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

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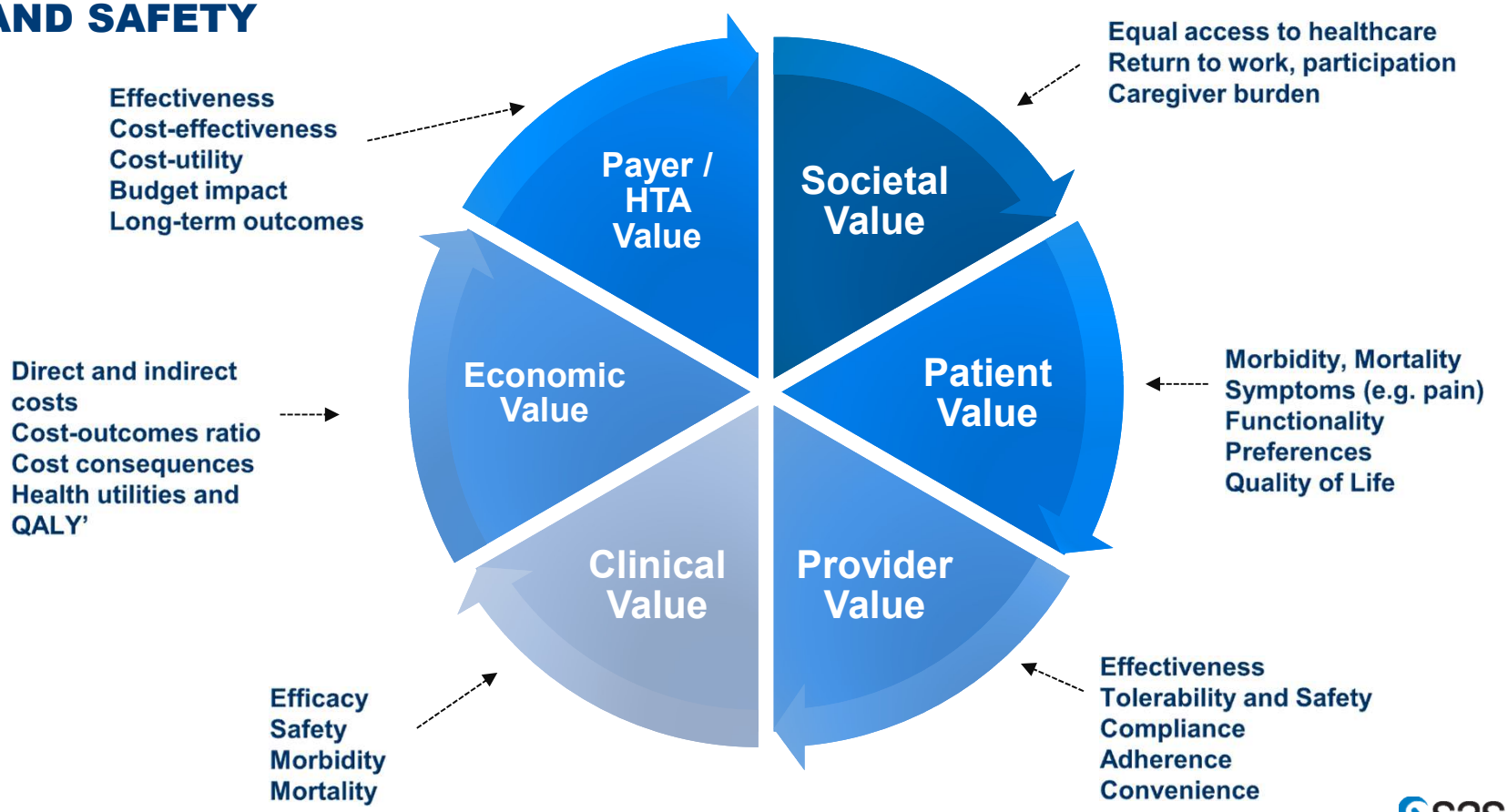
WARNING

- 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

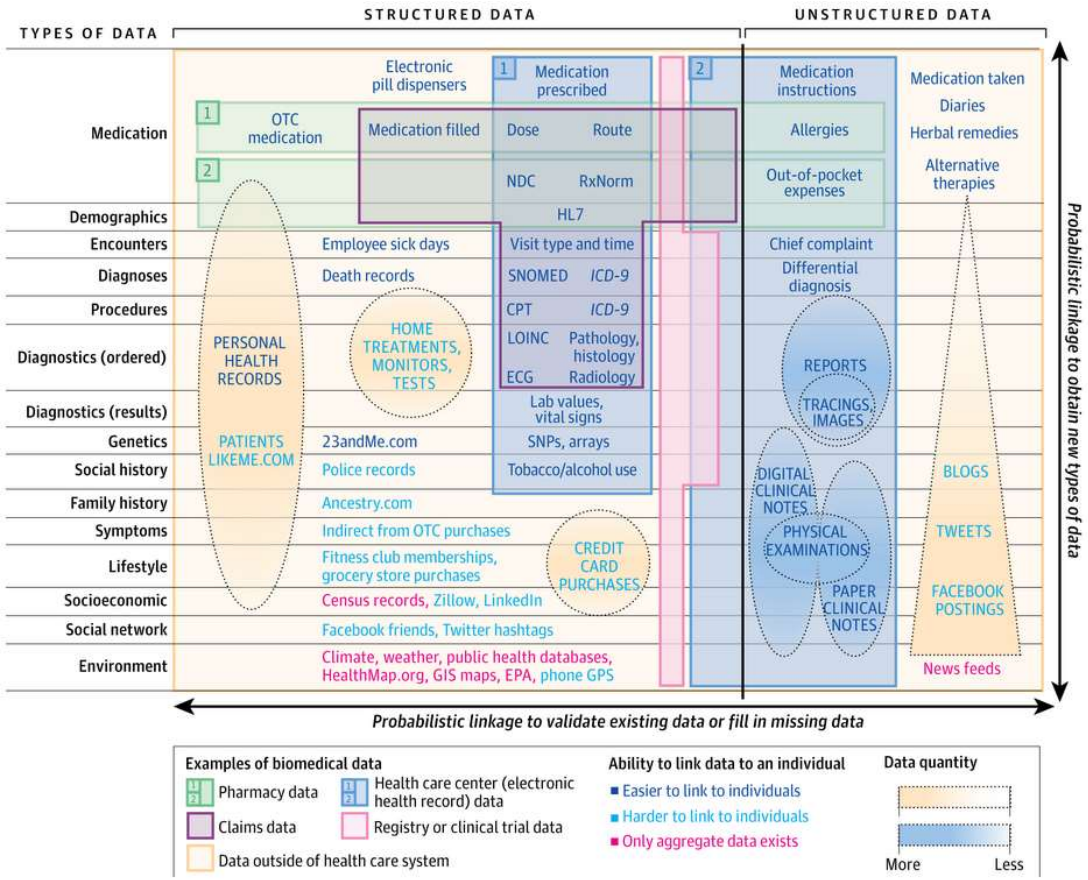
the proportion of patients with asthma and COPD who meet the common inclusion criteria in RCTs has been estimated to be as low as 3% and 7%, respectively.[1] It is extremely difficult to extrapolate data from an RCT into real life for a number of reasons, including patient preference, lower adherence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



