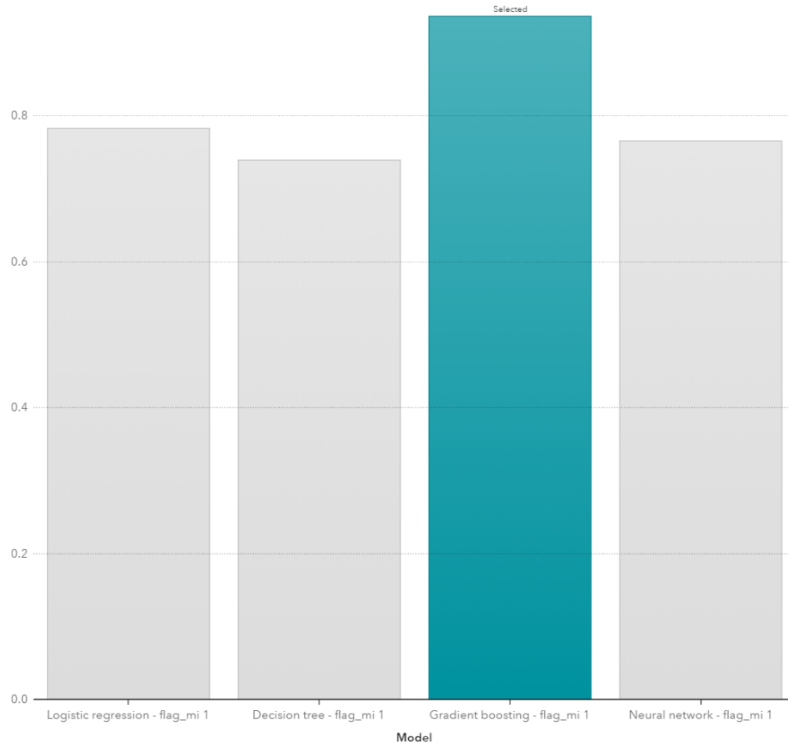
Link Absolute

Link

Select the Best Fit Model for Secondary Endpoints

Model Comparison flag_mi (event=1)

Fit Statistic
KS (Youden)



Meet Regulatory Requirements

Submit Code and Logs

The screenshot displays the SAS Studio interface with the following components:

- Top Bar:** SAS® Studio logo and a user icon.
- Menu Bar:** New, Options, View, Open, Save All.
- Left Panel (Tasks):** A tree view showing various tasks. Under "SAS Viya Machine Learning", "Supervised Learning", and "Gradient Boosting" are highlighted.
- Central Panel (Task Configuration):**
 - Run Buttons:** Run, Cancel, Copy to My Tasks.
 - Tabs:** DATA, OPTIONS, OUTPUT, INFORMATION.
 - DATA Tab:** Shows the dataset "PUBLIC.SYNTHEA_100K_NTP..." and options for Partition Data (Validation data, Test data) and ROLES (Target: Use a nominal target).
 - Task Console:** Shows "Task Console (0)" with "No items".
- Right Panel (Code Editor):** Displays SAS code for Gradient Boosting, including comments about generation and the actual PROC GRADBOOST code.

```
1 /*  
2 *  
3 * Task code generated by SAS® Studio 5.2  
4 *  
5 * Generated on '9/4/20, 4:18 PM'  
6 * Generated by 'robcol'  
7 * Generated on server 'CPOC-Viya-Services'  
8 * Generated on SAS platform 'Linux LIN X64 3.10.0-957.5.1.e  
9 * Generated on SAS version 'V.03.05M0P11112019'  
10 * Generated on browser 'Mozilla/5.0 (Windows NT 10.0; Win64  
11 * Generated on web client 'https://sashlab.eastus.cloudap  
12 */  
13  
14 ods noproctitle;  
15  
16 proc gradboost data=PUBLIC.SYNTHEA_100K_NTPROBNP;  
17     target VALUE_N / level=nominal;  
18     input DATE / level=interval;  
19 run;
```

Key Considerations

Synthetic Control Arms

- Not universal replacement for conventional control arms
 - Only applicable to well-known, predictable diseases with well-defined Standard of Care
 - RWD information may be difficult to extract or lack quality
 - Design and analytics may not fully control for all systematic issues and biases
- New tools and methodologies are needed to consolidate, organize, and structure RWD to generate research-grade evidence
 - Specific analytical approaches and evolving practices may address some challenges
 - Natural language processing and machine learning can be leveraged in this space

Quality Checklist for Researchers

Data Sources & Control Methods

External Control Data Sources

- Was the original data collection process similar to that of the clinical trial?
- Was the external control population sufficiently similar to the clinical trial population?
- Did the outcomes definitions of the external control match those of that clinical trial?
- Was the synthetic control data set sufficiently reliable and comprehensive?
- Were there any other major limitations to the dataset?

Synthetic Control Methods

- Did the clinical trial include a concurrent control arm? Is the synthetic control data the only control data?
- How was the synthetic control data matched to the intervention group?
- Were the results robust to sensitivity assumptions and potential biases?
- Were synthetic control comparisons possible for all clinically important outcomes?
- Are the results applicable to your patients?
- Were there any other major limitations to the synthetic control methods?

Next Step

Use *real* Real World Data...



The COVID-19 research database enables public health and policy researchers to use real-world data to better understand and combat the COVID-19 pandemic.

The database is a pro-bono, cross-industry collaborative, composed of institutions donating technology services, healthcare expertise, and de-identified data. The database is a public-private consortium

Do you want to join our efforts? Let us know!

<https://covid19researchdatabase.org/>

Any Questions ?

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sas.com



A series of horizontal bars of varying lengths and colors (teal, blue, and dark blue) are arranged on the left side of the slide, creating a modern, abstract background element.

Thank you !

sas.com

