



ST11: Synthetic Control Arms: Are They the Future of Drug Development?



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](#)

How are organizations using observational data today?

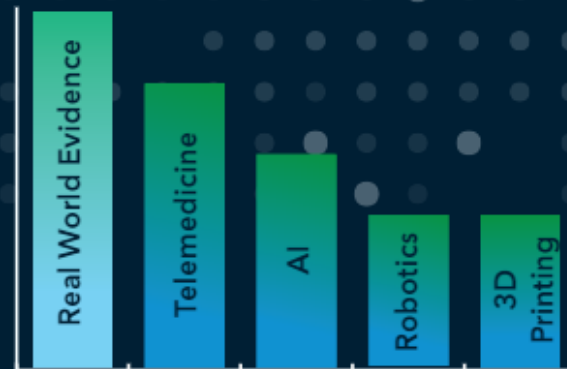
Life Sciences



82%

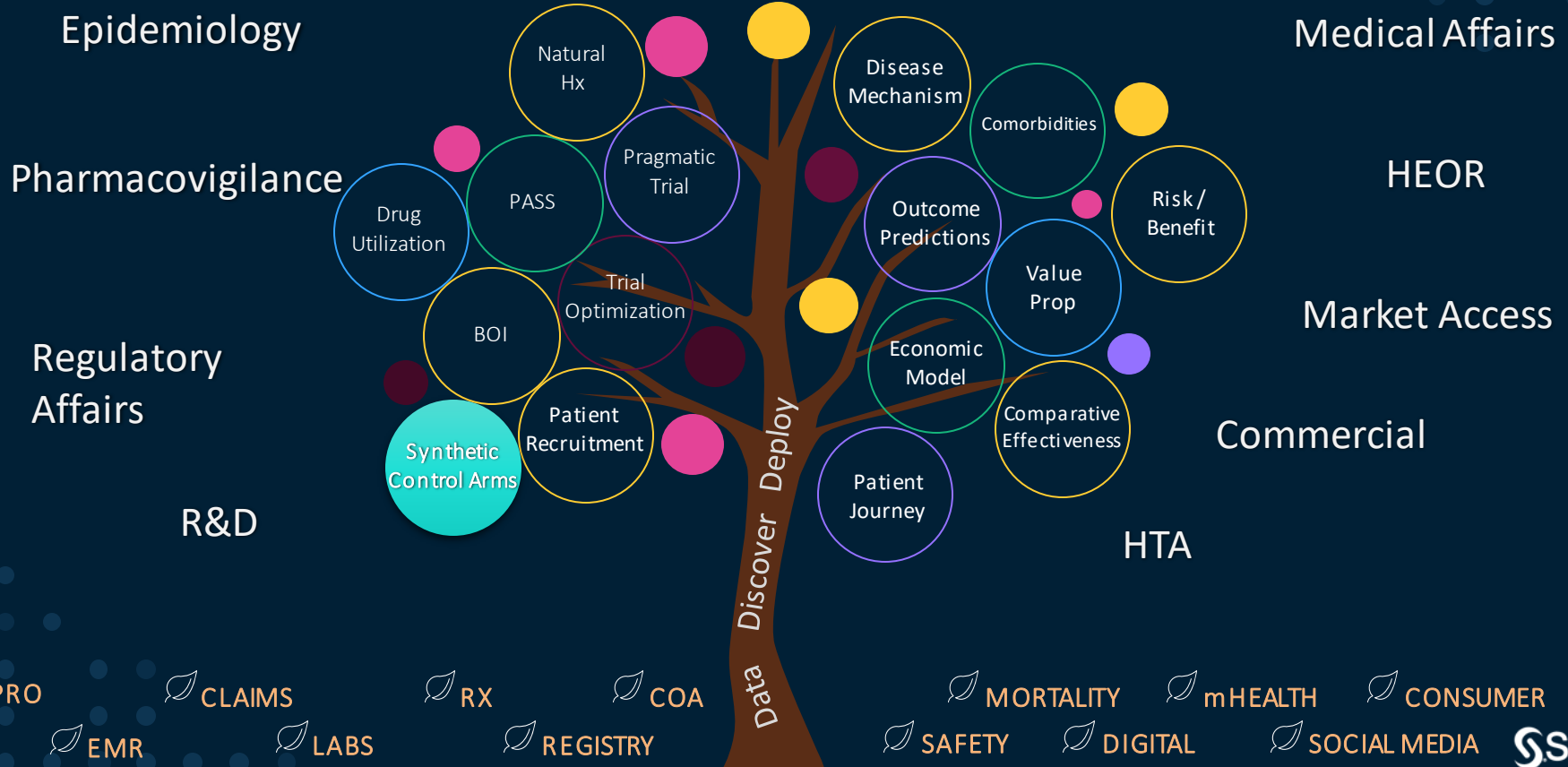
of respondents¹ indicated that the top benefits of Real World Data (RWD) are **adaptive trial design** and **synthetic control arms**