Source: “Finding the Missing Link for Big Biomedical Data”, Weber *et al.*, 2014, Downloaded From: http://www.jamafacial.com/ on 06/11/2014

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

EUROPEAN MEDICINES AGENCY

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

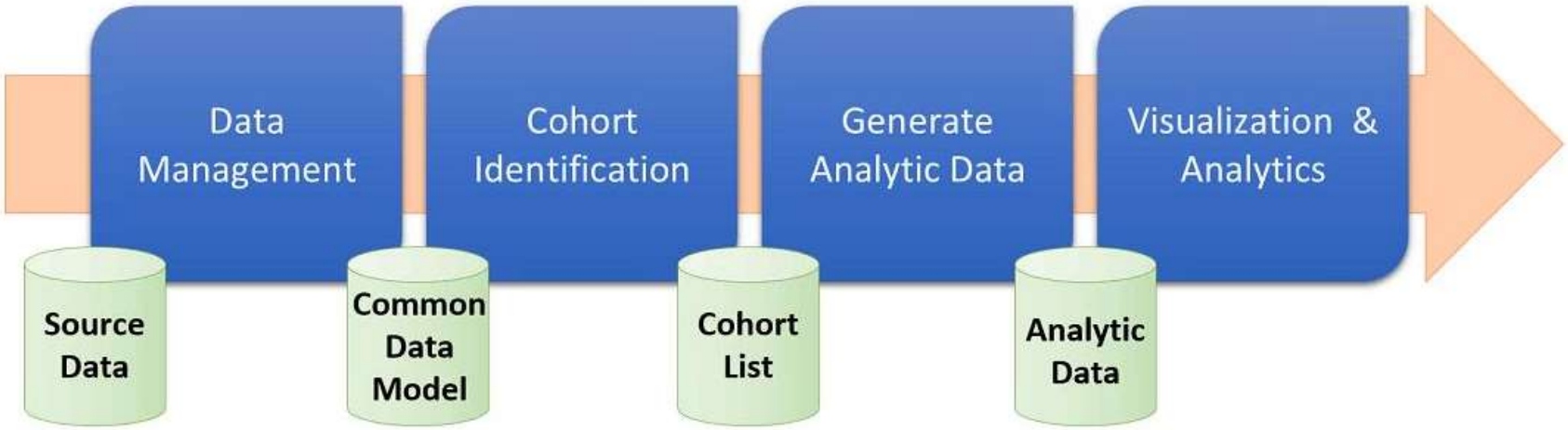
Unmet medical need is self-fulfilling.

