

# **ANALYSIS OF REAL WORLD DATA COMPLEMENTS THE QUALITY OF CLINICAL TRIAL SUBMISSIONS**

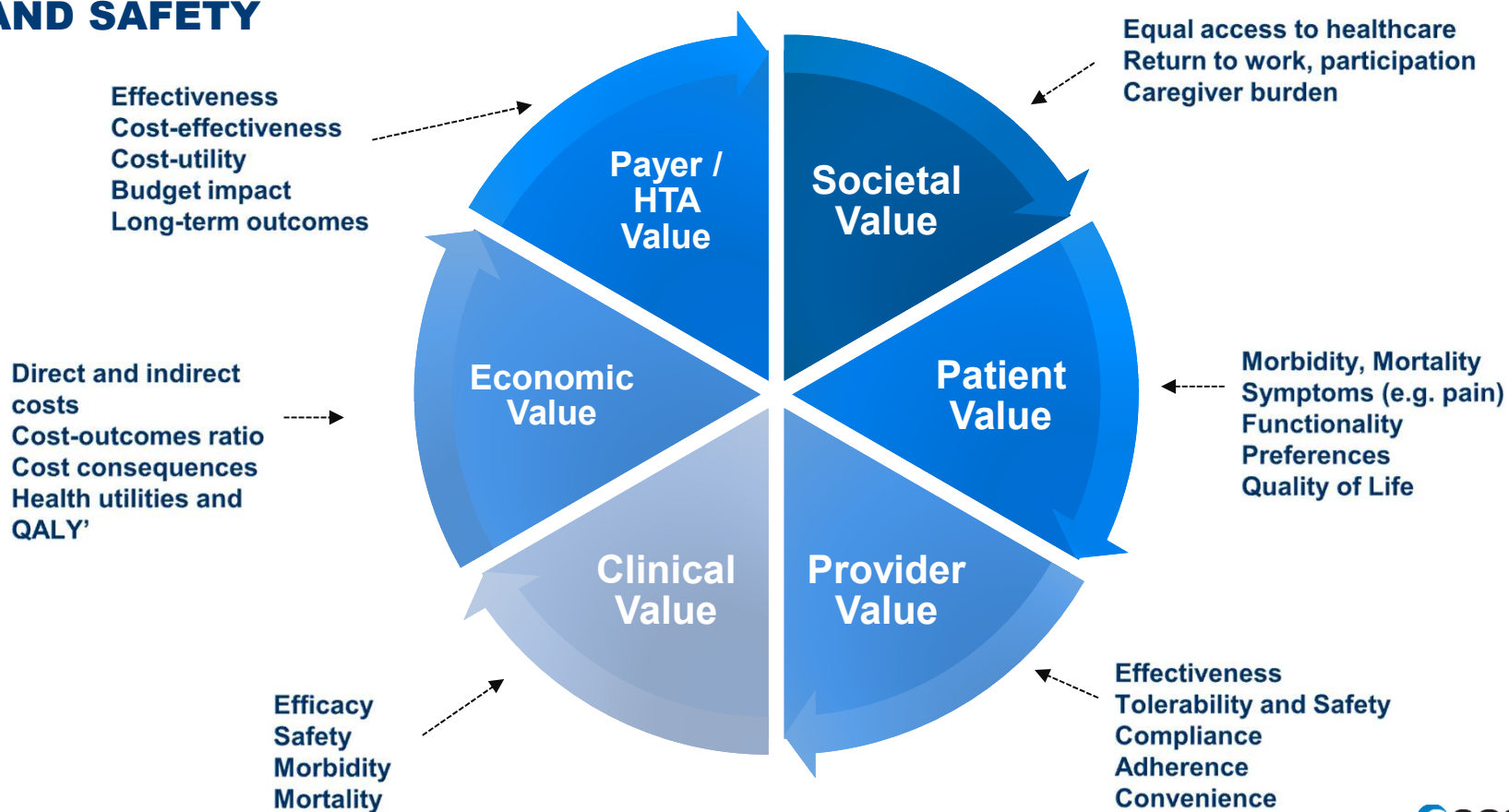
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ADVISORY INDUSTRY CONSULTANT AT SAS**



## WARNING

- This presentation is about real world problems, but still high-level
- This presentation might infect you with a new SAS “disease” – extending your SAS programming to new levels
- It is not only about programming, but also about in-memory analytics and yes, about UI solutions from SAS

## MAXIMIZING PRODUCT VALUE BY CONSIDERING MORE THAN EFFICACY AND SAFETY



Case Study: Maximise Product Value with Real World Evidence, Maria Kubin, VP at Bayer Healthcare – Eye for Pharma, April 2014.



AUDIT, RESEARCH AND GUIDELINE UPDATE

## Obtaining real-world evidence: the Salford Lung Study

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### ABSTRACT

We need to assess clinical treatments in real-life settings outside of randomised controlled trials (RCTs). Pragmatic RCT (pRCT) data can supplement RCTs by providing effectiveness information to support healthcare decisions. Electronic health records can facilitate concurrent safety monitoring and data collection without direct patient contact for large randomised study populations in pRCTs. The Salford Lung Study is the world's first phase III pRCT in asthma and chronic obstructive pulmonary disease (COPD), which aims to randomise over 7000 patients. This paper describes the hurdles overcome and the enormous effort and resource required to establish this comparative effectiveness study of a prelicence intervention.

**GlaxoSmithKline protocol HZC115151  
Asthma study clinicaltrials.gov registration  
NCT01706198**

the proportion of patients with asthma and COPD who meet the common inclusion criteria in RCTs has been estimated to be as low as 3% and 7%, respectively.<sup>1</sup> It is extremely difficult to extrapolate data from an RCT into real life for a number of reasons, including patient preference, lower adherence and comorbidities.

