

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.

## **RW<sub>02</sub> - Addressing industry disruptions in Clinical Trials with Real World Data in lieu of COVID<sub>19</sub>**

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/>

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# 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



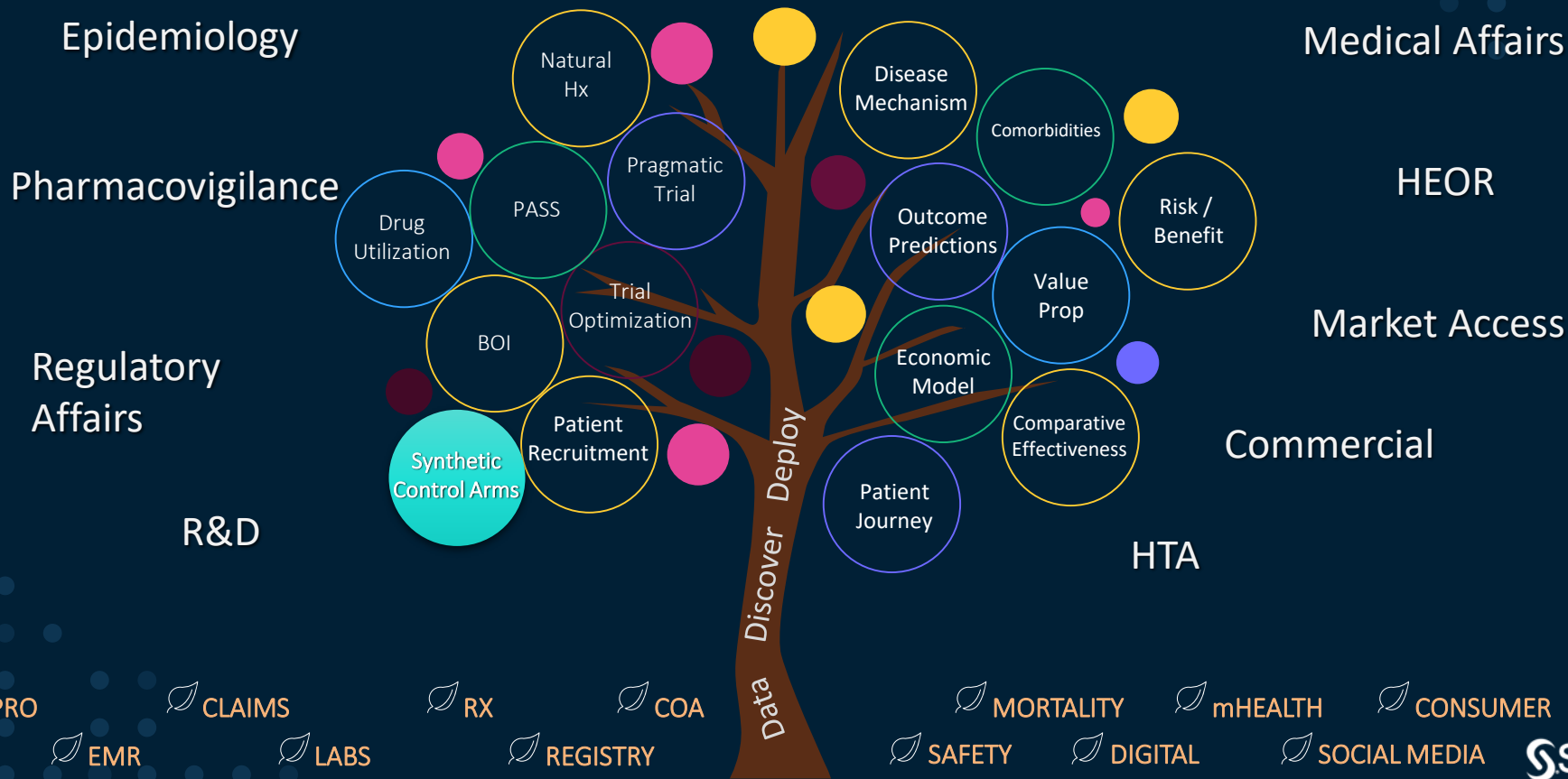
Using RWE may provide advantages in cost, cohort sizes and ethical considerations.

*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](https://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.