..a product lifecycle outlook

SITUATION | INDUSTRY CHALLENGES

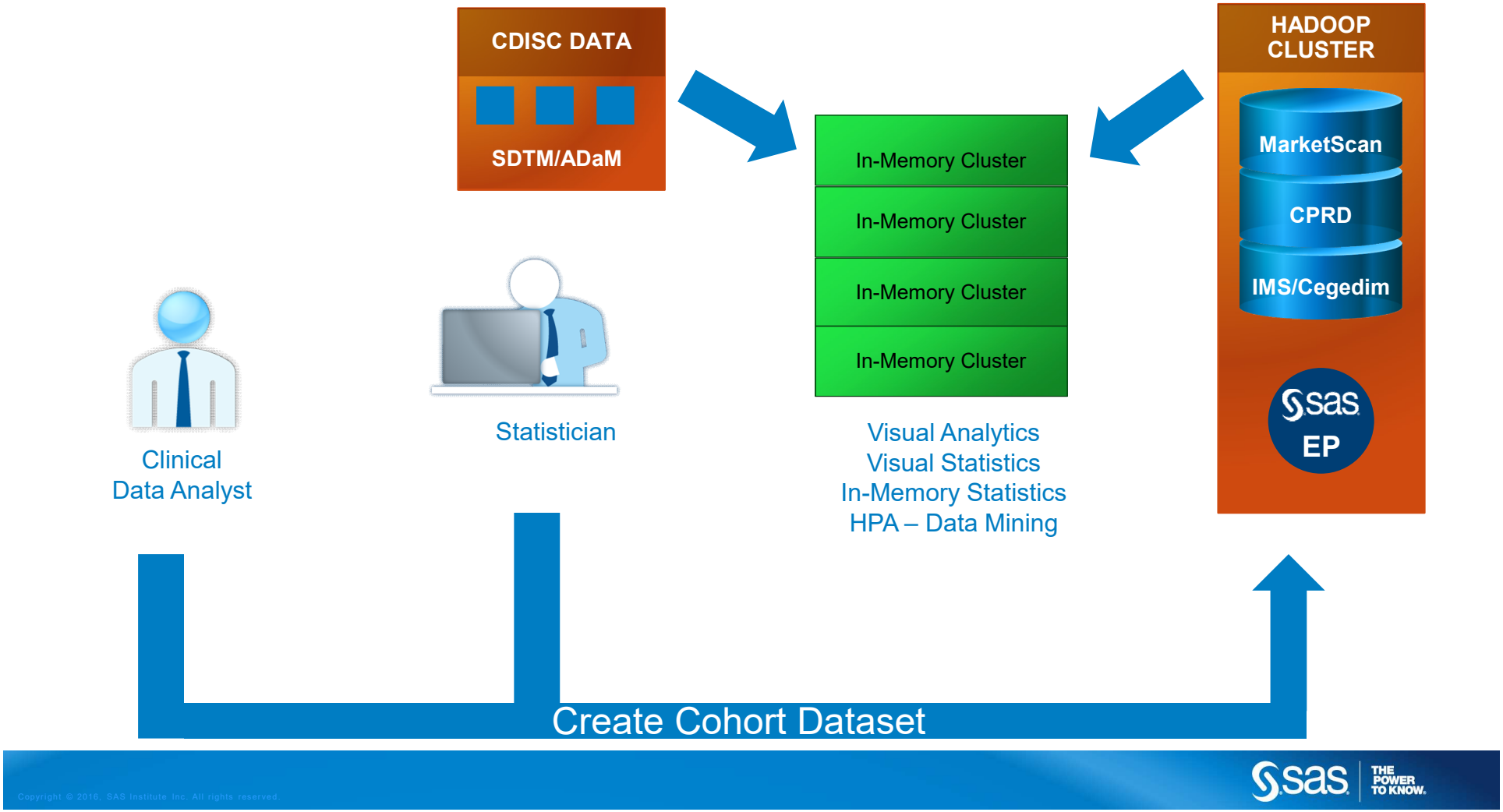
Critical Business Issue	Missed opportunities on potential research studies
Problems/Reasons	• Identification of patients for cohort study requires both clinical and technical expertise • Iterative process to build cohort list of patients • Data size and complex queries takes long execution • Multiple data sources; no industry standardization • Analytics are programmed for each cohort, time consuming
Specific Capabilities	• Data Management and repeatable ETL processes • Ability to apply complex query logic to identify patients that meet cohort specifications in near real-time • Ability to define cohorts based on an index-event • Specifying inclusion/exclusion criteria relative to the index event • Visually explore cohort characteristics • Apply repeatable analytical methodologies across cohorts

REAL WORLD EVIDENCE : PATH TO INSIGHT

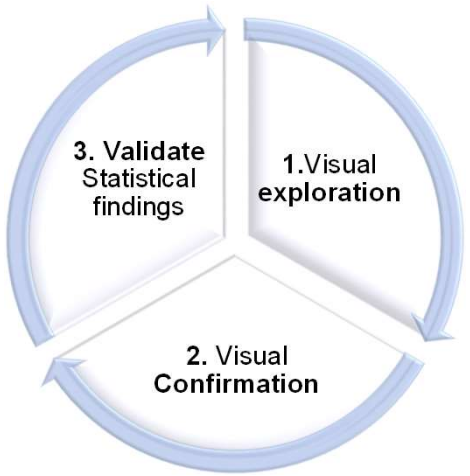


RWE ANALYTICS | USING COHORTS FROM RWE QUERIES

- 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

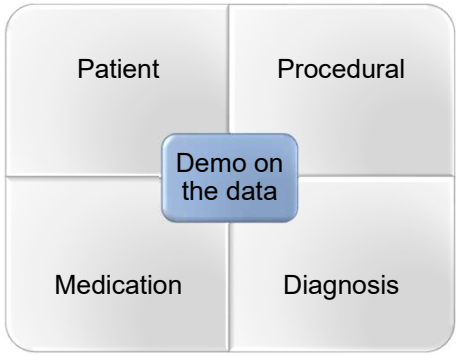
  How ? *using visual statistics capabilities*

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

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

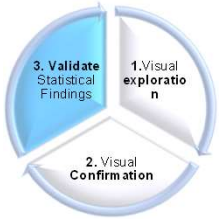
What data are we using ?