In contrast, 'real-world' studies assess *effectiveness* in large unselected populations, which include patients with comorbidities. Patients are under routine care, taking open-label treatment over a prolonged period, with no additional visits and no attempt to change adherence. Data are usually obtained using electronic health records, which provide long-term outcomes, including health economics, free from interviewer or recall bias. However, most effectiveness research is retrospective, limited by its non-randomised nature, and more robust study

## **CAN'T WE (DIFFERENT STUDY TYPES) JUST GET ALONG ?**

“Experiment, observation, and mathematics, individually and collectively, have a crucial role in providing the evidential basis for modern therapeutics. Arguments about the relative importance of each are an unnecessary distraction. Hierarchies of evidence should be replaced by accepting - indeed embracing - a diversity of approaches.”

- Sir Michael Rawlins, head, NICE, Lancet 2008



## EUROPEAN MEDICINES AGENCY : ADAPTIVE PATHWAYS

### ■ Definition

- EMA set up a regulatory route to allow new therapies for high medical need earlier to patients using iterative development in exchange for a restriction of the patient population, a conditional approval with appropriate benefit/risk management **and gathering sufficient “real life data”**.

### ■ Further description

- Adapt-SMART : IMI project to outline principles
- Pilot project by EMA in 2014 with good results

### ■ Implication for SAS programmers

- Real life data assessment and analytics
- Use your skills and modernized SAS environment (SAS Viya) to analyze patient registries and observational data
- Take results and ensure validated output for regulatory submission
- Input from patients is requested : ePRO, more data
- More involvement and evaluation from HTA's early on means going away from approval solely based on RCT efficacy and safety criteria : more holistic view of value of new product for patients



### Criteria for AP candidate selection

1. An **iterative** development plan: start in a well-defined subpopulation and **expand**, or have a Conditional Marketing Authorisation, maybe surrogate endpoints and **confirm**
2. **Real World Data** (safety and efficacy) can be acquired to supplement Clinical Trials
3. Input of all **stakeholders**, particularly HTAs, is fundamental

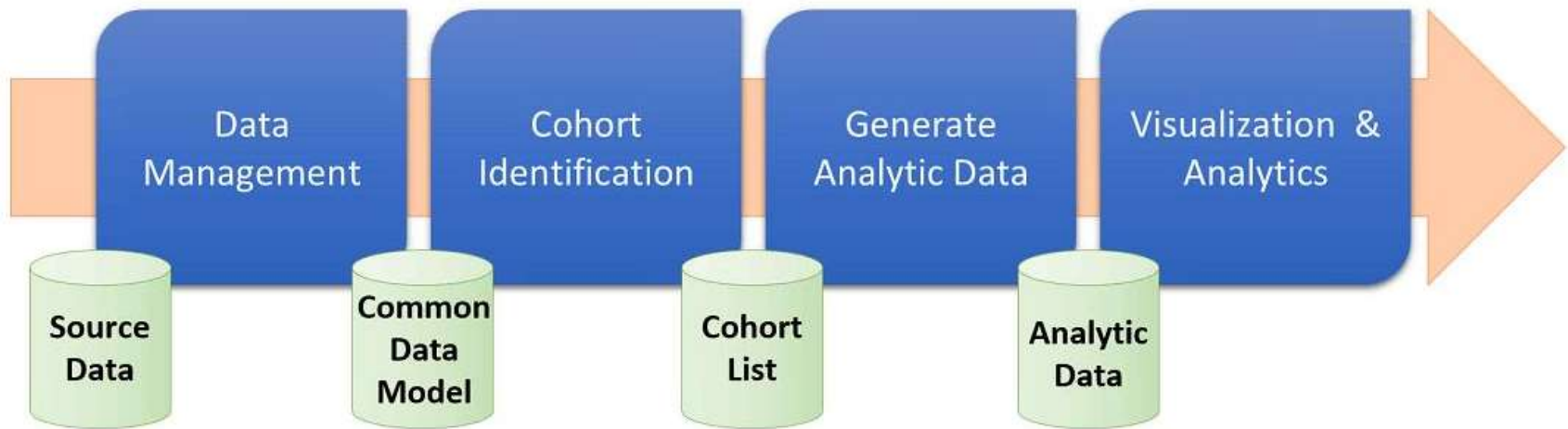
Unmet medical need is self-fulfilling.