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

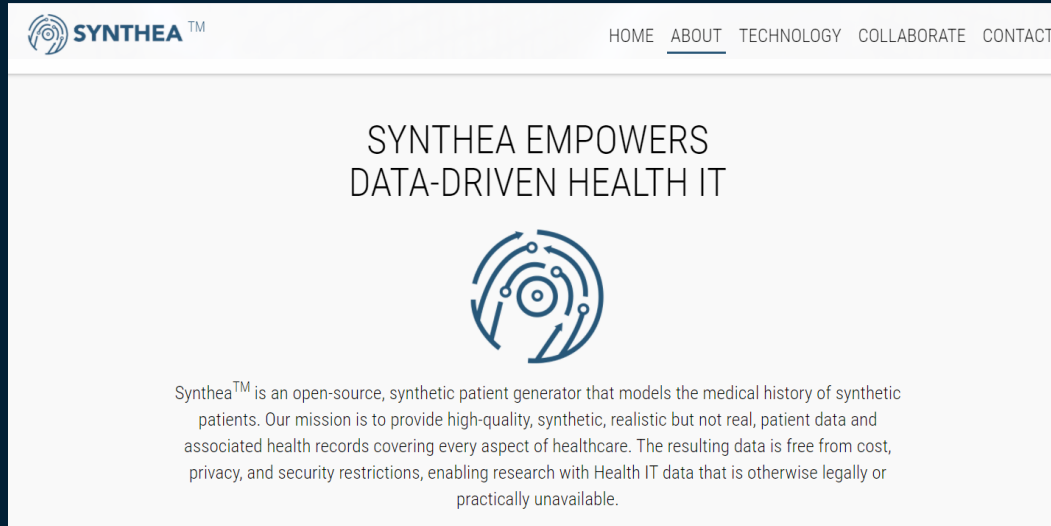
*\*partial list of eligibility criteria*

### 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




The screenshot shows the Synthea website homepage. At the top left is the Synthea logo, which consists of a stylized circular icon with concentric lines and dots, followed by the word "SYNTHEA" in a sans-serif font with a trademark symbol. To the right of the logo is a navigation menu with the links "HOME", "ABOUT", "TECHNOLOGY", "COLLABORATE", and "CONTACT". The "ABOUT" link is underlined. Below the navigation bar, the main heading reads "SYNTHEA EMPOWERS DATA-DRIVEN HEALTH IT". Underneath this heading is a large, stylized circular icon composed of blue lines and dots, resembling a network or a stylized 'S'. Below the icon, a paragraph of text describes Synthea as an open-source, synthetic patient generator that models the medical history of synthetic patients. The text states: "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."

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](https://www.sas.com/en_us/software/health.html)

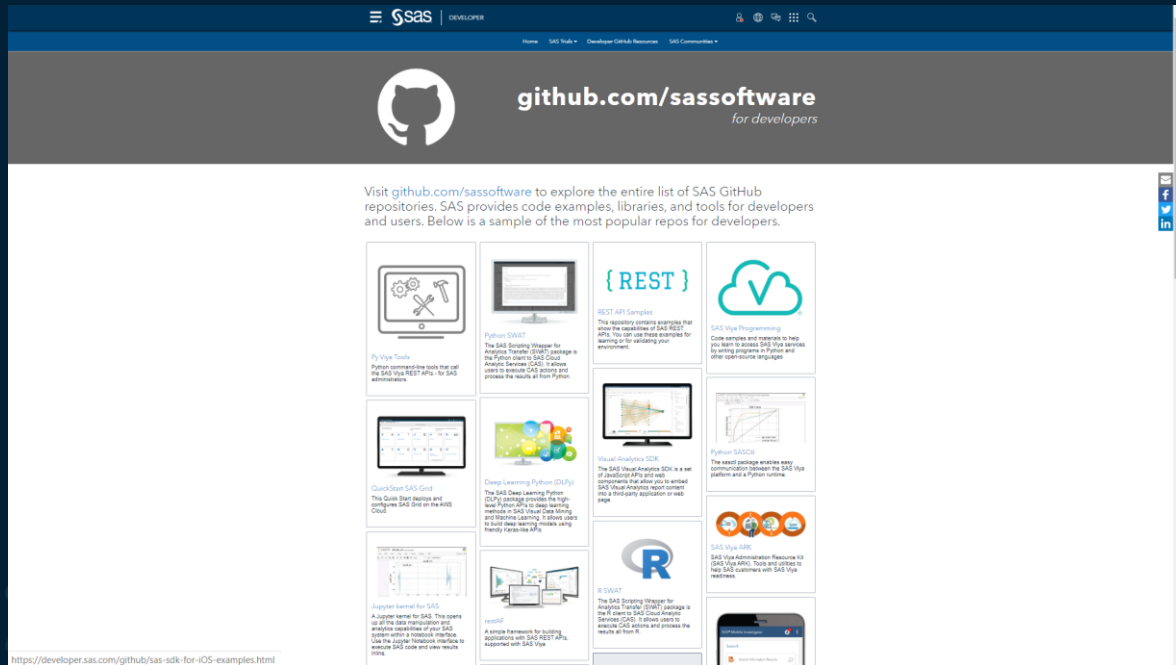
# Prepare Data with Programming Interface