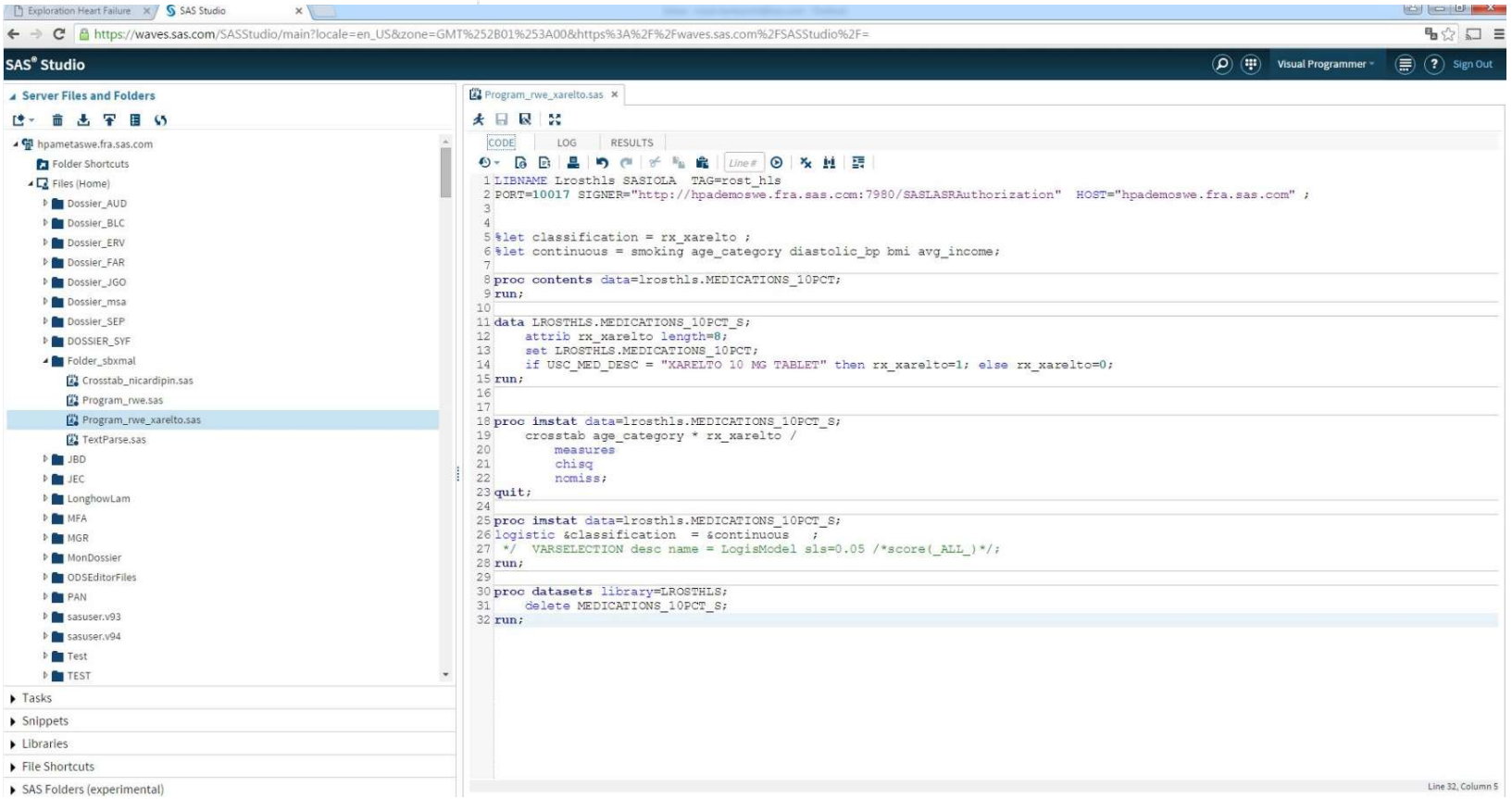
- Healthcare data (mixed EHR & Claims data)



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

Validate Statistical Findings





Validate Statistical Findings

Program_rwe_xarelto.sas

CODE | LOG | RESULTS

Likelihood Ratio	515.7663	8	<.0001

Parameter Estimates for ROST_HLS.MEDICATIONS_10PCT_S

Parameter	Estimate	Standard Error	z Value	Pr > |z|
Intercept	3.2388	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	0.09263	-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

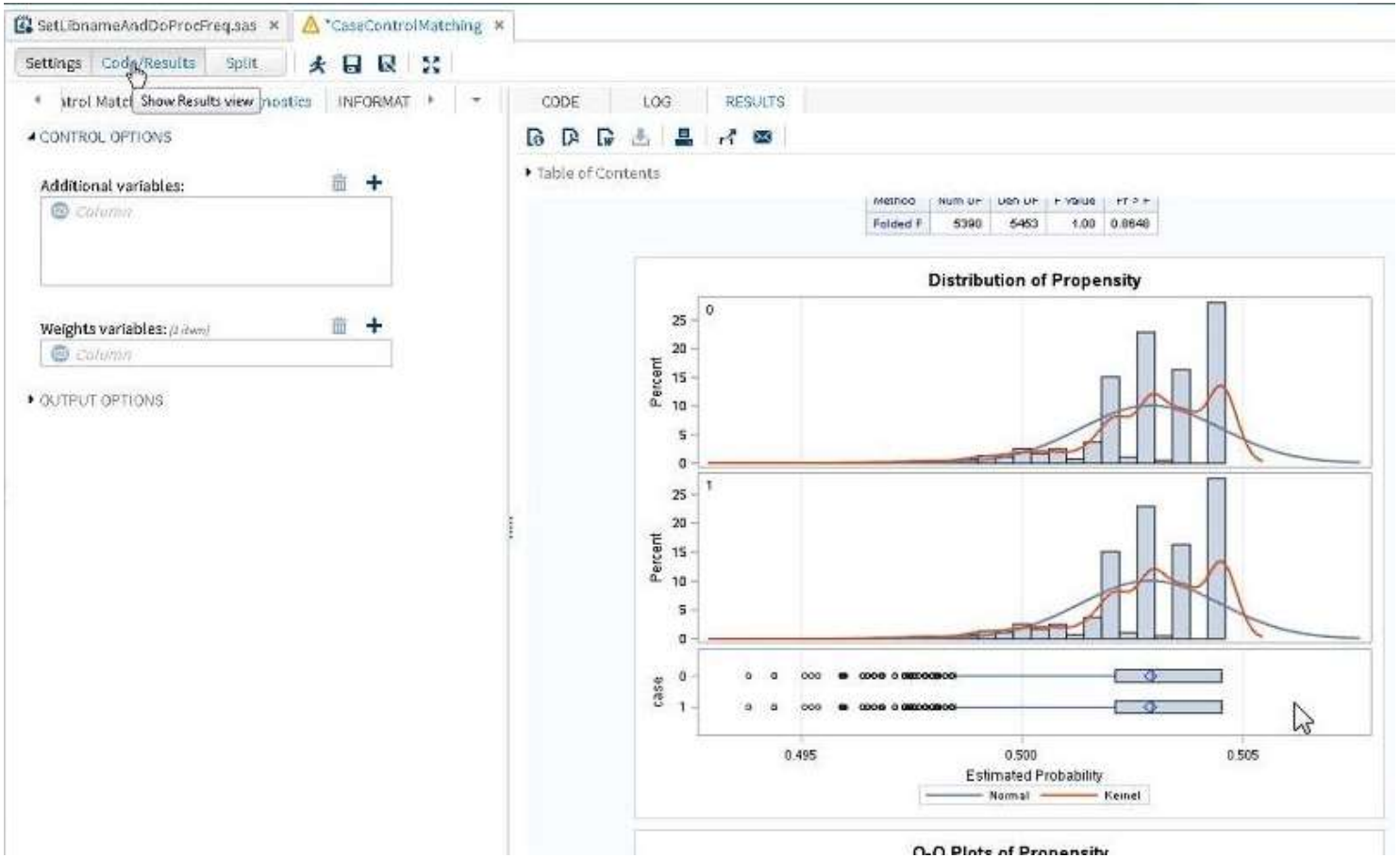
Type III Tests of Model Effects for ROST_HLS.MEDICATIONS_10PCT_S