..a product lifecycle outlook

## **SITUATION** | INDUSTRY CHALLENGES

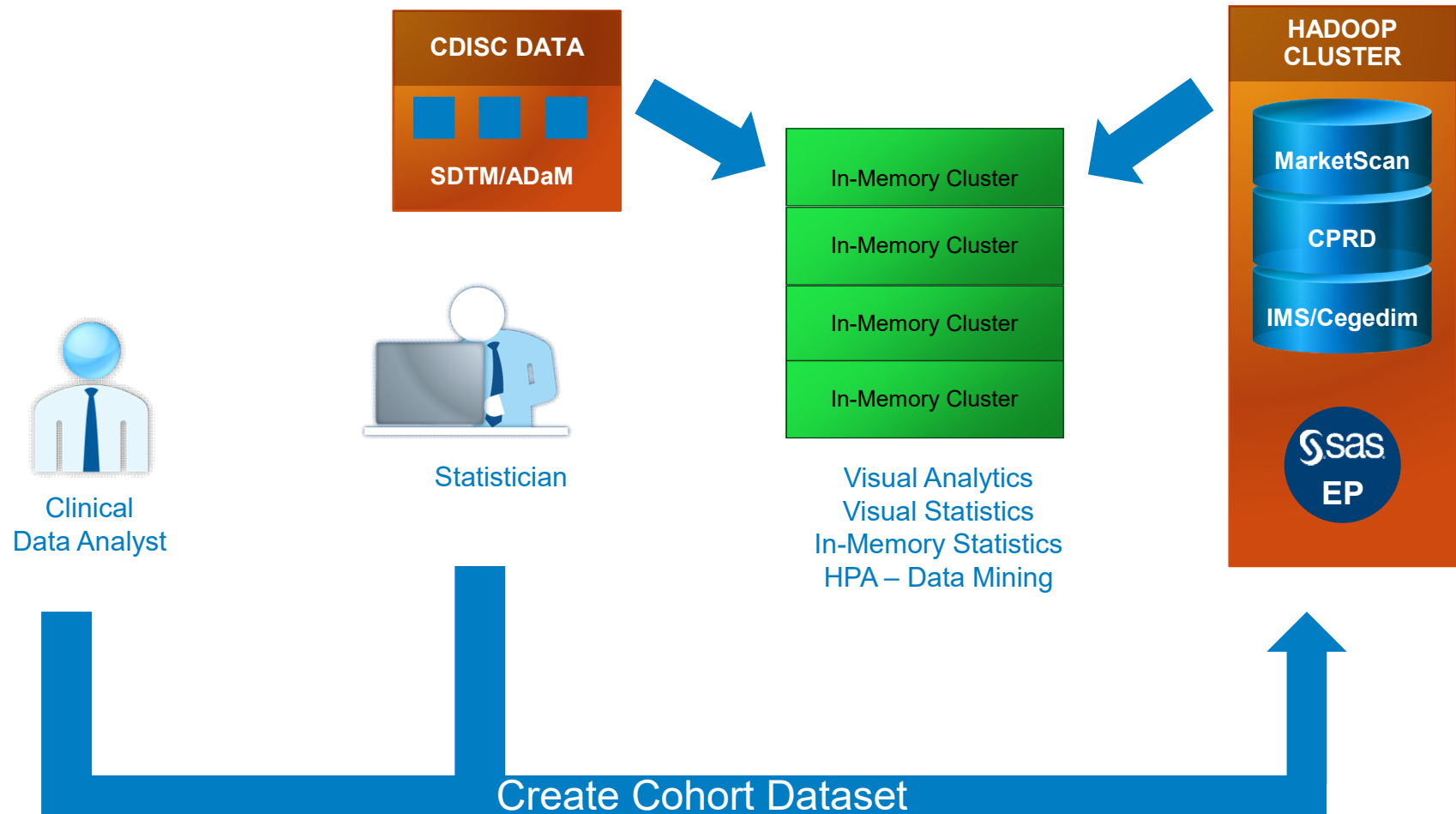
| <b>Critical Business Issue</b> | <b>Missed opportunities on potential research studies</b>                                                                                                                                                                                                                                                                                                                                                                                                                           |
|--------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Problems/Reasons               | <ul style="list-style-type: none"><li>• Identification of patients for cohort study requires both clinical and technical expertise</li><li>• Iterative process to build cohort list of patients</li><li>• Data size and complex queries takes long execution</li><li>• Multiple data sources; no industry standardization</li><li>• Analytics are programmed for each cohort, time consuming</li></ul>                                                                              |
| Specific Capabilities          | <ul style="list-style-type: none"><li>• Data Management and repeatable ETL processes</li><li>• Ability to apply complex query logic to identify patients that meet cohort specifications in near real-time</li><li>• Ability to define cohorts based on an index-event</li><li>• Specifying inclusion/exclusion criteria relative to the index event</li><li>• Visually explore cohort characteristics</li><li>• Apply repeatable analytical methodologies across cohorts</li></ul> |

## REAL WORLD EVIDENCE : PATH TO INSIGHT

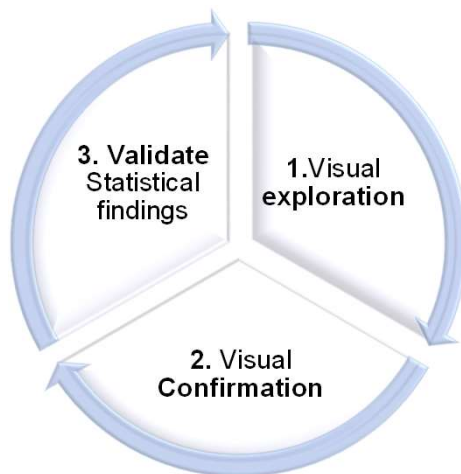


## **RWE ANALYTICS** | USING COHORTS FROM RWE QUERIES

- Query tool creates a list of patients included in the cohort
- Creation of standard analytic-ready datasets can be automated and feed into downstream processes including:
  - SAS® Visual Analytics reports and explorations – SAS Viya
  - SAS® Studio
  - JMP, R or other tools
- Other derived outputs can be generated easily using typical SAS technology (DMS SAS, SAS Data Integration Studio, SAS Studio)



## USING SAS TO ANALYZE HEALTHCARE DATA



- **Exploration** of the data to generate insights

*How ? using visual exploration capabilities*

- **Confirmation** of these insights statistically

*How ? using visual statistics capabilities*

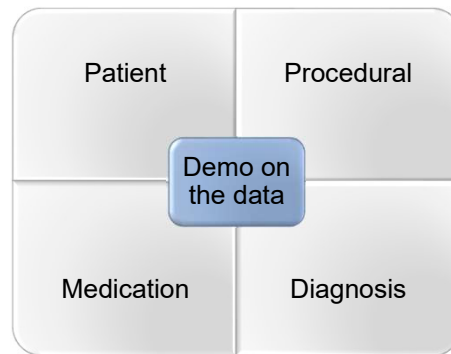
- Closing the loop – **Validate** Statistical findings

*How ? using in-memory statistics (code) in SAS Studio*

## USING SAS TO ANALYZE HEALTHCARE DATA

### What data are we using ?

- Healthcare data (mixed EHR & Claims data)



- IMPORTANT :
  - ✓ Structure of the data is equal to Real World Evidence (Healthcare) data
  - ✓ Content is '**simulated**' Heart Failure data
  - ✓ Data Preparation completed upfront

## USING SAS TO ANALYZE HEALTHCARE DATA

## Validate Statistical Findings



Exploration Heart Failure x SAS Studio

https://waves.sas.com/SASStudio/main?locale=en\_US&zone=GMT%252B01%253A00&https%3A%2F%2Fwaves.sas.com%2FSASStudio%2F=

