[PHUSE Netherland SDE 2022 – September 29th]

Real World Evidence in Action

Things to Consider for an Analytics Platform for Regulatory Submission

Fadi Glor
Health and Life Sciences Advisor

William Kuan
Industry Consultant, EMEA & AP Health and Life Sciences Practice

Copyright © SAS Institute Inc. All rights reserved.

Who is Fadi

- Engineer by degree
- PhD in London
  - PhIV study, looking for people with hypertension
  - Administering compounds from AZ, Pfizer and a placebo
  - No real RWD – was a classical case of Randomised Interventional Trials
    - Knew exactly how many patients we needed
    - Knew exactly what measurements were wanted
- Occupation
  - ESSEVEE
  - SAS
- This presentation reflects the opinions of the presenters and should not be construed or considered to represent regulatory authorities' views or policies.

Copyright © SAS Institute Inc. All rights reserved.

Who is Fadi

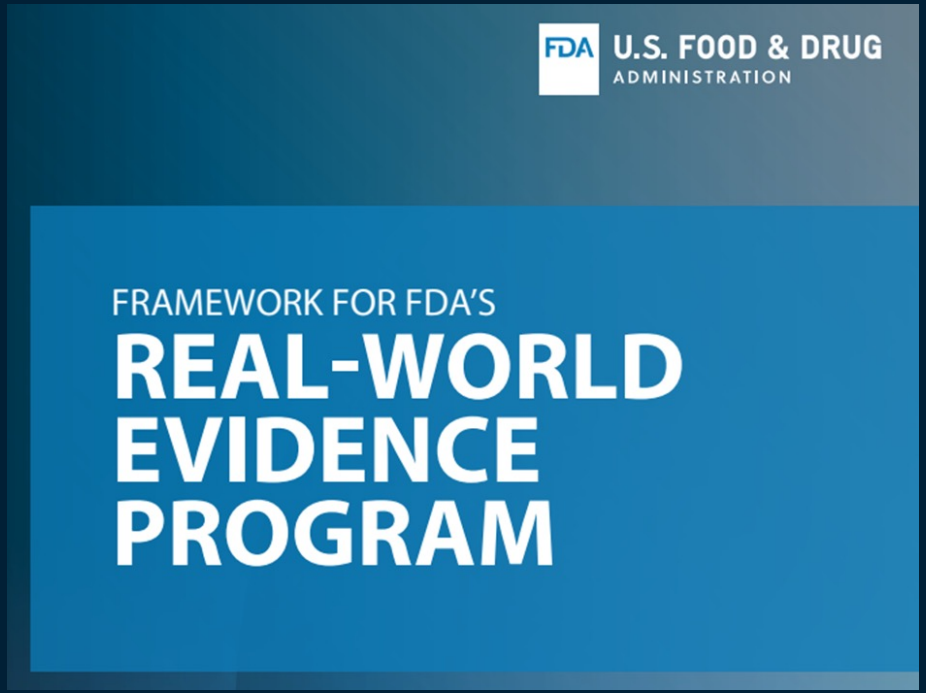
- Engineer by degree
- PhD in London
  - PhIV study, looking for people with hypertension
  - Administering compounds from AZ, Pfizer and a placebo
  - No real RWD – was a classical case of Randomised Interventional Trials
    - Knew exactly how many patients we needed
    - Knew exactly what measurements were wanted
- Occupation
  - ESSEVEE
  - SAS
- This presentation reflects the opinions of the presenters and should not be construed or considered to represent regulatory authorities' views or policies.

Copyright © SAS Institute Inc. All rights reserved.

In “the beginning”

= Dec 2018

https://www.fda.gov/media/120060/download



Copyright © SAS Institute Inc. All rights reserved.

European Medicines Agency
234,567 followers
3d •

EMA has endorsed a joint statement calling for international collaboration to enable the generation and use of real-world evidence for regulatory decision-making published today by the International Coalition of Medicines Regulatory Authorities.

In their statement, ICMRA members pledge to foster global efforts and further enable the integration of real-world evidence into regulatory decision-making. They identify four focus areas for regulatory cooperation on real-world data and real-world evidence.

#ICMRA #RealWorldEvidence #medicines #collaboration

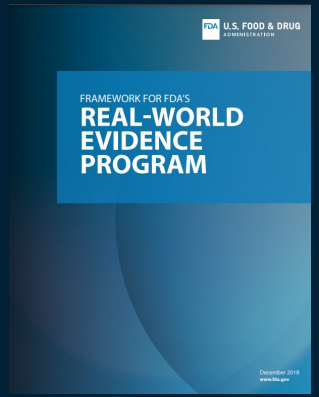
Global regulators call for international collaboration to integrate real-world evidence into regulatory decision-making - European Medicines Agency

ema.europa.eu • 2 min read

Real World Data (RWD) & Real World Evidence (RWE)

Potential use of RWE

- adding or modifying an indication (e.g. a change in dose, dose regimen, or route of administration)
- adding a new population;
- adding comparative effectiveness or safety information