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

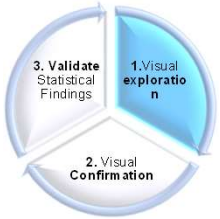
Effect	DF	Chi-Square	Pr>ChiSq
bodymass index	1	0.095431	0.7574
diastolic blood pressure	1	0.850678	0.3564
average income	1	0.064058	0.8002
age category	2	651.0934	<0.0001
smoking	3	1.901041	0.5932

CASE CONTROL / PROPENSITY SCORING

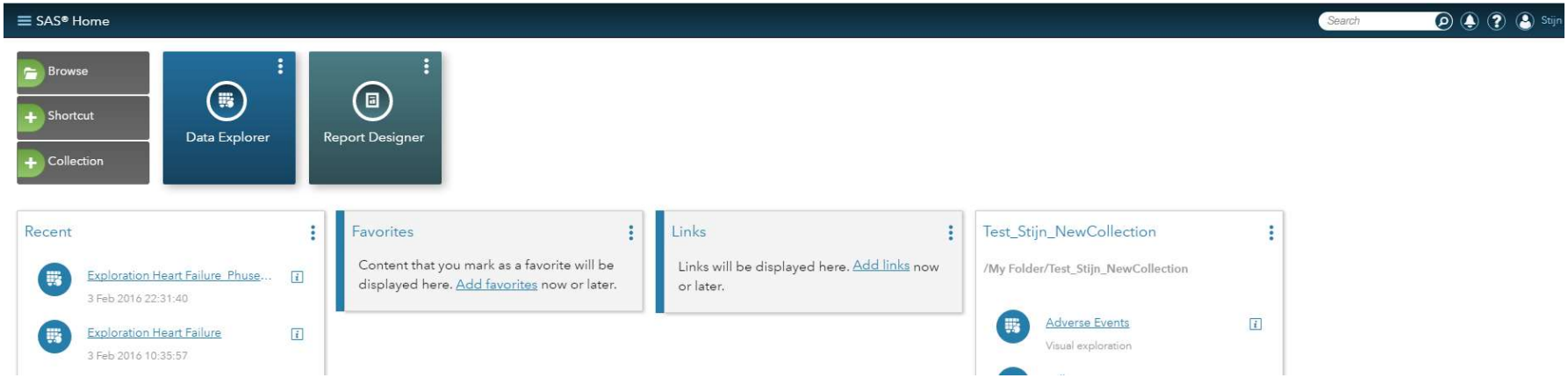


USING SAS TO ANALYZE HEALTHCARE DATA

Exploration of the data to generate insights



- SAS Visual Analytics Hub → Data Explorer