SAS® Studio

Server Files and Folders

- hpametaswe.fra.sas.com
  - Folder Shortcuts
    - Files (Home)
      - Dossier\_AUD
      - Dossier\_BLC
      - Dossier\_ERV
      - Dossier\_FAR
      - Dossier\_IGO
      - Dossier\_msa
      - Dossier\_SEP
      - DOSSIER\_SYF
      - Folder\_sbxml
        - Crosstab\_nicardipin.sas
        - Program\_rwe.sas
        - Program\_rwe\_xarelto.sas
        - TextParse.sas
      - JBD
      - JEC
      - LonghowLam
      - MFA
      - MGR
      - MonDossier
      - ODSEditorFiles
      - PAN
      - sasuser.v93
      - sasuser.v94
      - Test
      - TEST

Tasks

Snippets

Libraries

File Shortcuts

SAS Folders (experimental)

Program\_rwe\_xarelto.sas

CODE LOG RESULTS

```
1 LIBNAME lrosthls SASIOLA TAG=rosthls
2 PORT=10017 SIGNER="http://hpademoswe.fra.sas.com:7980/SASLASRAuthorization" HOST="hpademoswe.fra.sas.com" ;
3
4
5 %let classification = rx_xarelto ;
6 %let continuous = smoking age_category diastolic_bp bmi avg_income;
7
8 proc contents data=lrosthls.MEDICATIONS_10PCT;
9 run;
10
11 data lrosthls.MEDICATIONS_10PCT_S;
12   attrib rx_xarelto length=8;
13   set lrosthls.MEDICATIONS_10PCT;
14   if USC_MED_DESC = "XARELTO 10 MG TABLET" then rx_xarelto=1; else rx_xarelto=0;
15 run;
16
17
18 proc imstat data=lrosthls.MEDICATIONS_10PCT_S;
19   crosstab age_category * rx_xarelto /
20     measures
21       chisq
22       ncmis;
23 quit;
24
25 proc imstat data=lrosthls.MEDICATIONS_10PCT_S;
26   logistic &classification = &continuous ;
27   /* VARSELECTION desc name = LogisModel sls=0.05 /*score(_ALL_)*/;
28 run;
29
30 proc datasets library=LROSTHLS;
31   delete MEDICATIONS_10PCT_S;
32 run;
```

Line 32, Column 5

# USING SAS TO ANALYZE HEALTHCARE DATA

## Validate Statistical Findings



Program\_rwe\_xarelto.sas x

CODE LOG RESULTS

LIKELIHOOD RATIO

|                  |          |   |        |
|------------------|----------|---|--------|
| Likelihood Ratio | 515.7003 | 8 | <.0001 |
|------------------|----------|---|--------|

Parameter Estimates for ROST\_HLS.MEDICATIONS\_10PCT\_S

| Parameter                     | Estimate | Standard Error | z Value | Pr >  z |
|-------------------------------|----------|----------------|---------|---------|
| Intercept                     | 3.2398   | 0.3744         | 8.65    | <.0001  |
| smoking Current smoker        | -0.00807 | 0.1401         | -0.06   | 0.9540  |
| smoking Never smoked          | 0.1012   | 0.1232         | 0.82    | 0.4112  |
| smoking Not currently smoking | -0.04322 | 0.09283        | -0.47   | 0.6408  |
| smoking Previously smoked     | 0        | -              | -       | -       |
| age_category 25-44            | -2.2789  | 0.1061         | -21.48  | <.0001  |
| age_category 45-64            | 0.07933  | 0.08068        | 0.98    | 0.3255  |
| age_category 65-79            | 0        | -              | -       | -       |
| diastolic_bp                  | -0.00403 | 0.004374       | -0.92   | 0.3564  |
| bmi                           | -0.00139 | 0.004484       | -0.31   | 0.7574  |
| avg_income                    | 6.891E-7 | 2.723E-6       | 0.25    | 0.8002  |

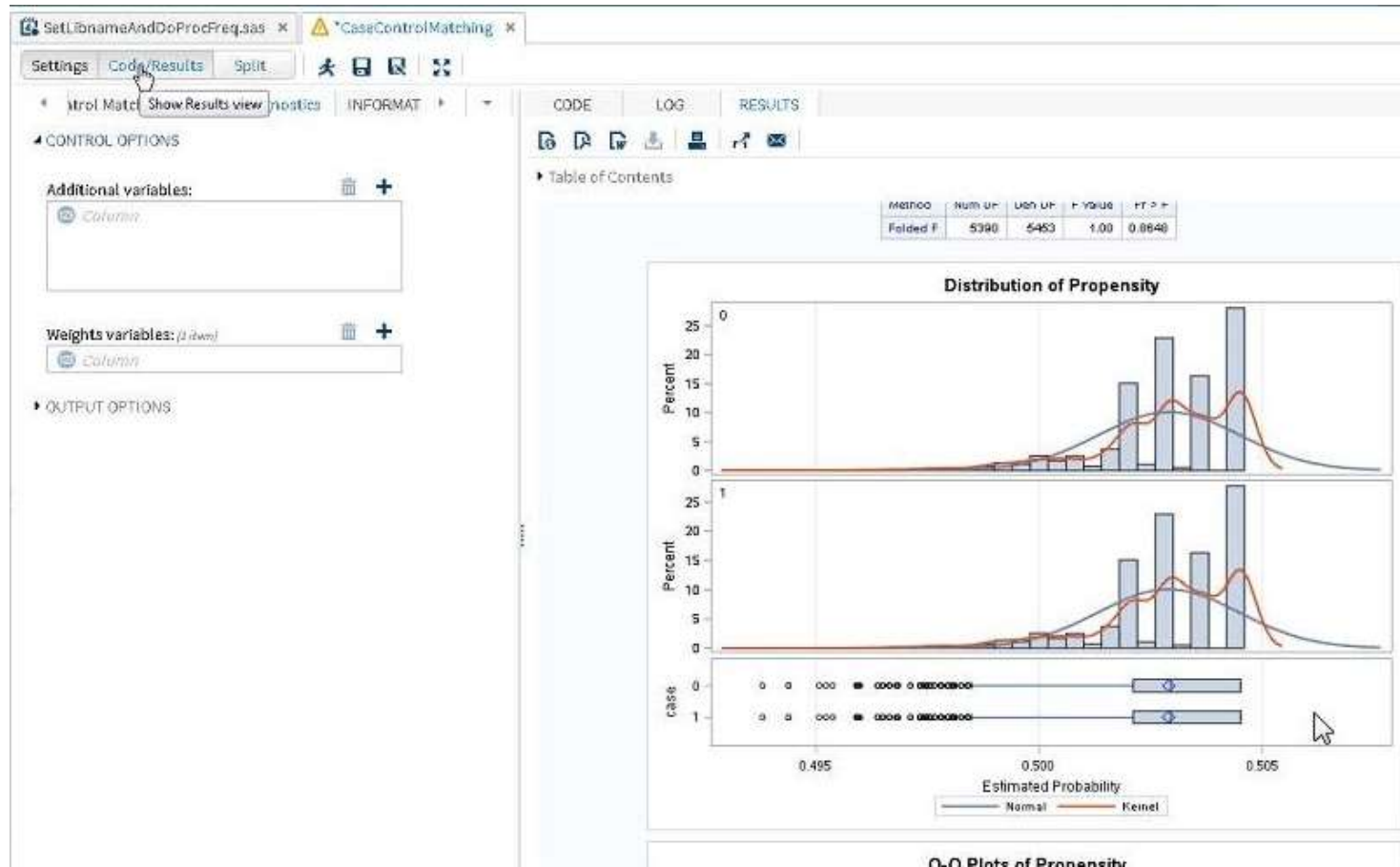
Type III Tests of Model Effects for ROST\_HLS.MEDICATIONS\_10PCT\_S