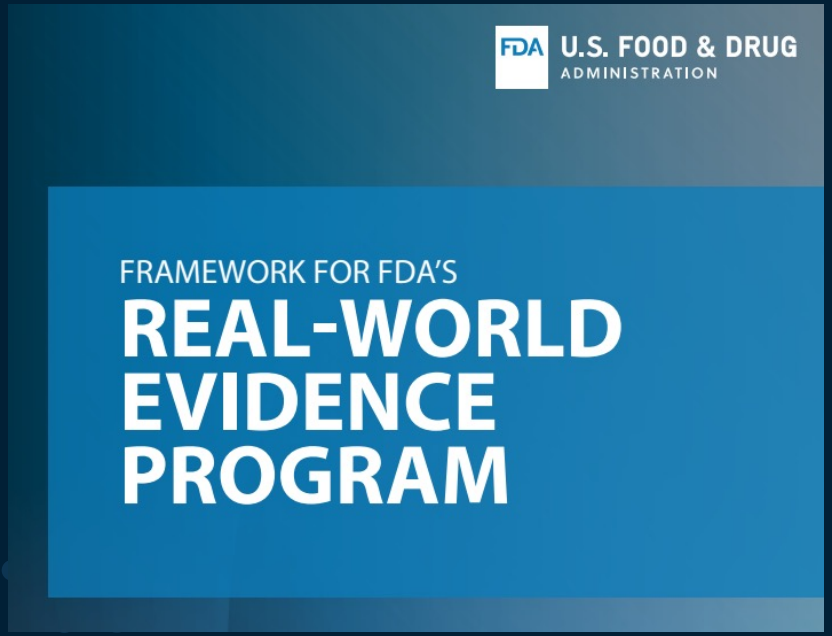


Framework for FDA's RWE Program

Copyright © SAS Institute Inc. All rights reserved.

Real World Data (RWD)

Examples

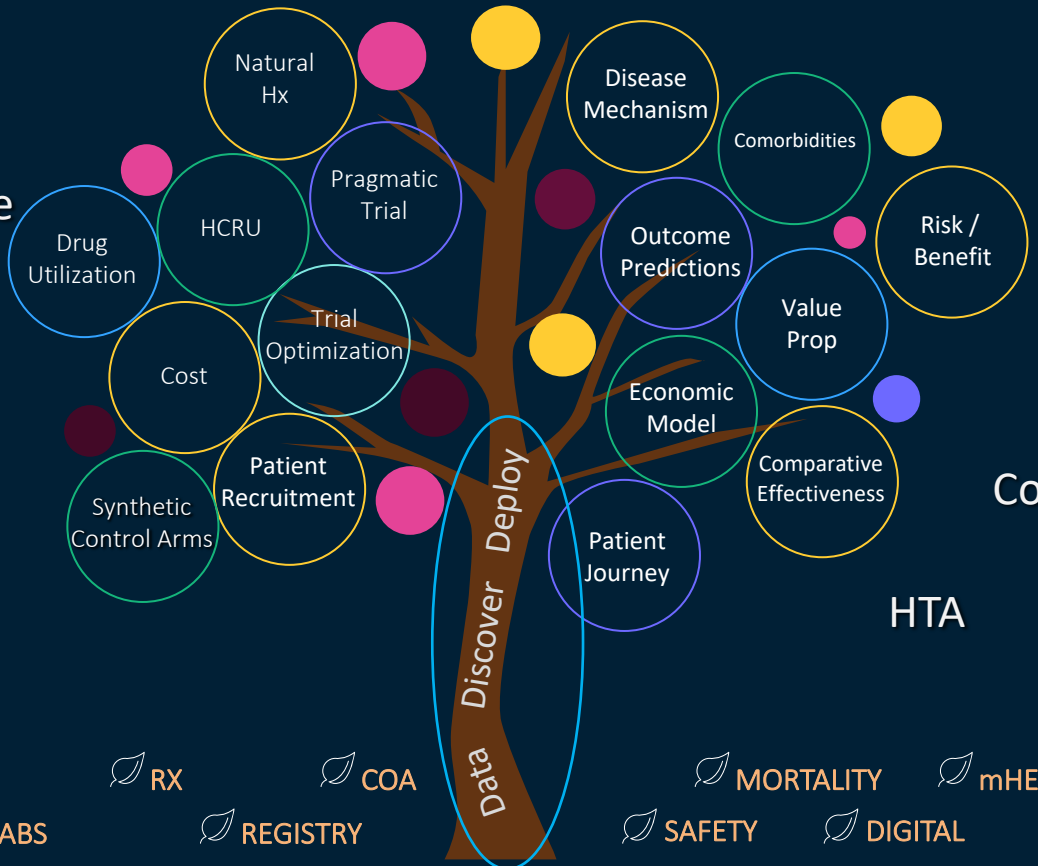


- Electronic health records (EHRs)
- Claims and billing activities
- Product and disease registries
- Patient-generated data including in home-use settings
- Data gathered from other sources that can inform on health status, such as mobile devices

Framework for FDA's RWE Program

Copyright © SAS Institute Inc. All rights reserved.

Stakeholders and Use Cases



Epidemiology

Medical Affairs

Pharmacovigilance

HEOR

Market Access

Regulatory Affairs

Commercial

R&D

HTA

PRO CLAIMS RX COA MORTALITY mHEALTH CONSUMER

EMR LABS REGISTRY SAFETY DIGITAL SOCIAL MEDIA

Copyright © SAS Institute Inc. All rights reserved.

Guidance on RWE

Date Published	Title
December 2018	Framework for FDA's Real-World Evidence Program
May 2019	Submitting Documents Utilizing Real-World Data and Real-World Evidence to FDA for Drugs and Biologics
September 2021	Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products
October 2021	Data Standards for Drug and Biological Product Submissions Containing Real-World Data
November 2021	Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products
December 2021	Considerations for the Use of Real-World Data and Real-World Evidence To Support Regulatory Decision-Making for Drug and Biological Products

https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence

Copyright © SAS Institute Inc. All rights reserved.