Health Care



***"Real world evidence** will have the greatest impact on managing COVID-19"²*

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		

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, CFZ533 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

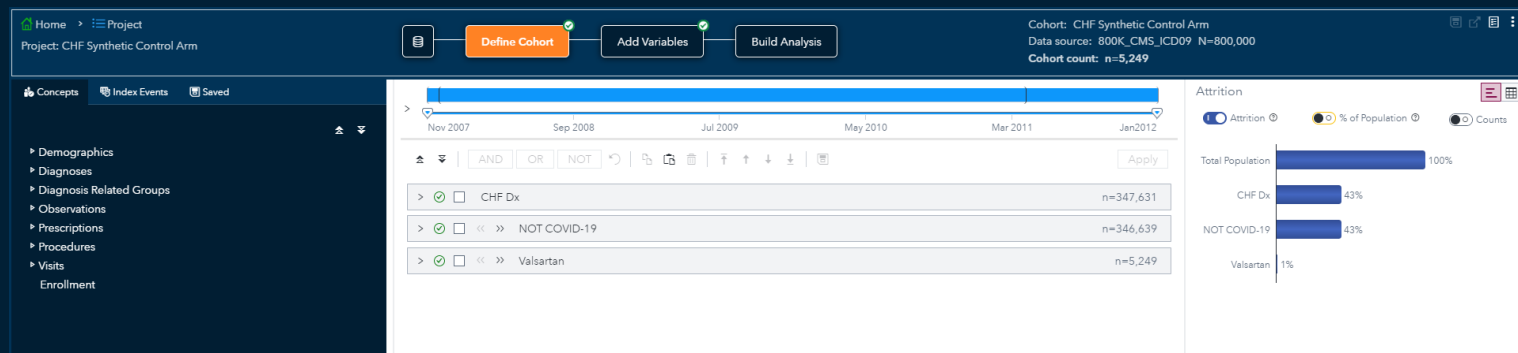
[Go to](#) ▾

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.

Define Synthetic Control Arm*



SAS® Health: Cohort Builder - Build Cohorts

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
NT-proBNP	Custom Variable - Hybrid	Count = 1574