| Effect       | Num DF | Chi-Square | Pr > ChiSq |
|--------------|--------|------------|------------|
| smoking      | 3      | 1.90       | 0.5932     |
| age_category | 2      | 651.09     | <.0001     |
| diastolic_bp | 1      | 0.85       | 0.3564     |
| bmi          | 1      | 0.10       | 0.7574     |
| avg_income   | 1      | 0.06       | 0.8002     |

Dimensions Iteration History Convergence Fit Statistics Type III Test Parameter Estimates Response Profile

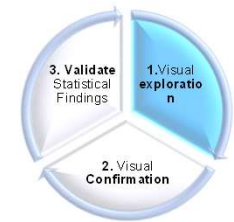
| Effect                   | DF | Chi-Square | Pr > ChiSq |
|--------------------------|----|------------|------------|
| bodymass index           | 1  | 0.095431   | 0.7574     |
| diastolic blood pressure | 1  | 0.850678   | 0.3564     |
| average income           | 1  | 0.064058   | 0.8002     |
| age category             | 2  | 651.0934   | <0.0001    |
| smoking                  | 3  | 1.901041   | 0.5932     |

## CASE CONTROL / PROPENSITY SCORING



## USING SAS TO ANALYZE HEALTHCARE DATA

## Exploration of the data to generate insights



- SAS Visual Analytics Hub → Data Explorer

The screenshot displays the SAS Visual Analytics Hub interface. At the top, there is a navigation bar with the SAS logo, a search bar, and user information (Stijn). Below the navigation bar, the main content area is divided into several sections:

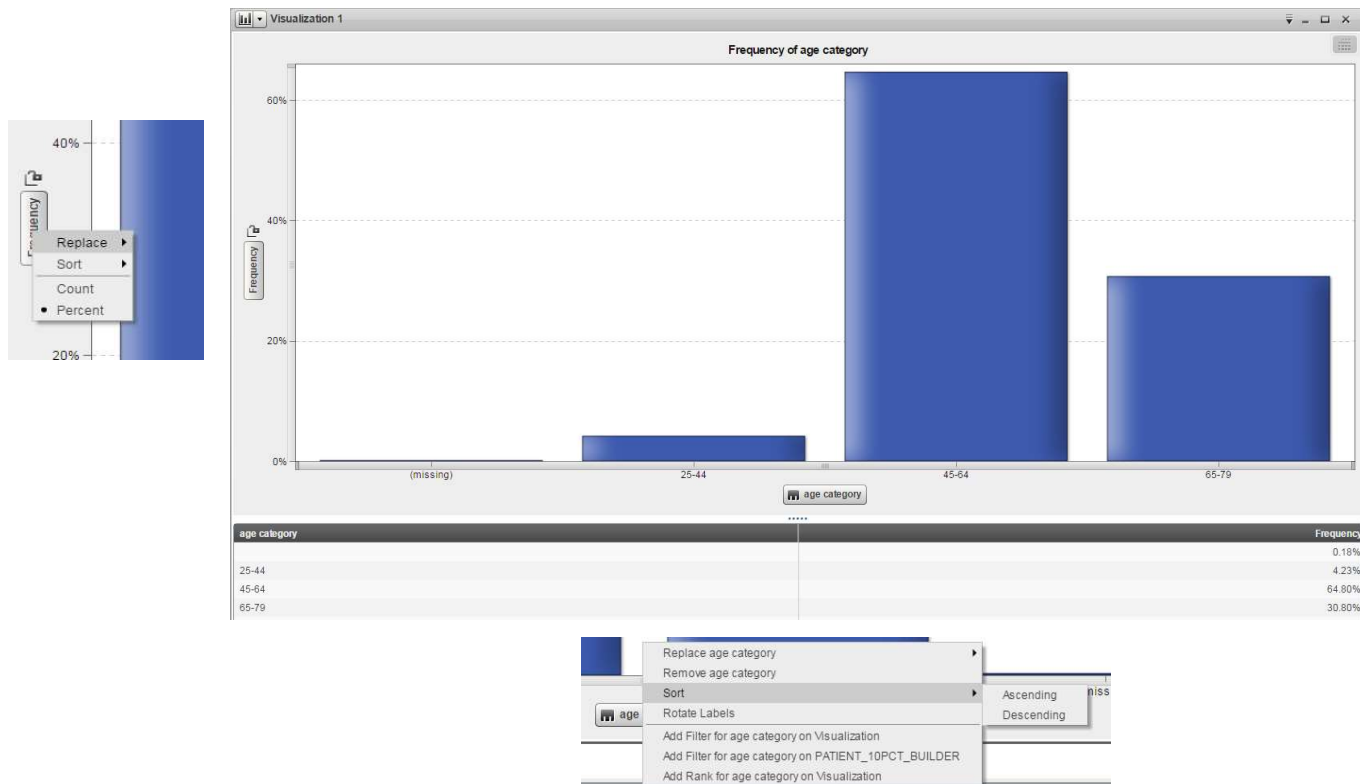
- Left Sidebar:** Contains three tiles: "Browse", "Shortcut", and "Collection".
- Top Row:** Two large tiles labeled "Data Explorer" and "Report Designer".
- Recent Collections:** A section titled "Recent" showing two collections: "Exploration Heart Failure Phase..." (dated 3 Feb 2016 22:31:40) and "Exploration Heart Failure" (dated 3 Feb 2016 10:35:57).
- Favorites:** A section titled "Favorites" with a message: "Content that you mark as a favorite will be displayed here. [Add favorites](#) now or later."
- Links:** A section titled "Links" with a message: "Links will be displayed here. [Add links](#) now or later."
- Test\_Stijn\_NewCollection:** A section titled "Test\_Stijn\_NewCollection" showing a collection named "Adverse Events" (Visual exploration) under the path "/My Folder/Test\_Stijn\_NewCollection".