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 of available libraries, including 'PUBLIC' which is expanded to show sub-libraries like '100K\_CONDITIONS', '100K\_ENCOUNTERS', etc. The main workspace is titled '\* New\_Synthea\_Prep.sas' and contains the following SAS code:

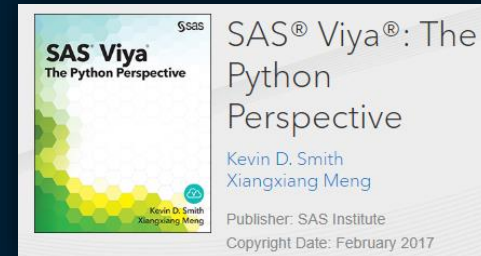
```
1  options mprint mlogic;
2  options obs=MAX;
3
4  /*
5   Request from Sherrine:
6   Flags: CHF, COVID, Entresto (Valsartan), MI or CABG, BP (>=100mmHg), Stroke, ACS
7   Continuous variables: Age at CHF-Dx, NT-proBNP, NT-proBNP date,
8   */
9
10 /* Connect to Public CASLIB */
11 options cashost="CPOC-Viya-CAS" 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
```

The status bar at the bottom indicates the file path: 'File: /home/robcol/sasuser.viya/New\_Synthea\_Prep.sas', the current position: 'Line 10 Column 31', and the encoding: 'UTF-8'. On the right side of the status bar, there are buttons for 'Recover (19)' and 'Submission (0)'.

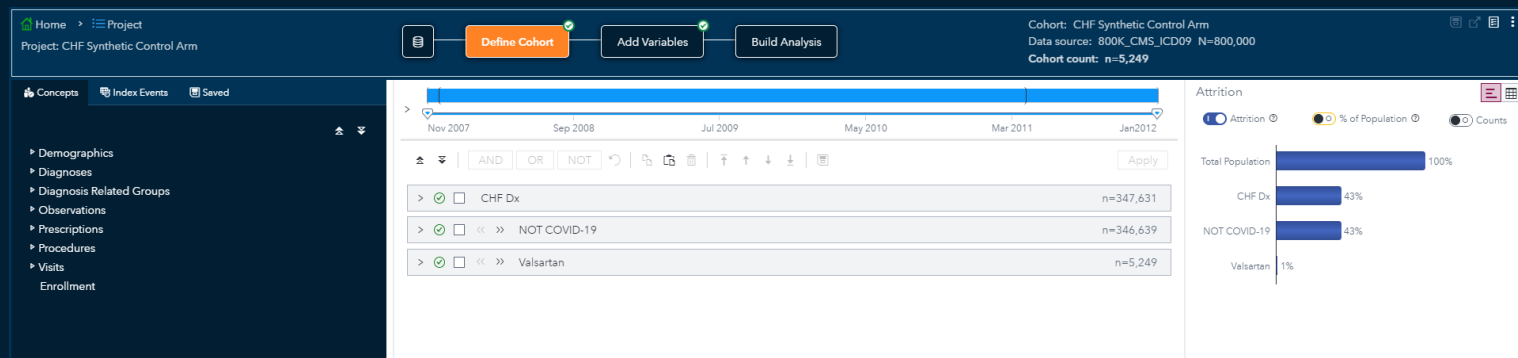
**SAS & Open Source**  
Powered by SAS® Health