The most recent publication

May 2022

Publications and Guidance

- Framework for FDA's Real-World Evidence Program (PDF - 2.6MB)
- Guidance: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products
- Guidance: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Pr
- Guidance: Co To Support R
- Guidance: Da Real-World D
- Guidance: Su Evidence to F
- Guidance: Use of Electronic Health Records in Clinical Investigations
- Guidance: Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices
- Publication 2020: Randomized, observational, interventional, and real-world- What's in a name? (PDF - 420MB)
- Publication 2022: Real-World Evidence- Where Are We Now? (PDF - 161KB)


PERSPECTIVE

REAL-WORLD EVIDENCE — WHERE ARE WE NOW?

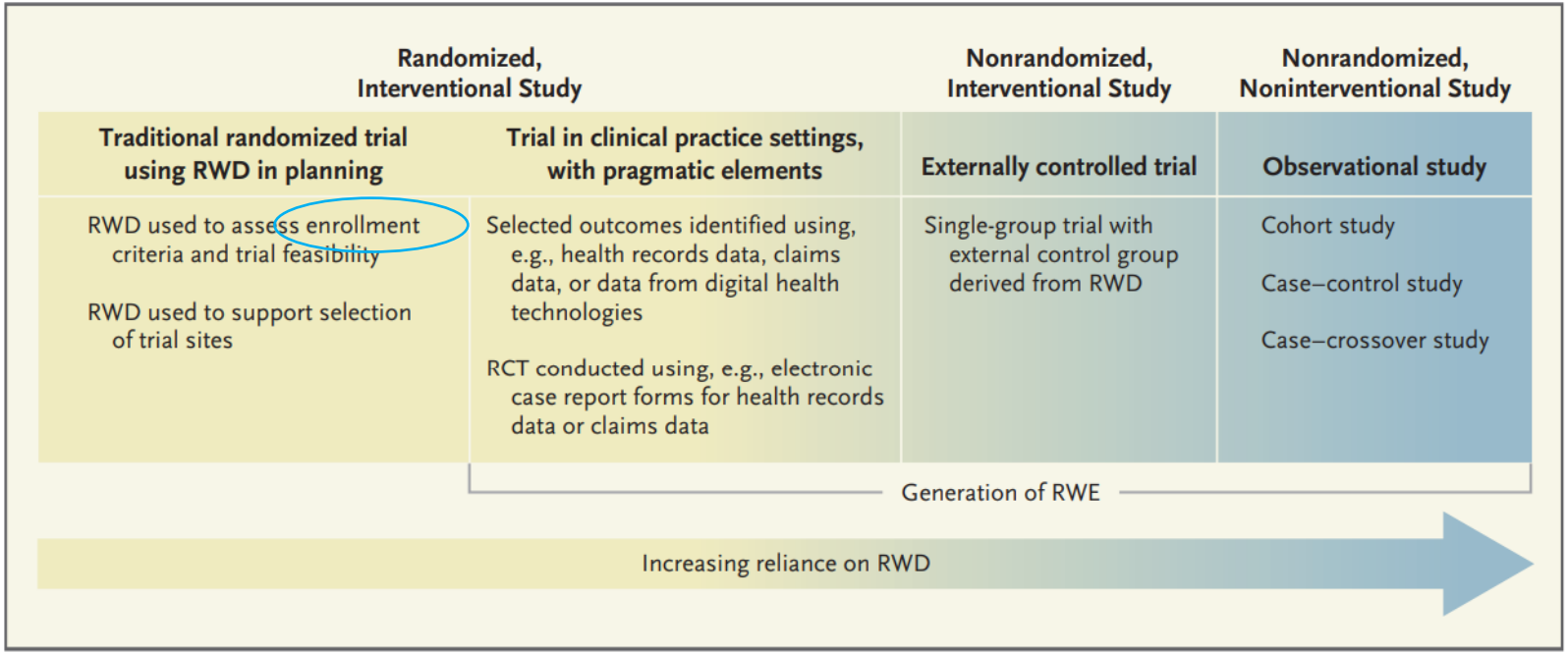
Real-World Evidence — Where Are We Now?

John Concato, M.D., M.P.H., and Jacqueline Corrigan-Curay, J.D., M.D.

Real-World Evidence – Where Are We Now?

Copyright © SAS Institute Inc. All rights reserved.

Degree of reliance on RWD varies with the type of study design



Reliance on RWD in Representative Types of Study Design.

RCT denotes randomized, controlled trial; RWD real-world data; and RWE real-world evidence.

J. Concato, et al., N Engl J Med 2022; 386:1680-1682

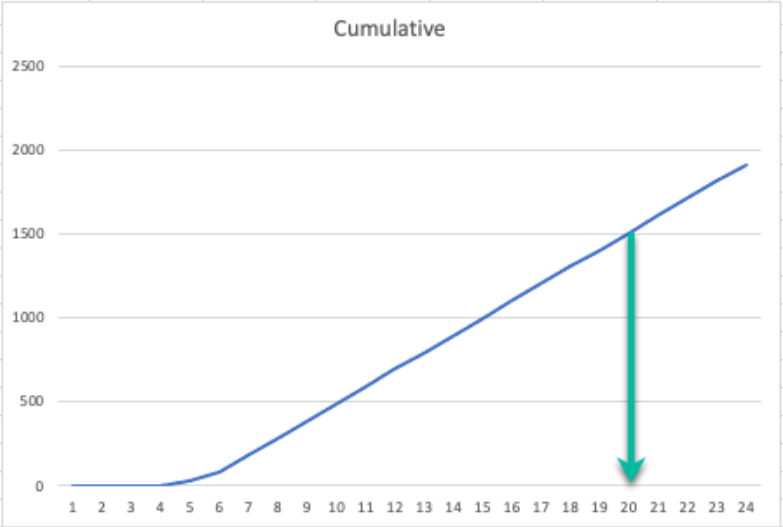
Copyright © SAS Institute Inc. All rights reserved.