## USING SAS TO ANALYZE HEALTHCARE DATA

### Exploration of the data to generate insights

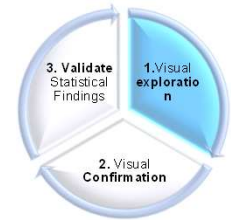


- New Visualization → Explore the **PATIENT** data (*Age Category*) using a Bar Chart



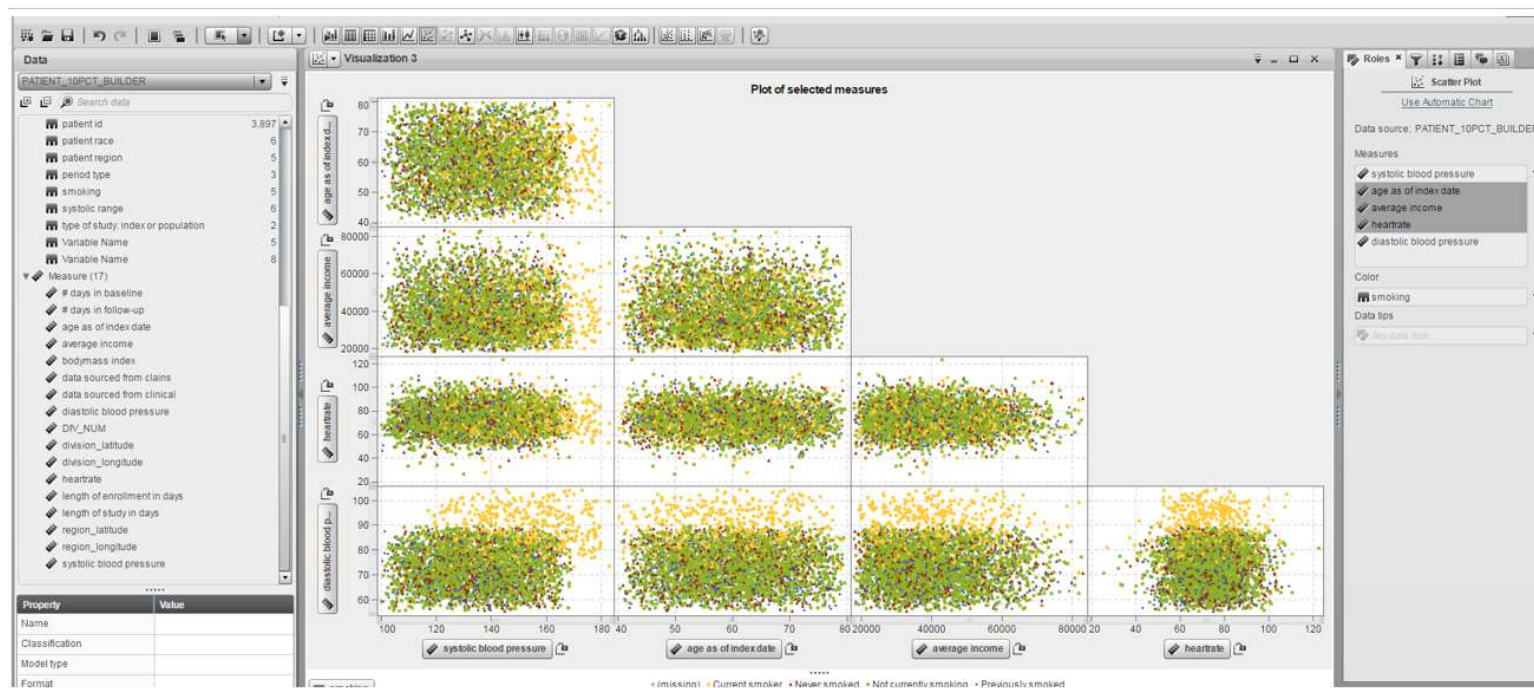
## USING SAS TO ANALYZE HEALTHCARE DATA

## Exploration of the data to generate insights



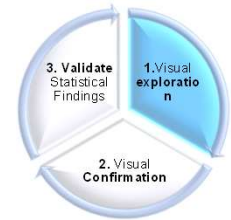
Measures: Diastolic & Systolic, etc.