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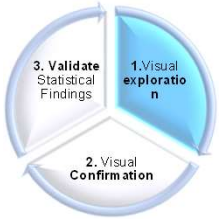
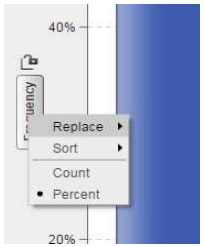
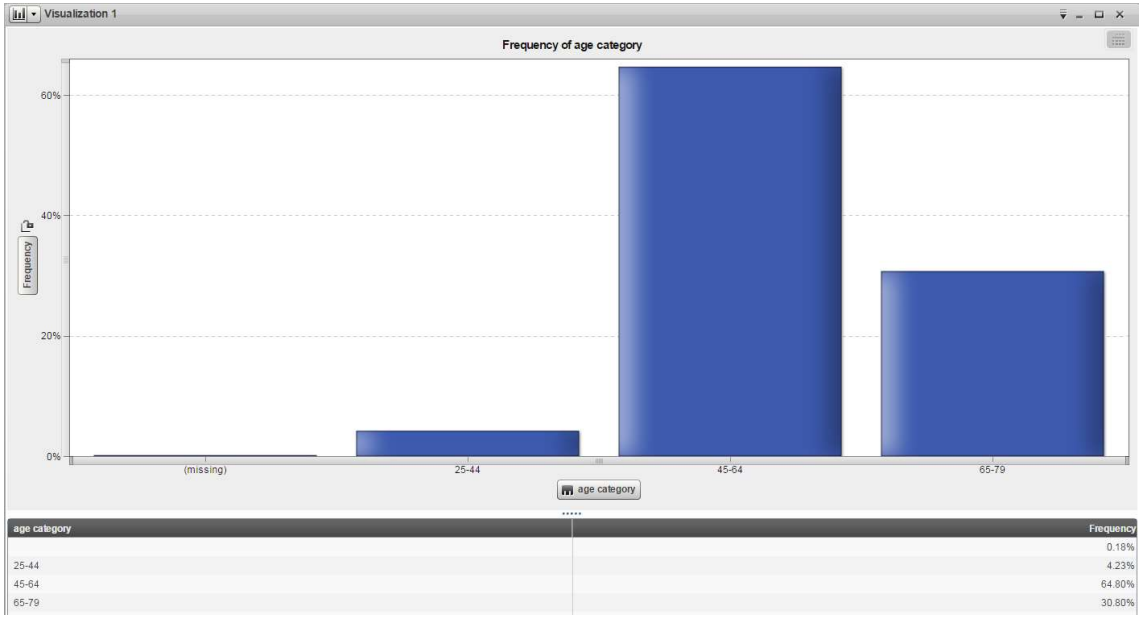
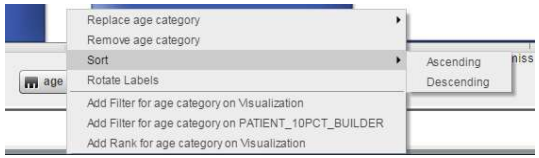


- New Visualization → Explore the **PATIENT** data (*Age Category*) using a Bar Chart





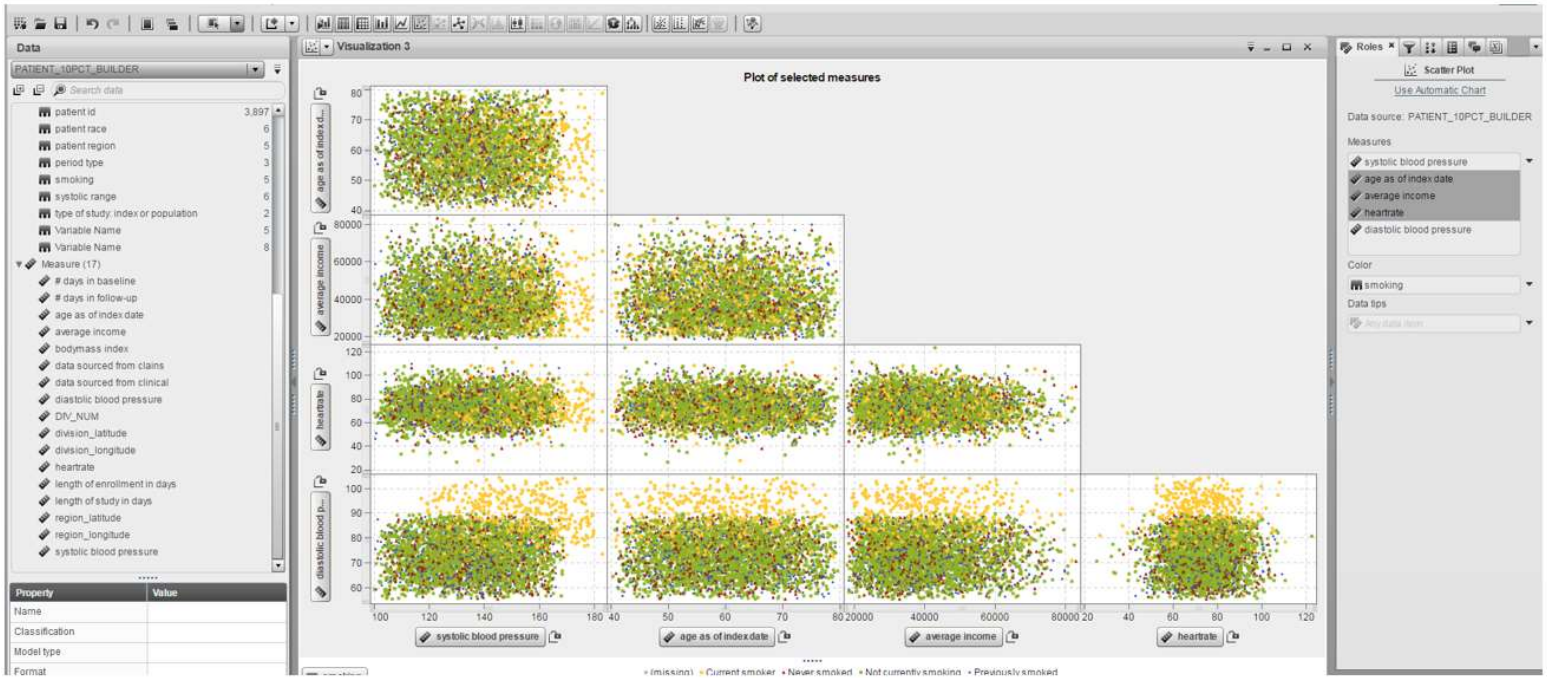


USING SAS TO ANALYZE HEALTHCARE DATA

Exploration of the data to generate insights

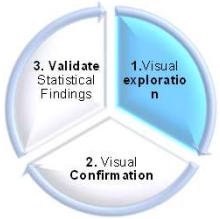
Measures: Diastolic & Systolic, etc.