Projecting Enrollment

Excel Calculations

Type	Sites	Delay	Mothly
Group A	3	5	10
Group B	3	4	8
Group C	4	6	12

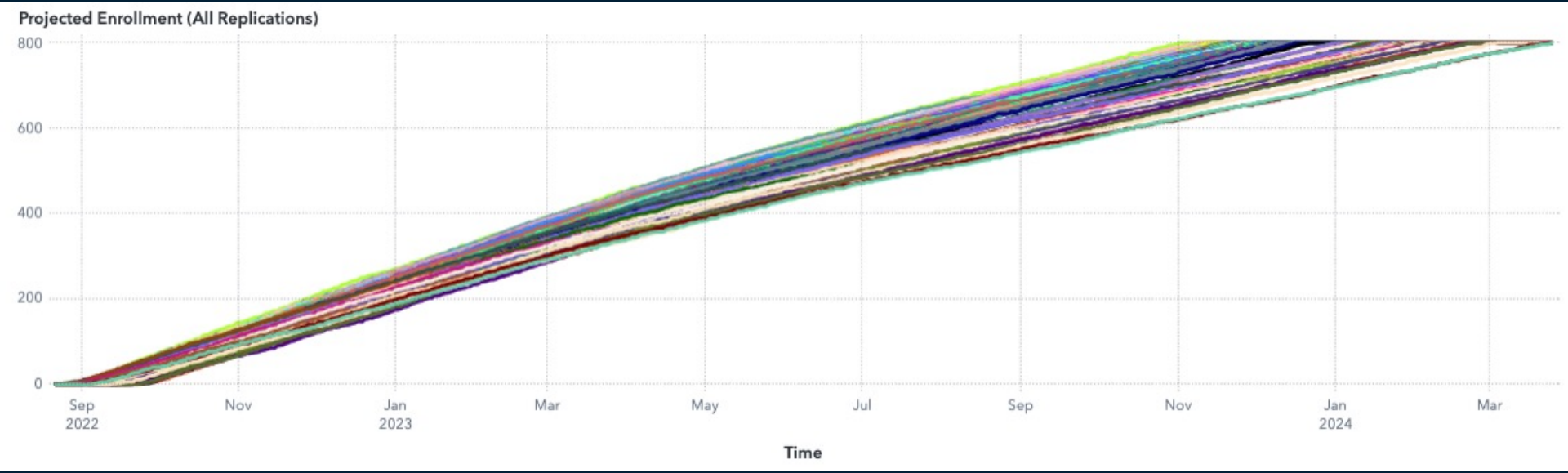
Month	A	B	C	Total	Cumulative
1				0	0
2				0	0
3				0	0
4				0	0
5		24		24	24
6	30	24		54	78
7	30	24	48	102	180
8	30	24	48	102	282
9	30	24	48	102	384
10	30	24	48	102	486
11	30	24	48	102	588
12	30	24	48	102	690
13	30	24	48	102	792
14	30	24	48	102	894
15	30	24	48	102	996
16	30	24	48	102	1098
17	30	24	48	102	1200
18	30	24	48	102	1302
19	30	24	48	102	1404
20	30	24	48	102	1506
21	30	24	48	102	1608
22	30	24	48	102	1710
23	30	24	48	102	1812
24	30	24	48	102	1914



Copyright © SAS Institute Inc. All rights reserved.

Simulating Enrollment

Solving the Problems with Multiple Replications



Copyright © SAS Institute Inc. All rights reserved.

Simulating Enrollment

Calculate Probabilities of Success

			Success Rate Range		
Target Name	**Target Date**	**Success Rate**	**Best**	**Median**	**Worst**
Dates					
First Country Approval	Not provided	N/A	July 26, 2022	August 6, 2022	August 25, 2022
First Site Startup	August 31, 2022	46%	August 19, 2022	September 1, 2022	September 21, 2022
First Subject Screening	Not provided	N/A	August 23, 2022	September 5, 2022	September 25, 2022
First Subject Enrollment	September 15, 2022	89%	August 23, 2022	September 6, 2022	September 25, 2022
First Subject's First Visit	Not provided	N/A	August 30, 2022	September 13, 2022	October 2, 2022
First Subject's Last Visit	Not provided	N/A	February 19, 2023	March 5, 2023	March 24, 2023
End of Enrollment	December 31, 2023	69%	November 2, 2023	December 1, 2023	March 25, 2024
Last Subject's First Visit	Not provided	N/A	November 9, 2023	December 8, 2023	April 1, 2024
Last Subject's Last Visit	Not provided	N/A	April 30, 2024	May 29, 2024	September 21, 2024
Cost	**Target Cost**	**Success Rate**	**Best**	**Median**	**Worst**
Estimated Cost	$2,900,000	61%	$2,802,916	$2,885,824	$2,974,546

Copyright © SAS Institute Inc. All rights reserved.