*Prior to Age and MI eligibility criteria applied

Enroll Control Arm

CHF

☐ 0 ☒ 1

COVID

☒ 0 ☐ 1

Valsartan

☐ 0 ☒ 1

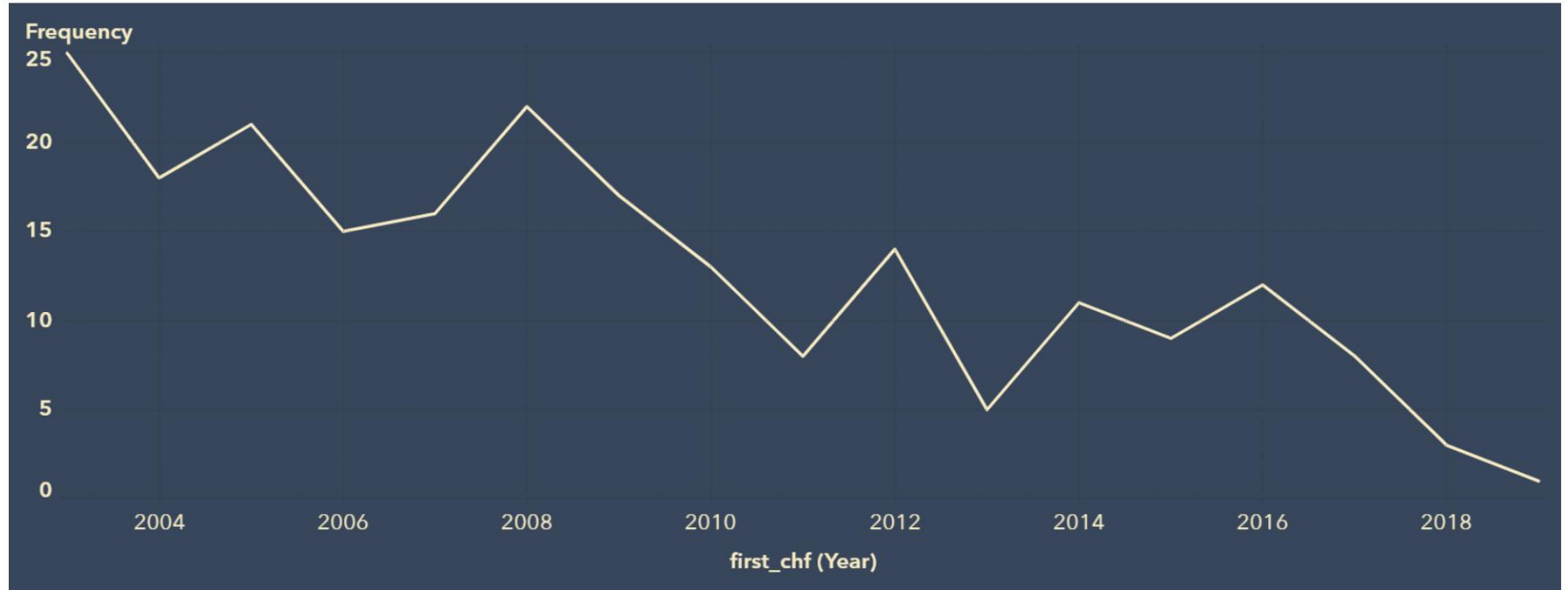
BP >100 mmHg

☐ 1

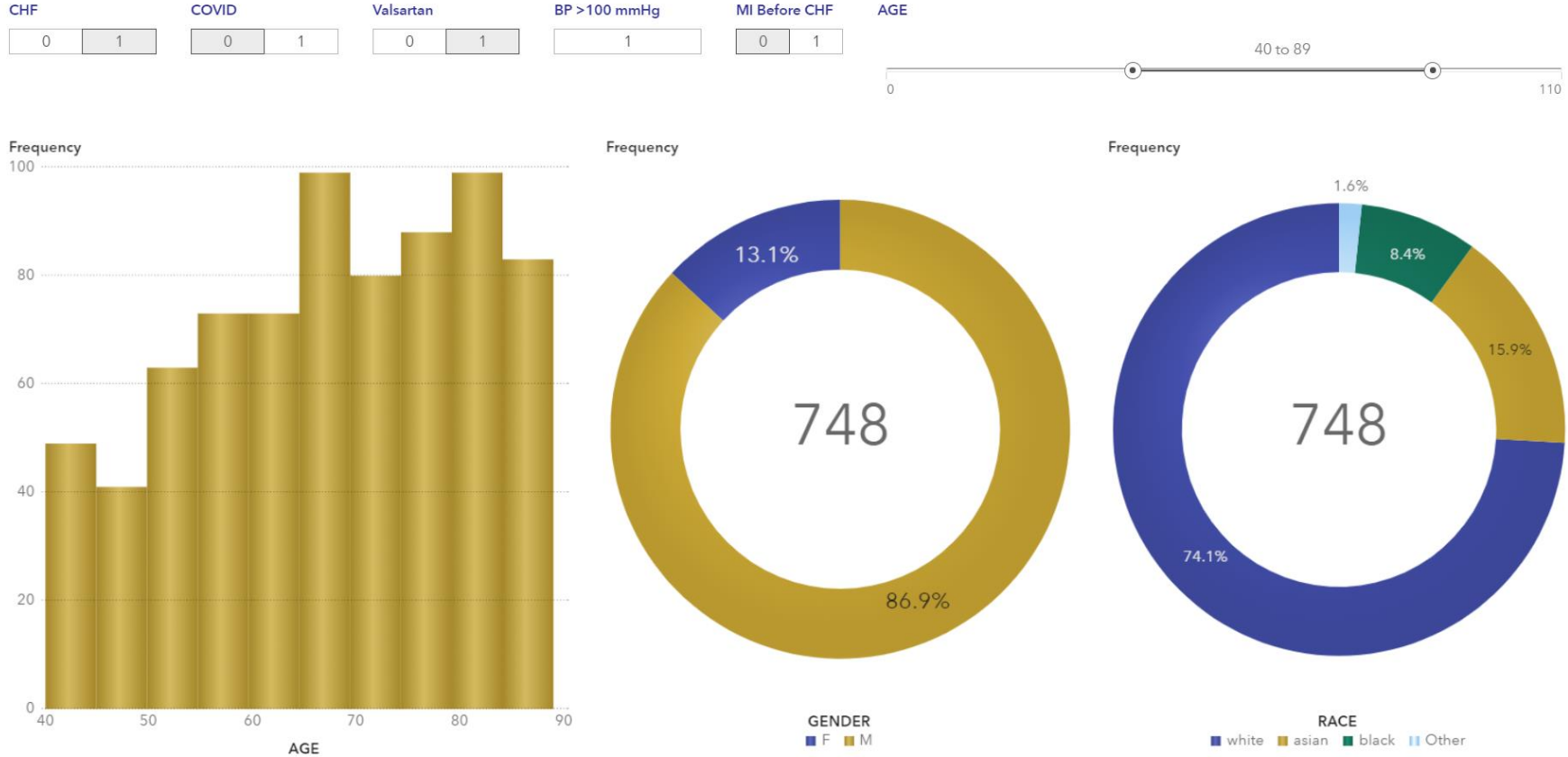
MI Before CHF

☒ 0 ☐ 1

AGE

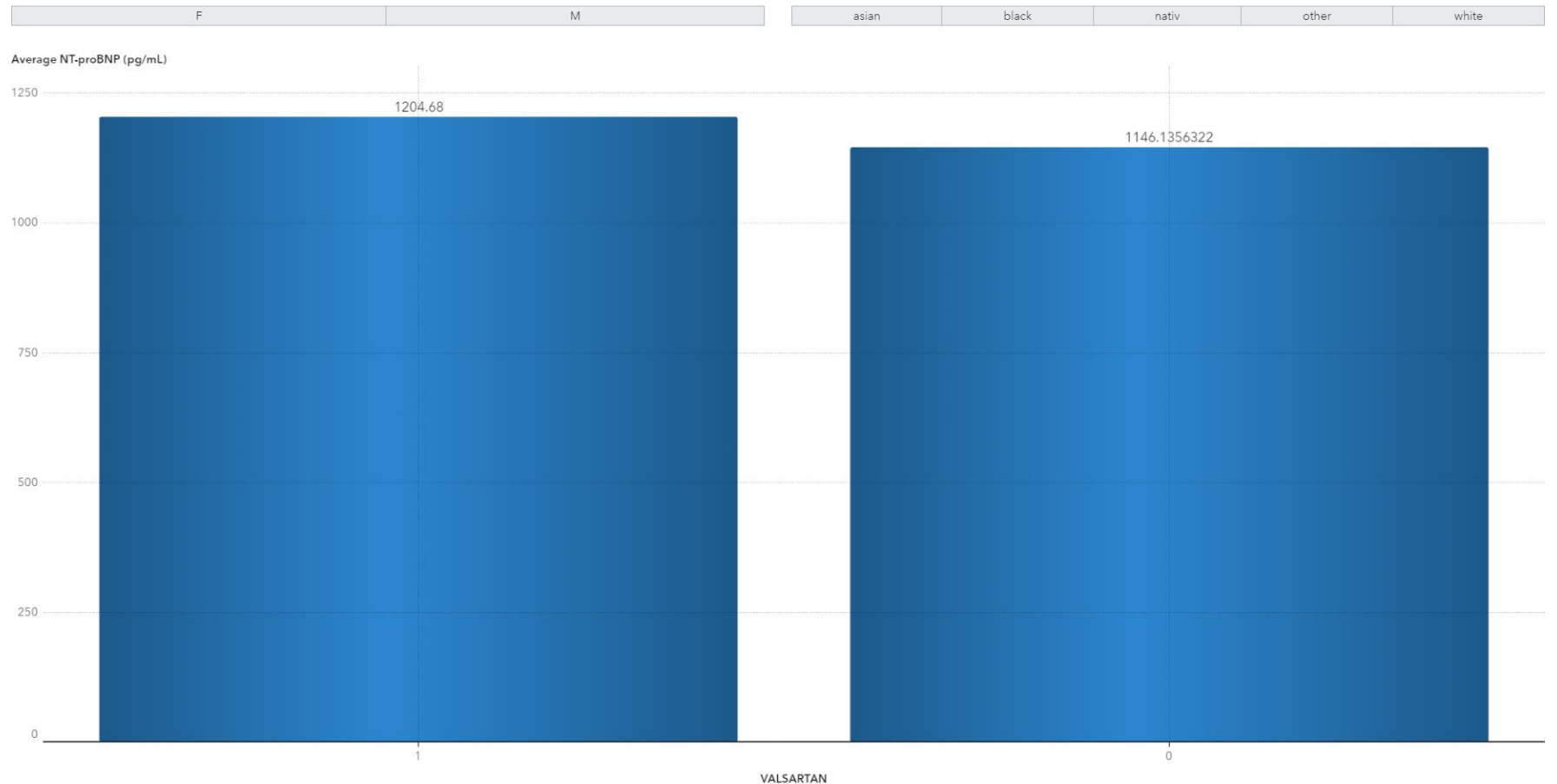