Color: Smoking (Variable)



USING SAS TO ANALYZE HEALTHCARE DATA

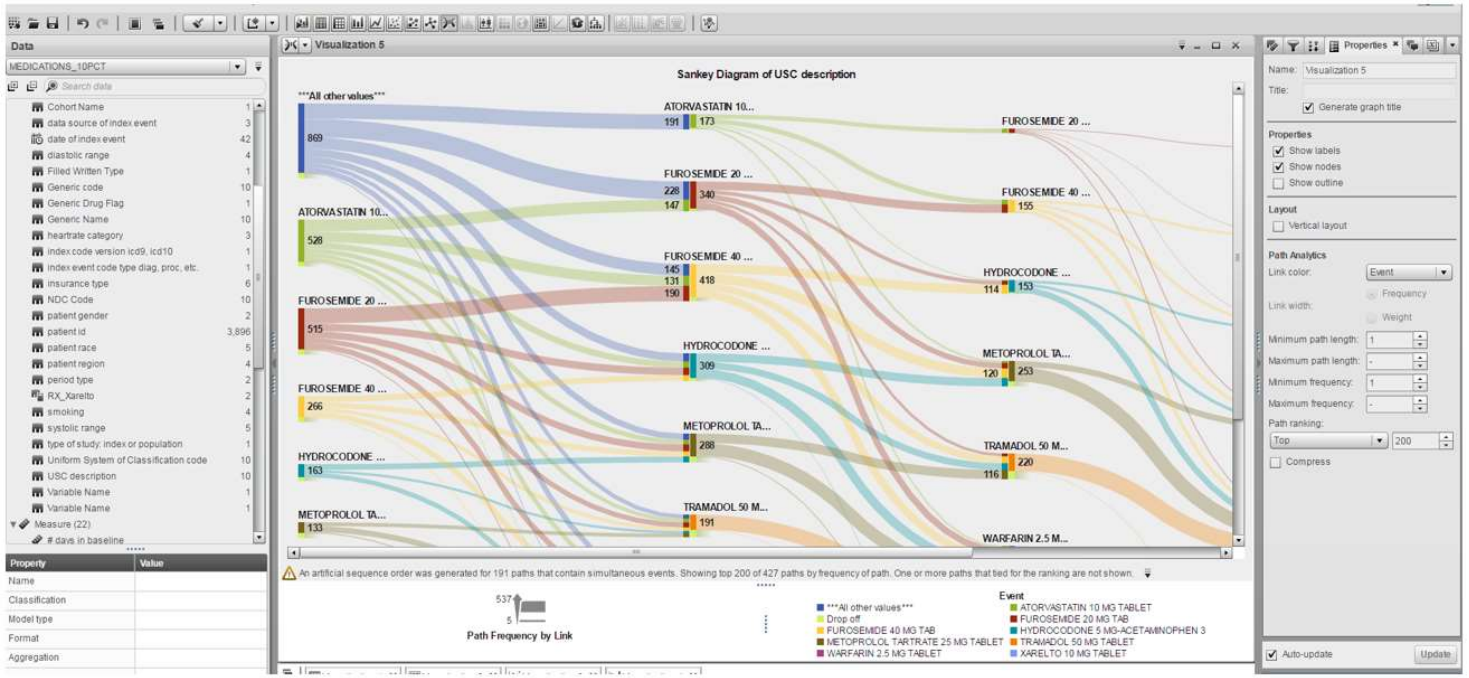
Exploration of the data to generate insights



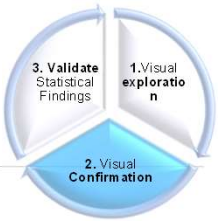
Properties – Line Color: Event

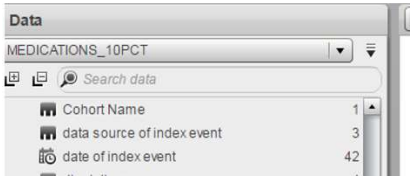
Each Medication is an event → has a separate color.