Simulating Enrollment

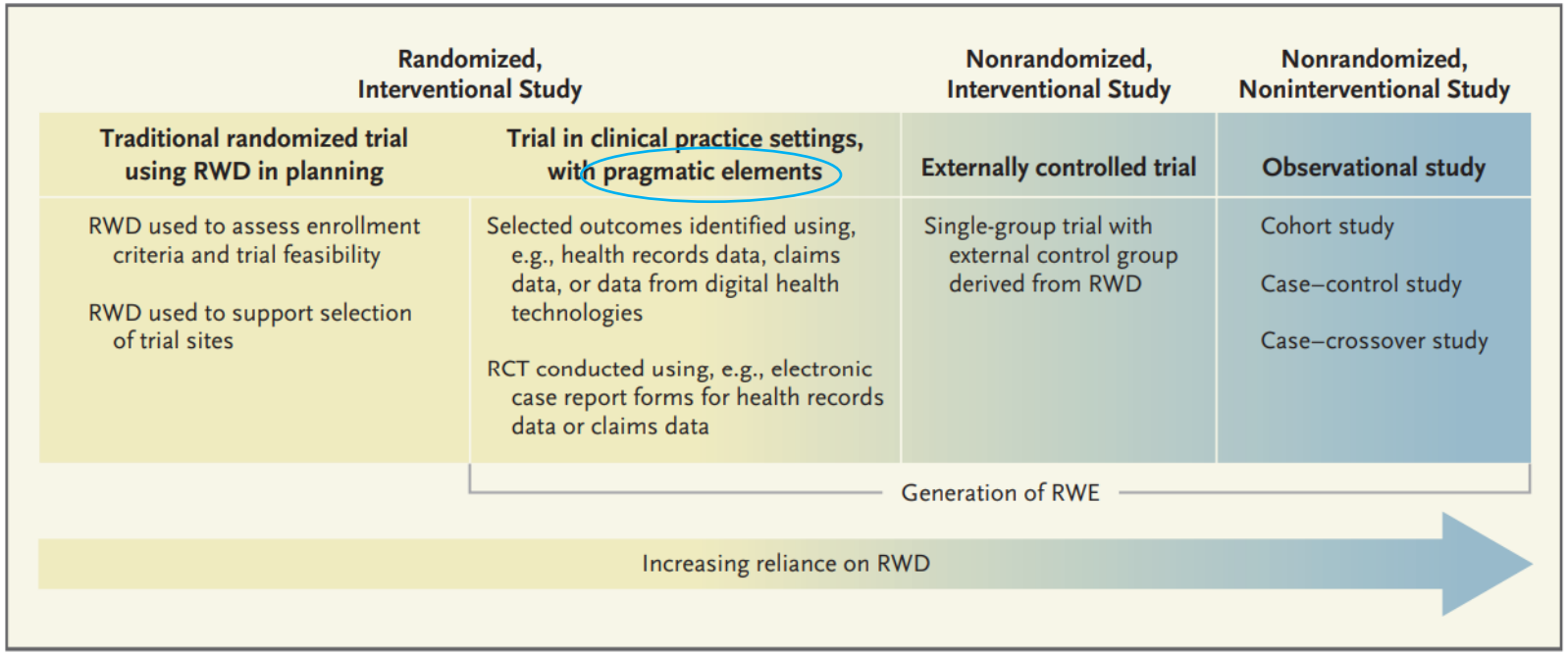
Scenario Management

Scenario Success Rates for Optional Target Dates

	Cardiology Baseline	Cardio Faster Startup
First Country Approval	N/A	N/A
First Site Startup	46%	100%
First Subject Screening	N/A	N/A
First Subject Enrollment	89%	100%
First Subject's Last Visit	N/A	N/A
Last Subject's Last Visit	N/A	N/A
End of Enrollment	69%	70%

Copyright © SAS Institute Inc. All rights reserved.

Degree of reliance on RWD varies with the type of study design



Reliance on RWD in Representative Types of Study Design.

RCT denotes randomized, controlled trial; RWD real-world data; and RWE real-world evidence.

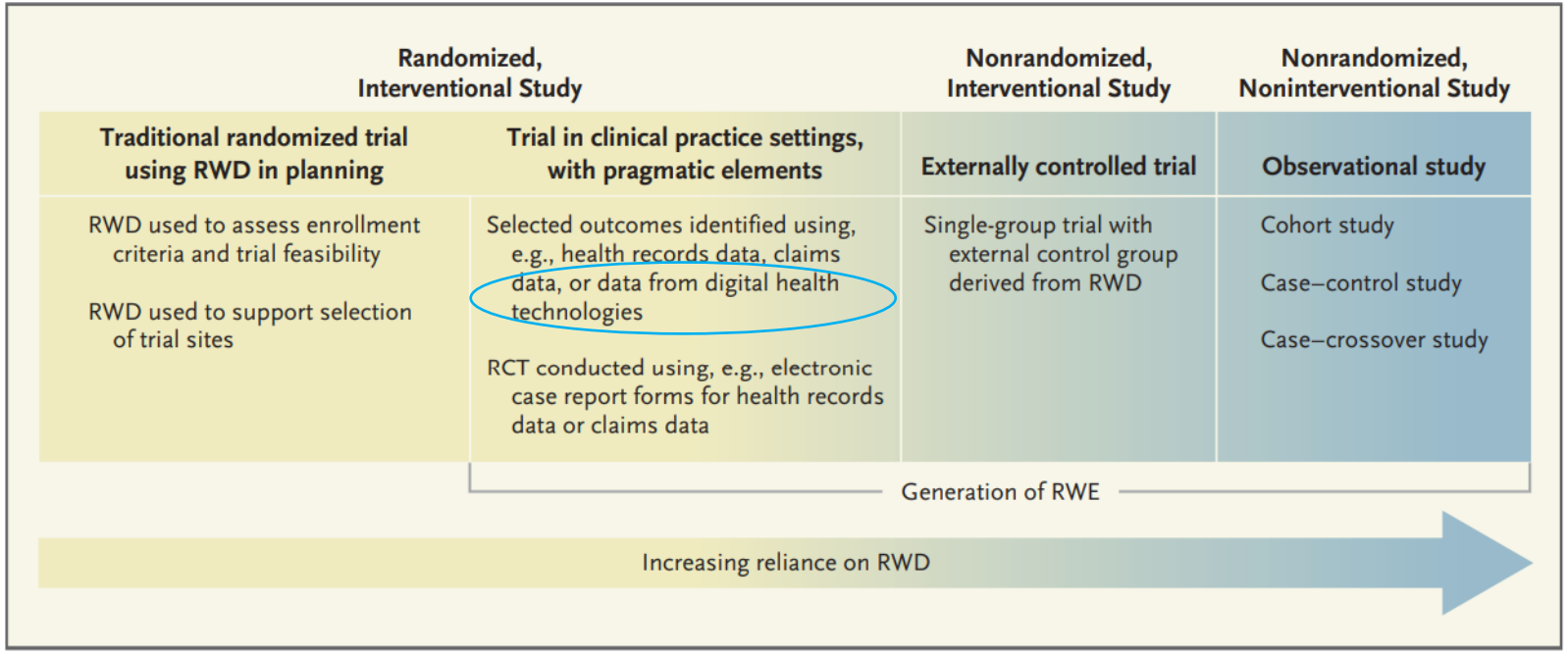
J. Concato, et al., N Engl J Med 2022; 386:1680-1682