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



# 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

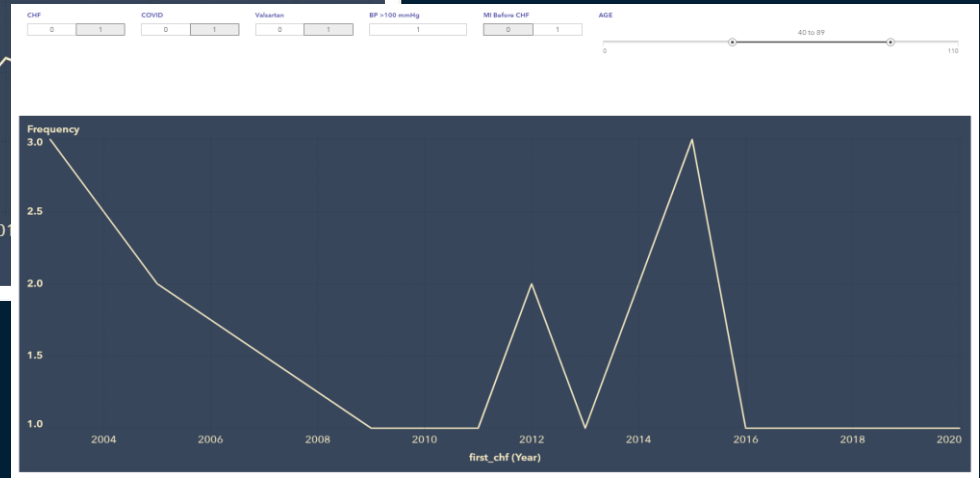