Color: Smoking (Variable)



## USING SAS TO ANALYZE HEALTHCARE DATA

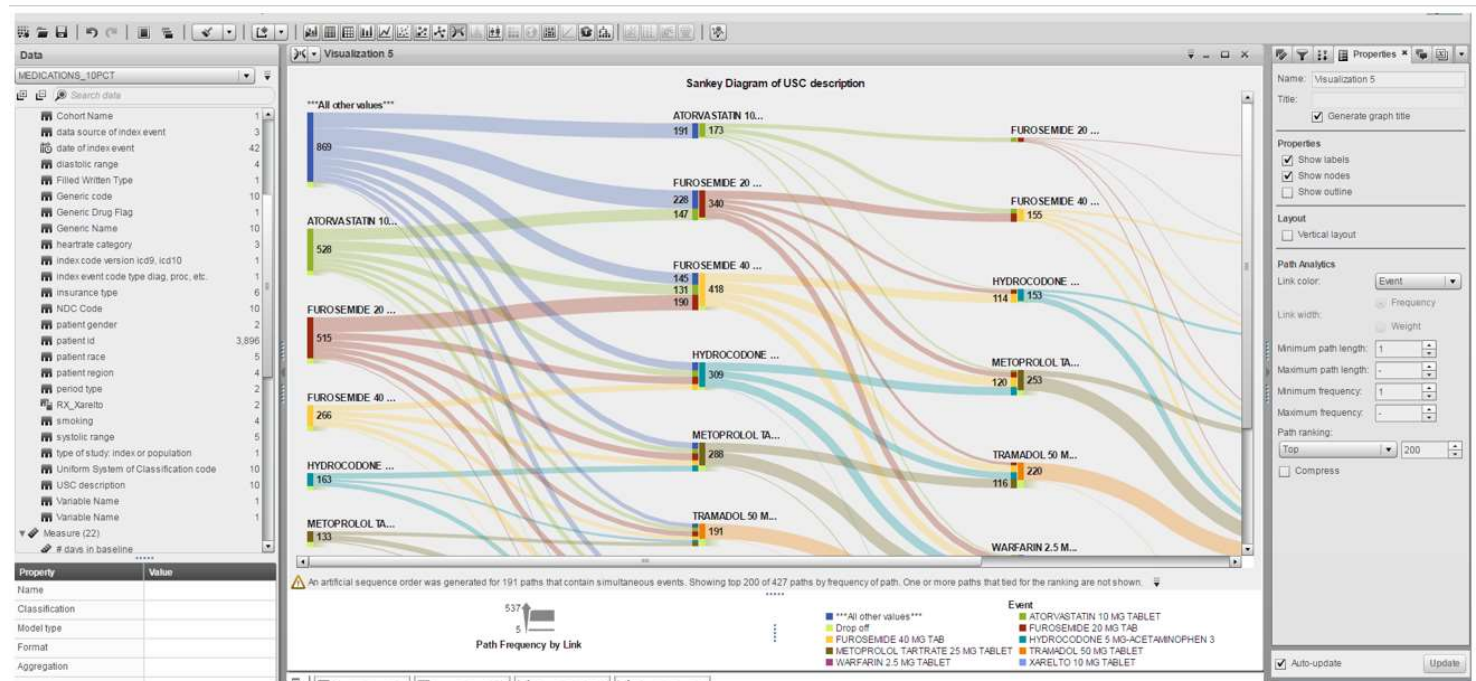
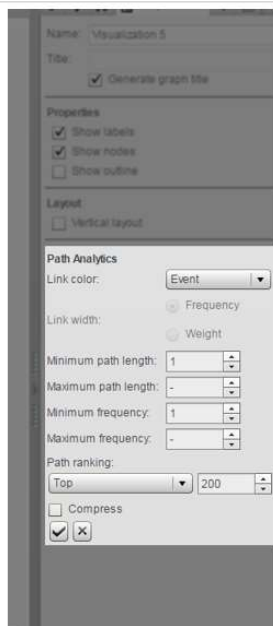
## Exploration of the data to generate insights



Properties – Line Color: Event

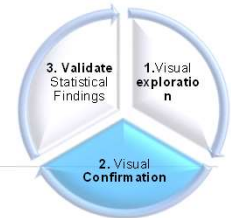
Each Medication is an event → has a separate color.

Switching in time from therapy



## USING SAS TO ANALYZE HEALTHCARE DATA

## Confirmation of insights statistically



| Data                       |    |
|----------------------------|----|
| MEDICATIONS_10PCT          |    |
| Search data                |    |
| Cohort Name                | 1  |
| data source of index event | 3  |
| date of index event        | 42 |