Copyright © SAS Institute Inc. All rights reserved.

Figure 1: Magic Quadrant for Data Quality Solutions

Source: Gartner (September 2021)

Degree of reliance on RWD varies with the type of study design



Reliance on RWD in Representative Types of Study Design.

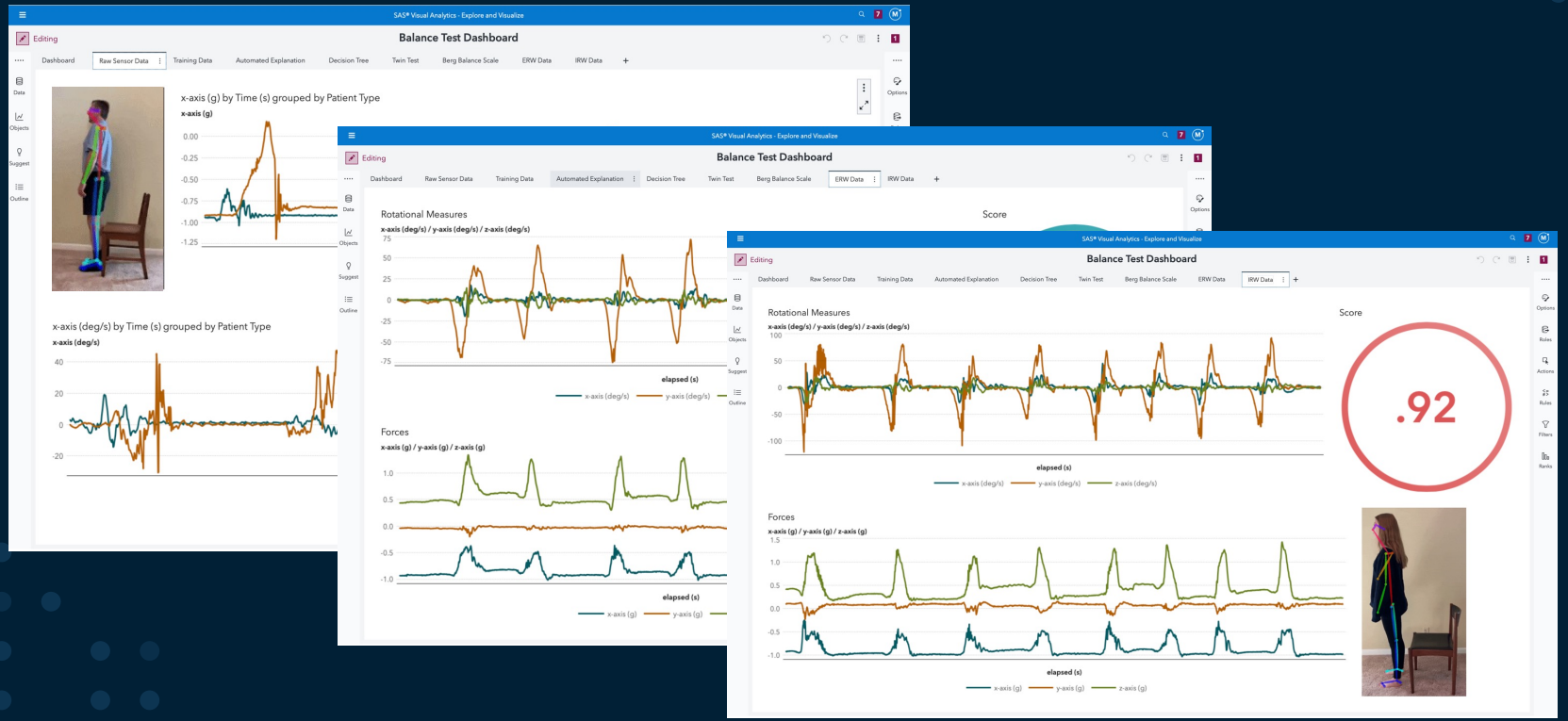
RCT denotes randomized, controlled trial; RWD real-world data; and RWE real-world evidence.