Filter

Demographics  
Risk Factors  
Saved

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

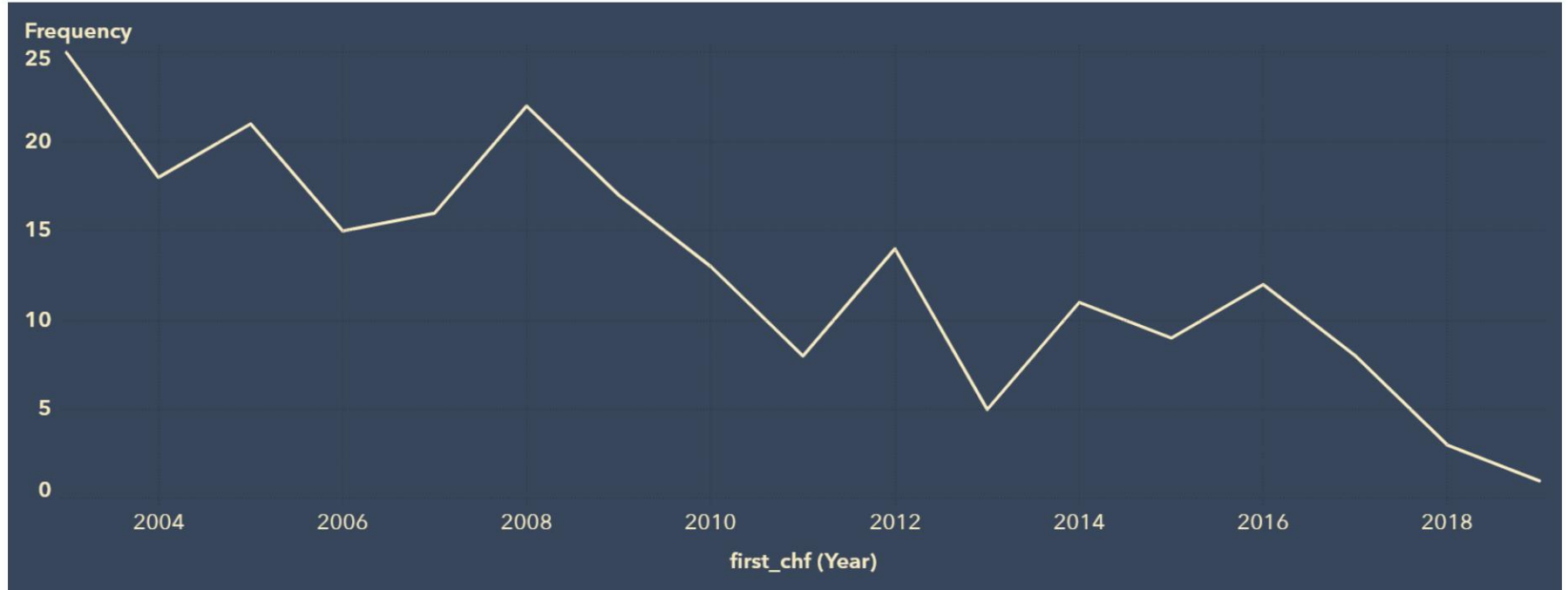