Report Baseline Data*



*Age and MI eligibility criteria applied

Test Primary Endpoint: NT-proBNP Levels

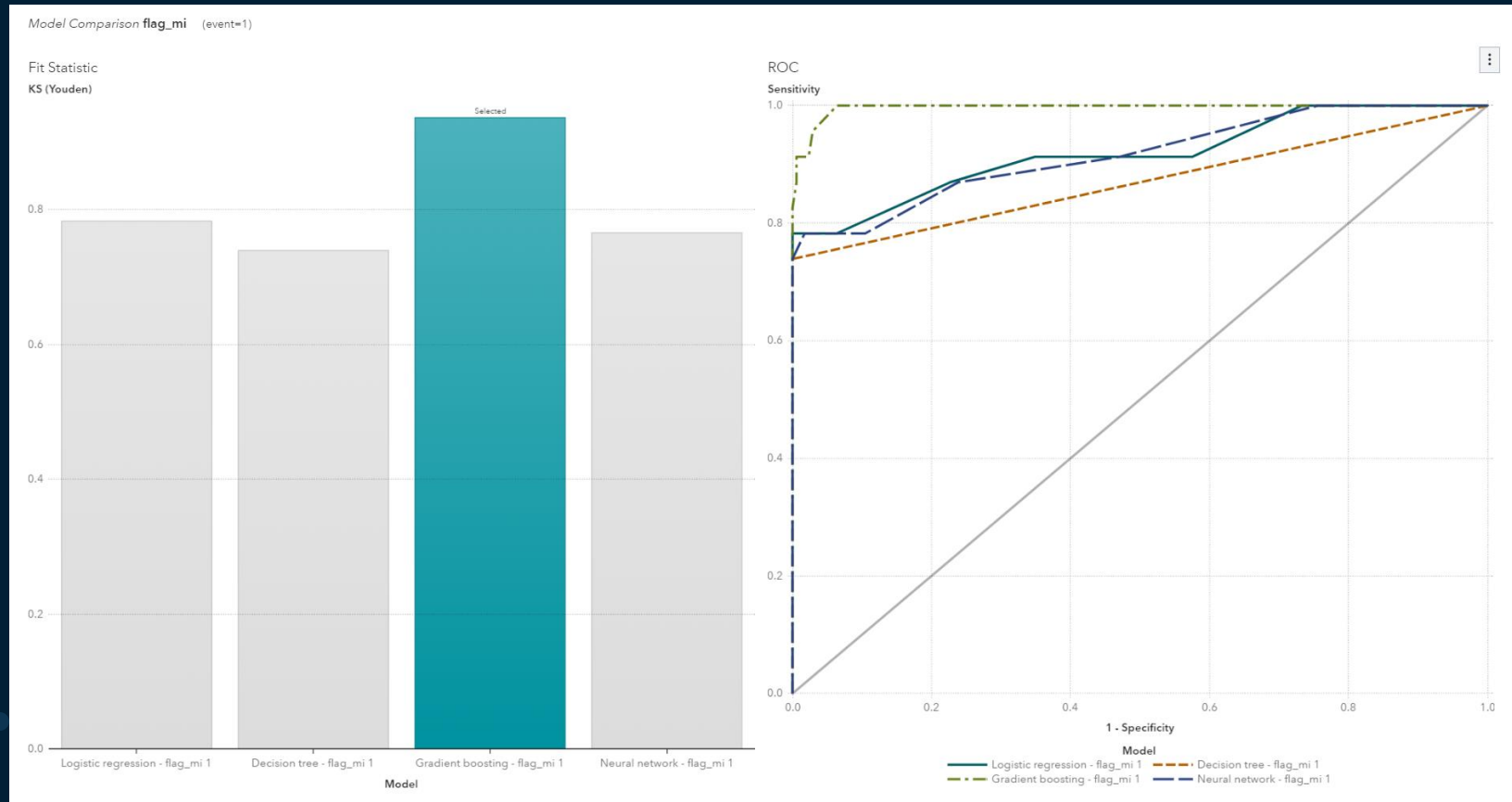


Test Secondary Endpoint: Myocardial Infarction (MI)

Predictive analytics and machine learning defined in the SAS as well as *ad hoc* analyses executed quickly



Select the Best Fit Model for Secondary Endpoints



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?

A series of horizontal bars of varying lengths and colors (teal, blue, and green) are positioned on the left side of the slide, creating a decorative border.

Thank you!
Sherrine.Eid@sas.com

sas.com