J. Concato, et al., N Engl J Med 2022; 386:1680-1682

Copyright © SAS Institute Inc. All rights reserved.

Digital Biomarkers - Endpoints

Enabling Decentralized / Hybrid Clinical Trials



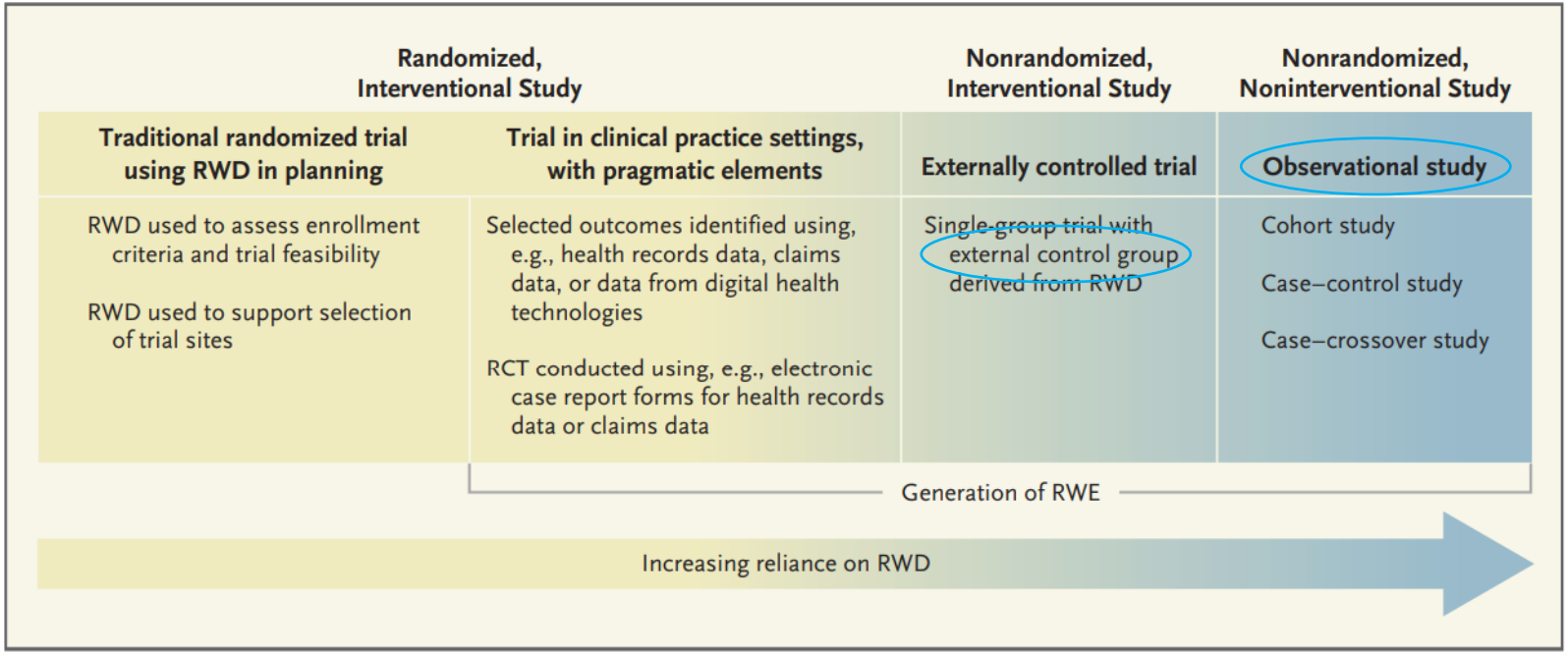
Copyright © SAS Institute Inc. All rights reserved.

Figure 1: Magic Quadrant for Data Science and Machine Learning Platforms

Figure 1: Magic Quadrant for Data Quality Solutions

Figure 1: Magic Quadrant for Data Science and Machine Learning Platforms

Degree of reliance on RWD varies with the type of study design



Reliance on RWD in Representative Types of Study Design.

RCT denotes randomized, controlled trial; RWD real-world data; and RWE real-world evidence.

J. Concato, et al., N Engl J Med 2022; 386:1680-1682

Copyright © SAS Institute Inc. All rights reserved.

FDA approves new use of transplant drug based on real-world evidence

Observational study - 2021

FDA approved a new use for Prograf (tacrolimus) ***based on a non-interventional (observational) study providing real-world evidence (RWE) of effectiveness****. FDA approved Prograf for use in combination with other immunosuppressant drugs to prevent organ rejection in adult and pediatric patients receiving lung transplantation*

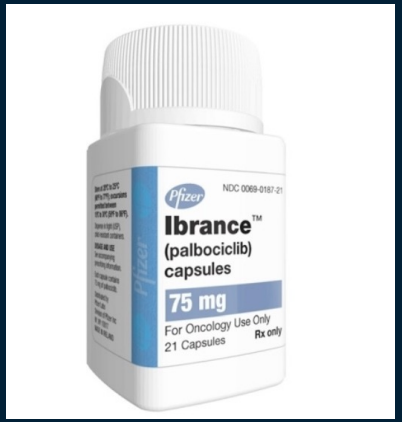
https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-new-use-transplant-drug-based-real-world-evidence

Pfizer Uses EHR Data to Support Expanded Indication for Male Breast Cancer

Observational study - 2019

*"**The approval is based on RWD** from electronic health records and post-marketing reports of Ibrance™ in male patients sourced from three databases: IQVIA Insurance database, Flatiron Health Breast Cancer database and the Pfizer global safety database"*

https://www.raps.org/news-and-articles/news-articles/2019/4/pfizer-uses-ehr-data-to-support-expanded-indicatio



Copyright © SAS Institute Inc. All rights reserved.