BP >100 mmHg

☐ 1

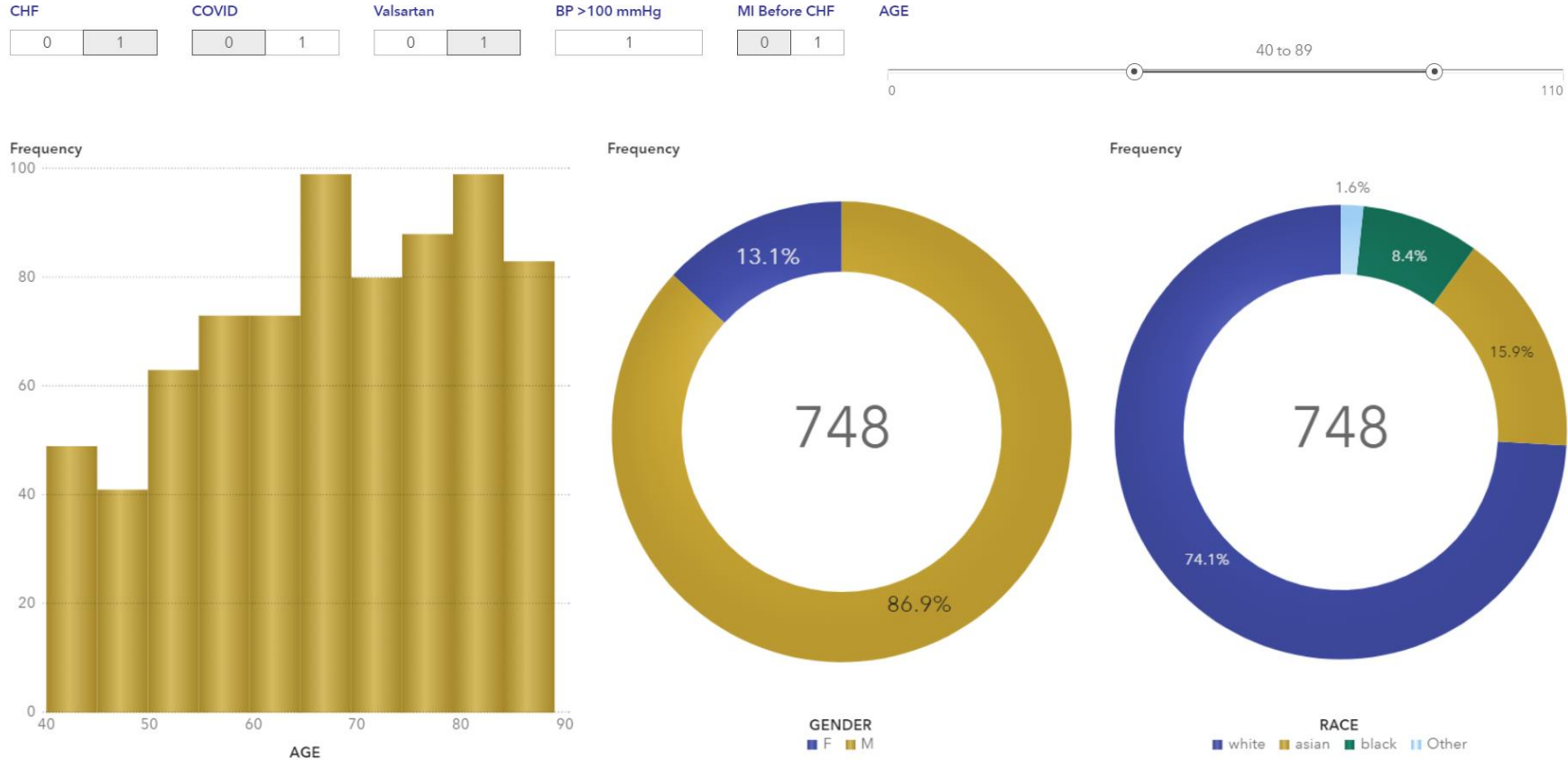
MI Before CHF

☐ 0 ☒ 1

AGE

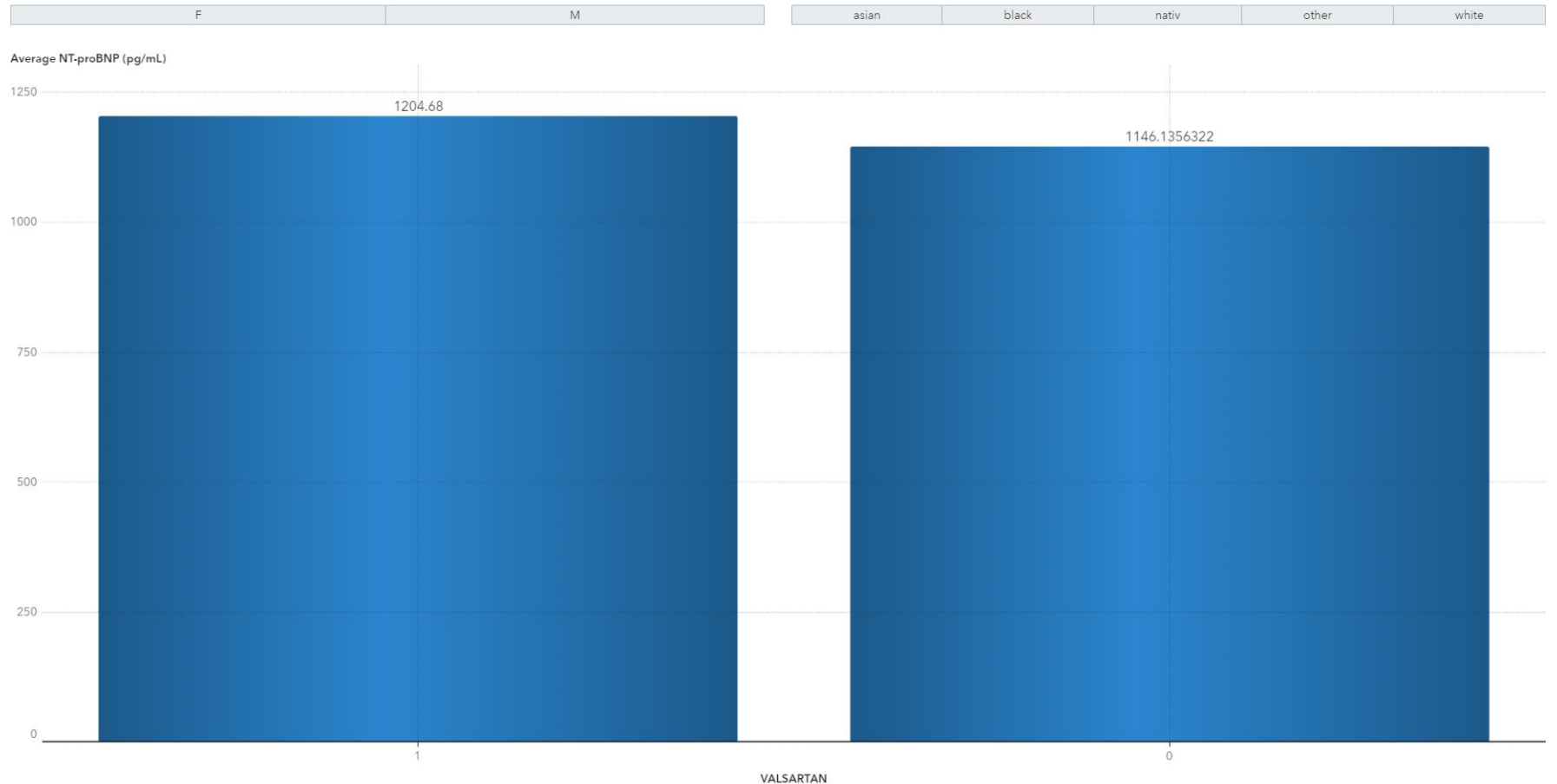