### New VISUALIZATION

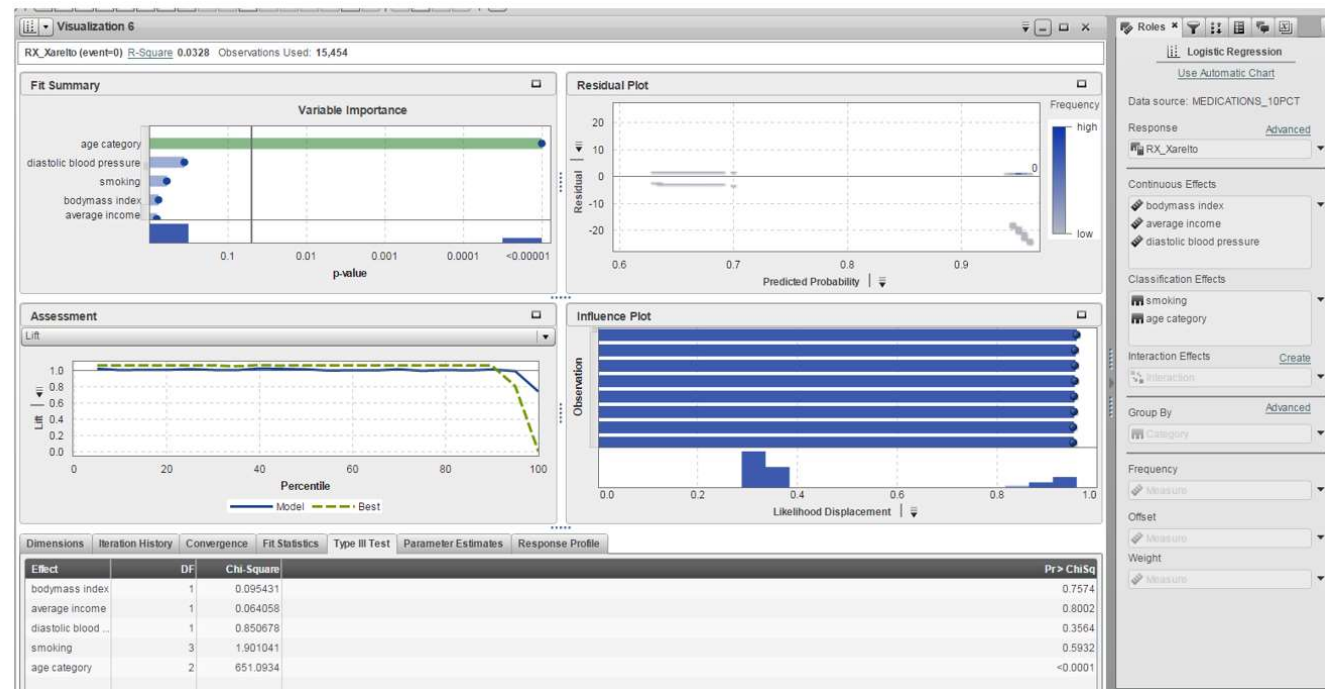
Select "Medications\_10PCT" Data

### New Logistic Regression Model

Age is the only variable that is statistically significant in the logistic regression model.

So the age category is predictive whether the patient is likely to be prescribed Xarelto.

We have seen during explorations younger patients where prescribed primarily Xarelto.



## USING SAS TO ANALYZE HEALTHCARE DATA

## Confirmation of insights statistically



### Model Comparison

**Model Comparison**

Data source: MEDICATIONS\_10PCT

Response: RX\_Xarelto

Level: 0

Group By: (none)

Available models:

Selected models:

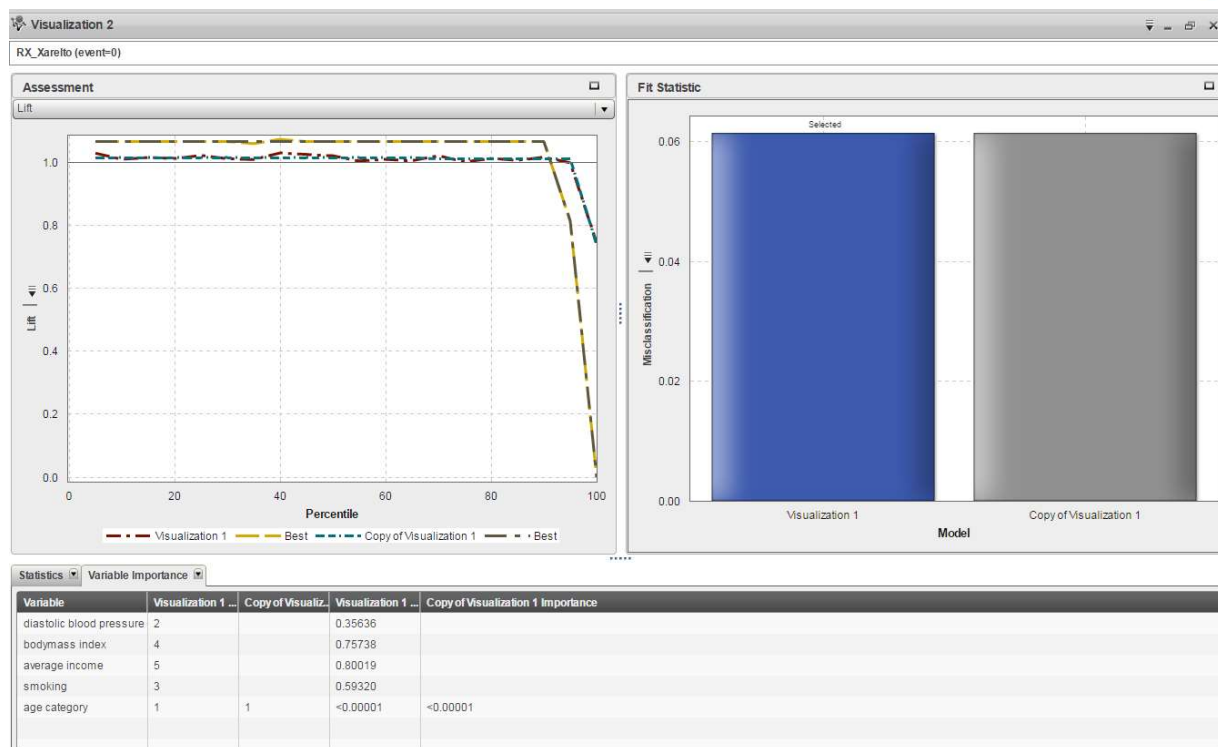
- Visualization 1
- Copy of Visualization 1

Model Comparison - Compares decision trees, linear regressions, logistic regressions, and generalized linear models with matching criteria.

OK Cancel

No difference between the 2 Logical Regression models. Normal as first one already made it clear that AGE was/is the only Clin. Stat. Significant Variable.

In reality you could potentially compare Regression model with another statistical model e.g. decision tree; linear regression.



## SUMMARY

- Use SAS programming skills in a new world
- Use new capabilities to confirm hypotheses on patients
- Inclusion/exclusion scenario testing
- Adherence of patients to therapy
- Patient-reported data
- Wearables / devices
- Efficacy / safety

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