Switching in time from therapy



Confirmation of insights statistically

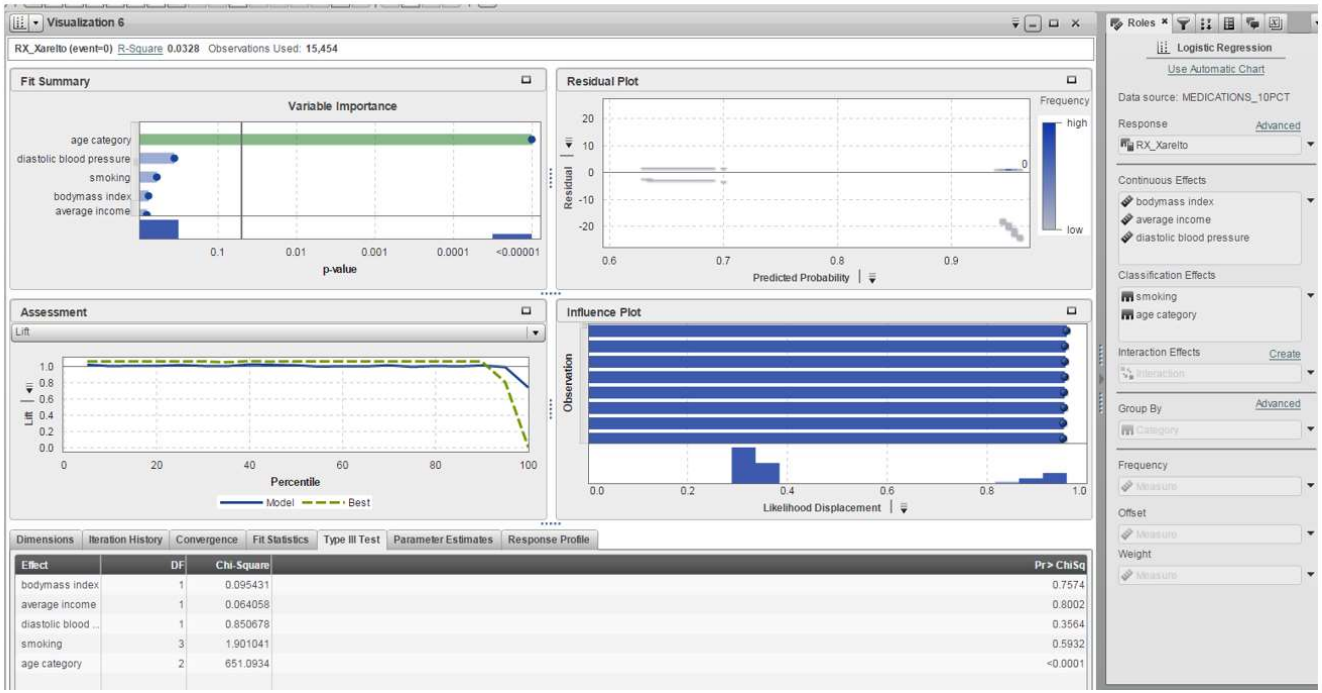




New VISUALIZATION

Select "Medications_10PCT" Data

New Logical Regression Model

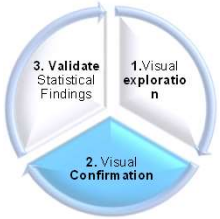


Age is the only variable that is statistically significant in the logistic regression model.

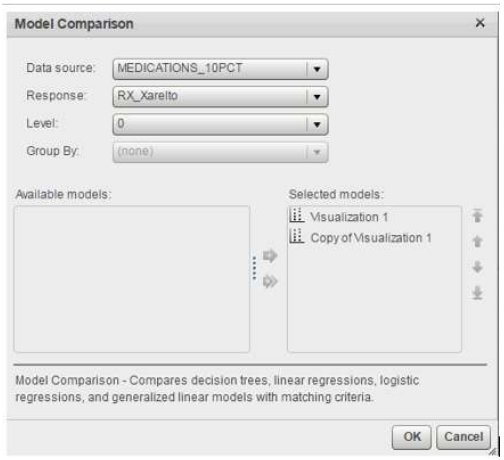
So the age category is predictive whether the patient is likely to be prescribed Xarelto.

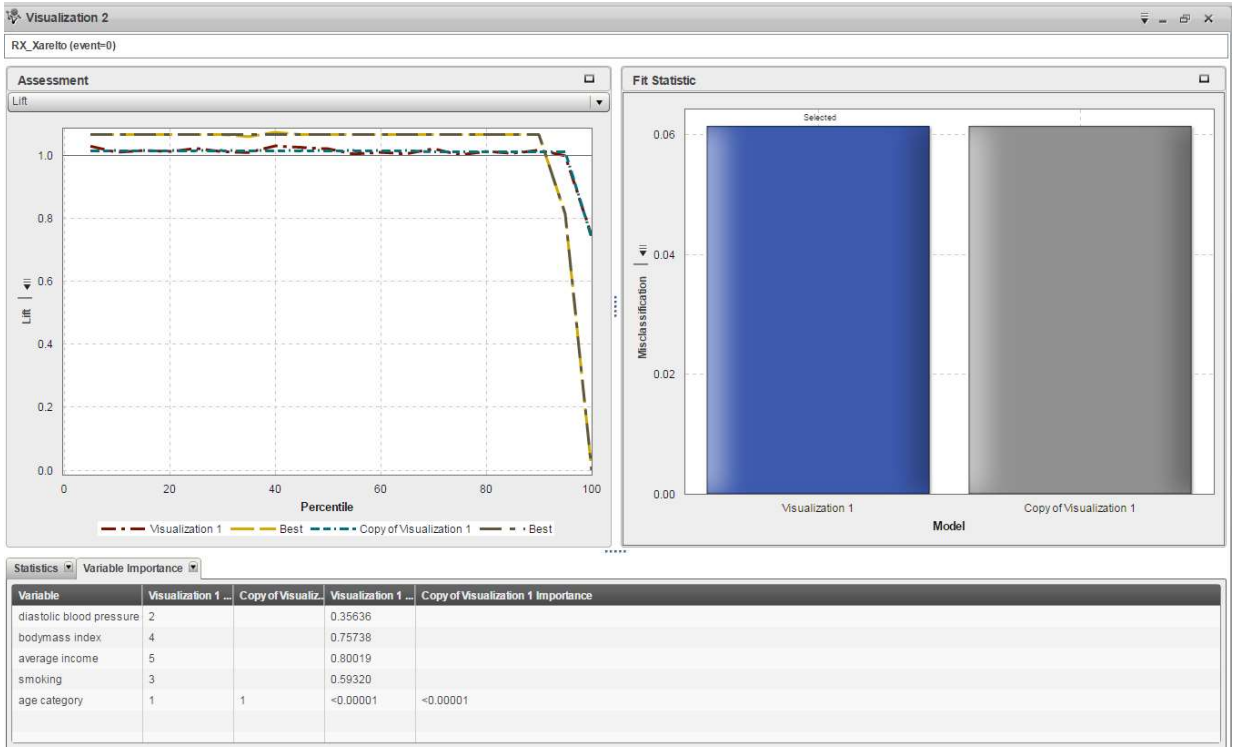
We have seen during explorations younger patients where prescribed primarily Xarelto.

Confirmation of insights statistically



Model Comparison





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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