# Report Baseline Data\*



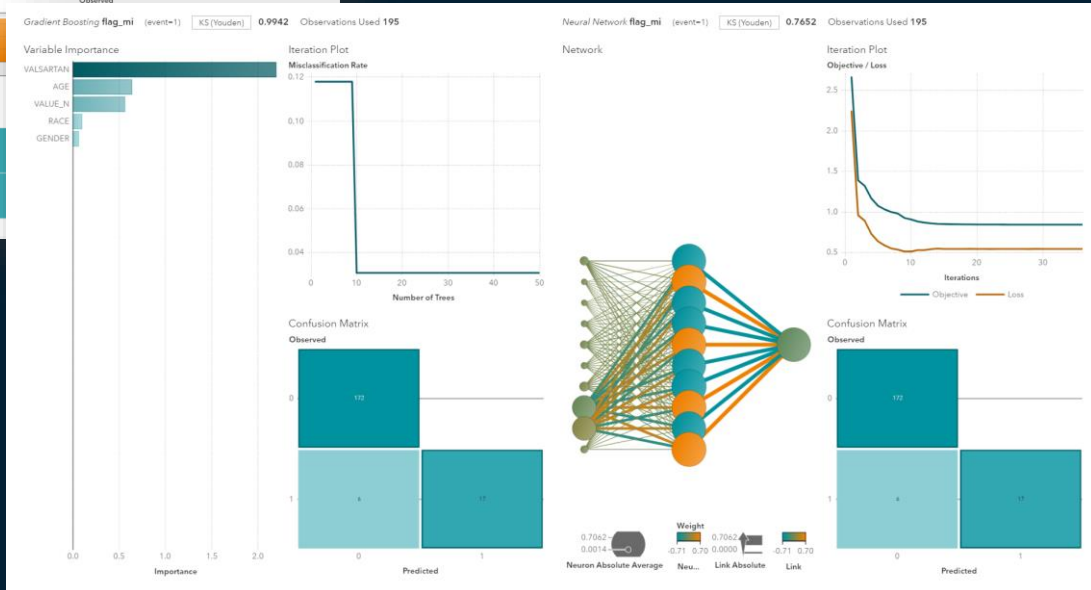
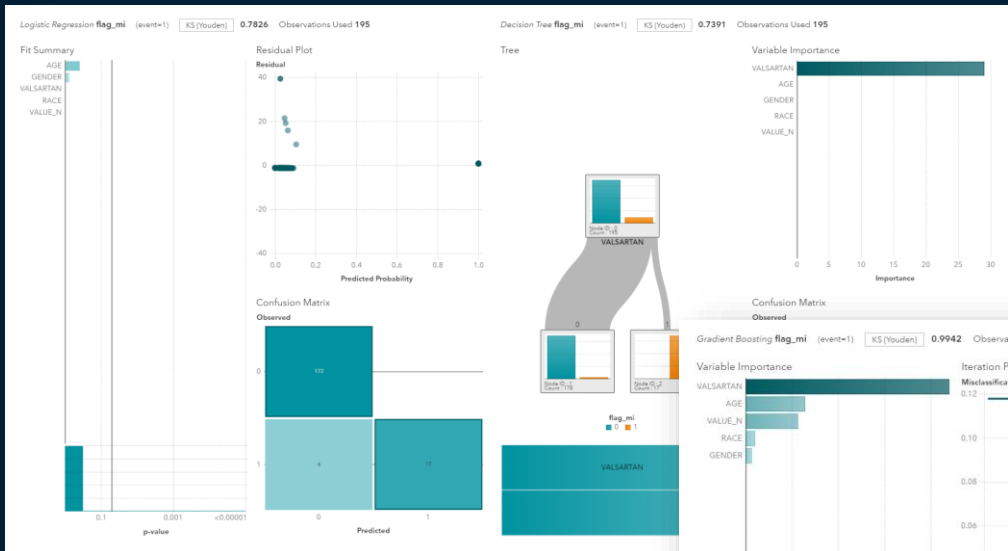
\*Age and MI eligibility criteria applied

# Test Primary Endpoint: NT-proBNP Levels



# Test Secondary Endpoint: Myocardial Infarction (MI)

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

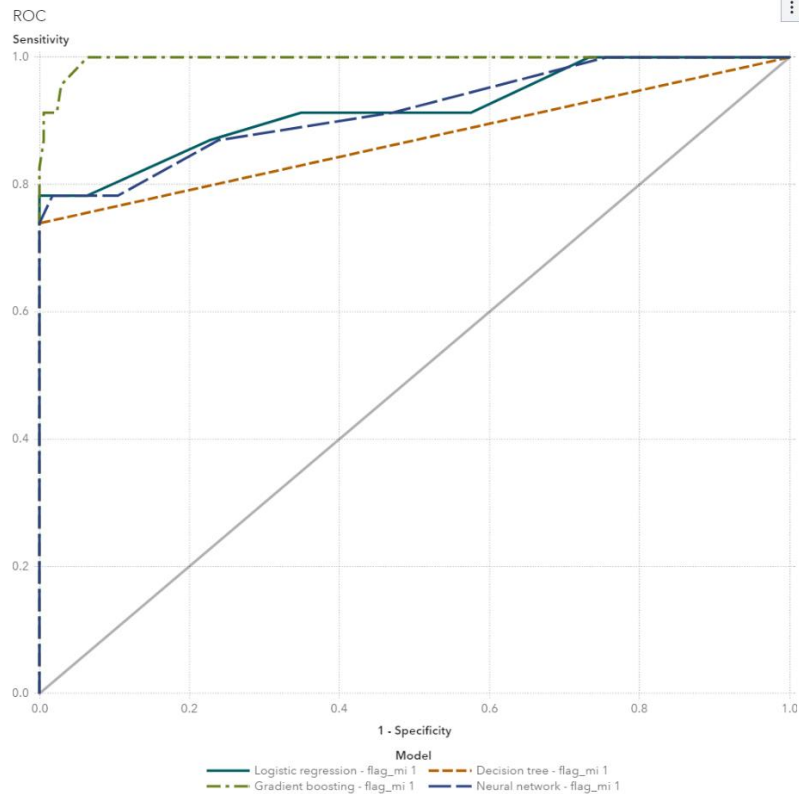
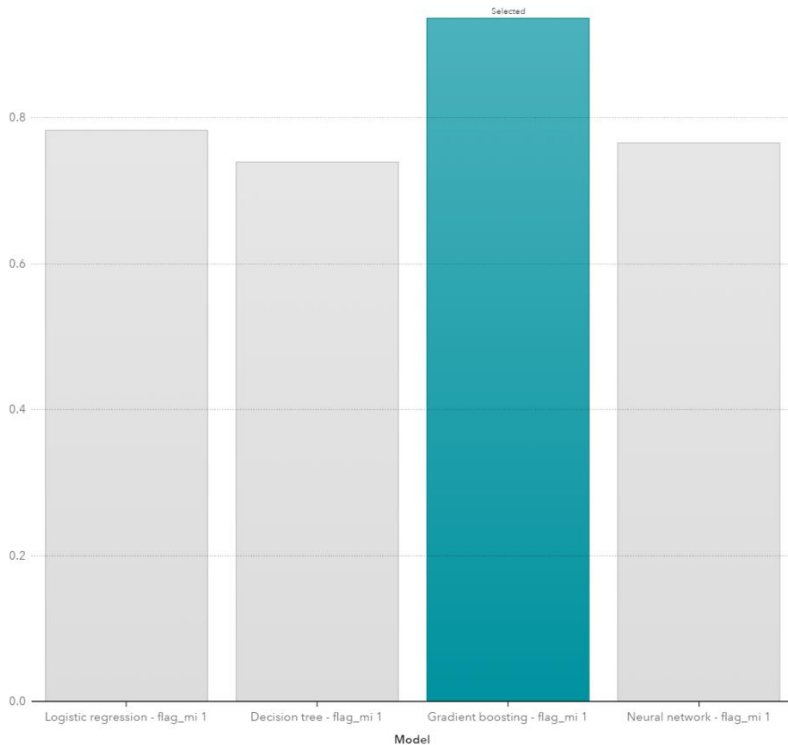


# Select the Best Fit Model for Secondary Endpoints

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 "Machine Learning", "Supervised Learning", and "Gradient Boosting" are expanded. The "Gradient Boosting" task is selected.
- Center Panel (Configuration):** Tabs for DATA, OPTIONS, OUTPUT, and INFORMATION. The "DATA" tab is active, showing:
  - DATA:** A dropdown menu set to "PUBLIC.SYNTHEA\_100K\_NTP..." with a folder icon.
  - Partition Data:** A section stating "Input data contains training data. Include:" with checkboxes for "Validation data" and "Test data", both of which are unchecked.
  - ROLES:** A section with a "Target" subsection where "Use a nominal target" is selected with a radio button.
- Right Panel (Code Editor):** Tabs for Code and Log. The "Code" tab is active, displaying SAS 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;
```
- Bottom Bar:** Status bar showing "Gradient Boosting [temp]" and "Line 1 Column 1". On the right, there are buttons for "Recover (19)" and "Submission (0)".

# 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 ?

[https://www.linkedin.com/in/sherrineeid/  
Sherrine.Eid@sas.com](https://www.linkedin.com/in/sherrineeid/Sherrine.Eid@sas.com)

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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](https://sas.com)