Synthetic Control Arms

Externally controlled trial

- Data sources
  - historical clinical trials
  - Registries, electronic health records
- Why we use it?
  - If traditional RCTs is unethical, impractical, or infeasible
  - Rare diseases, small number of eligible patients
  - Single-arm trial

The CDER approval also highlights the fact that an observational design is not synonymous with use of secondary data.[2] When primary data collection occurs in noninterventional studies, such as those using registries that collect data in a standardized format, investigators may encounter fewer challenges than they do with electronic health records, medical claims, or other sources, in terms of variability in the conduct and timing of clinical assessments. More general issues related to data quality include clinical relevance and reliability

By reducing or eliminating the need to enroll control participants, a synthetic control arm can ***increase efficiency, reduce delays, lower trial costs, and speed lifesaving therapies to market***.

Davi, Ruthie, et al. "Informing single-arm clinical trials with external controls." Nature Reviews Drug Discovery 19.12 (2020): 821-822.

Synthetic control arms can save time and money in clinical trials

Copyright © SAS Institute Inc. All rights reserved.

Synthetic Control Arms - Types

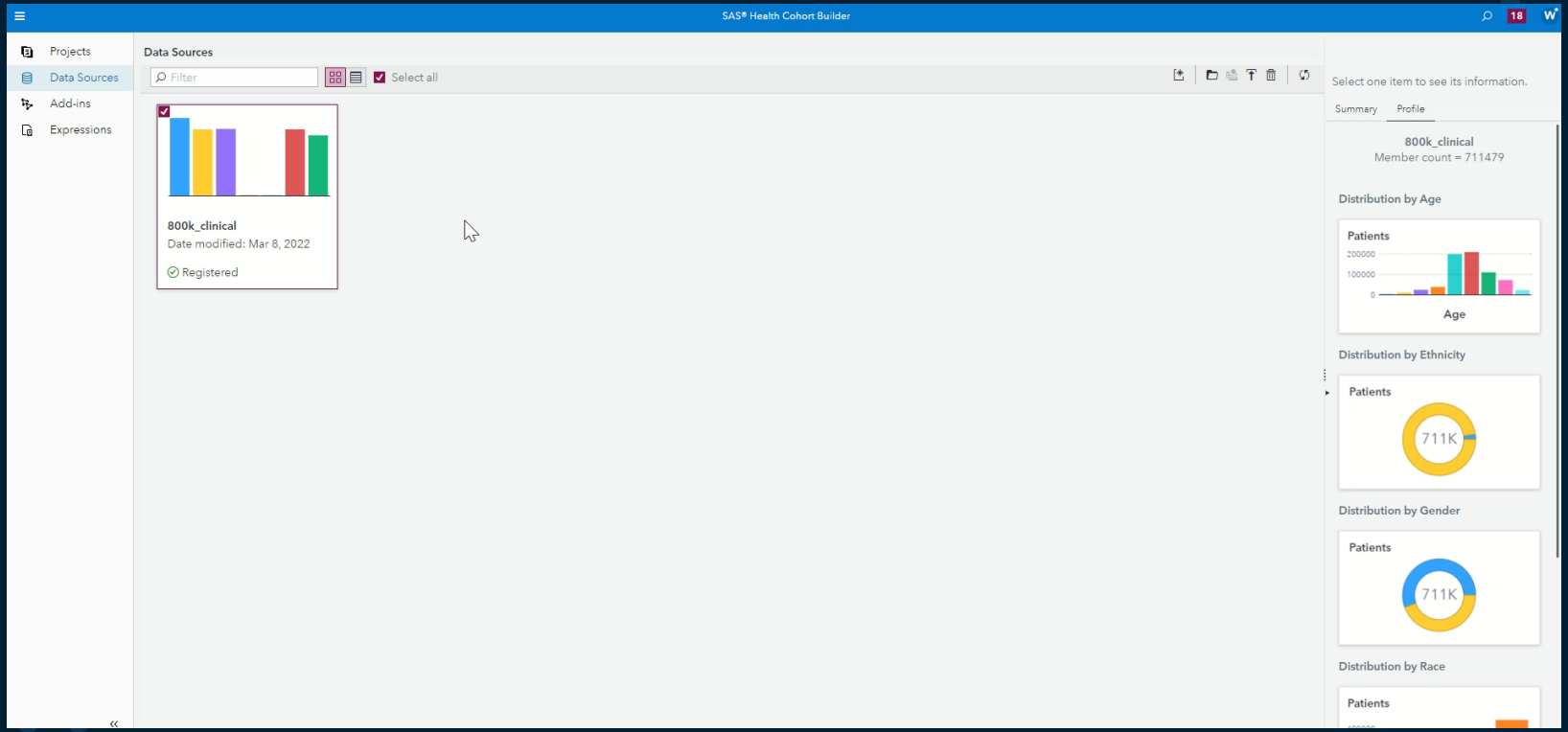
	External Control Cohort Inception Date	Possible Types of Data Collection	
		Retrospective	Prospective
Contemporaneous External Control	On or after the first patient enrollment in the clinical trial		
Historical External Control	Before the first patient enrollment in the clinical trial		
Hybrid External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

Real-world evidence to support regulatory decision-making for medicines: Considerations for external control arms

Copyright © SAS Institute Inc. All rights reserved.

Demo

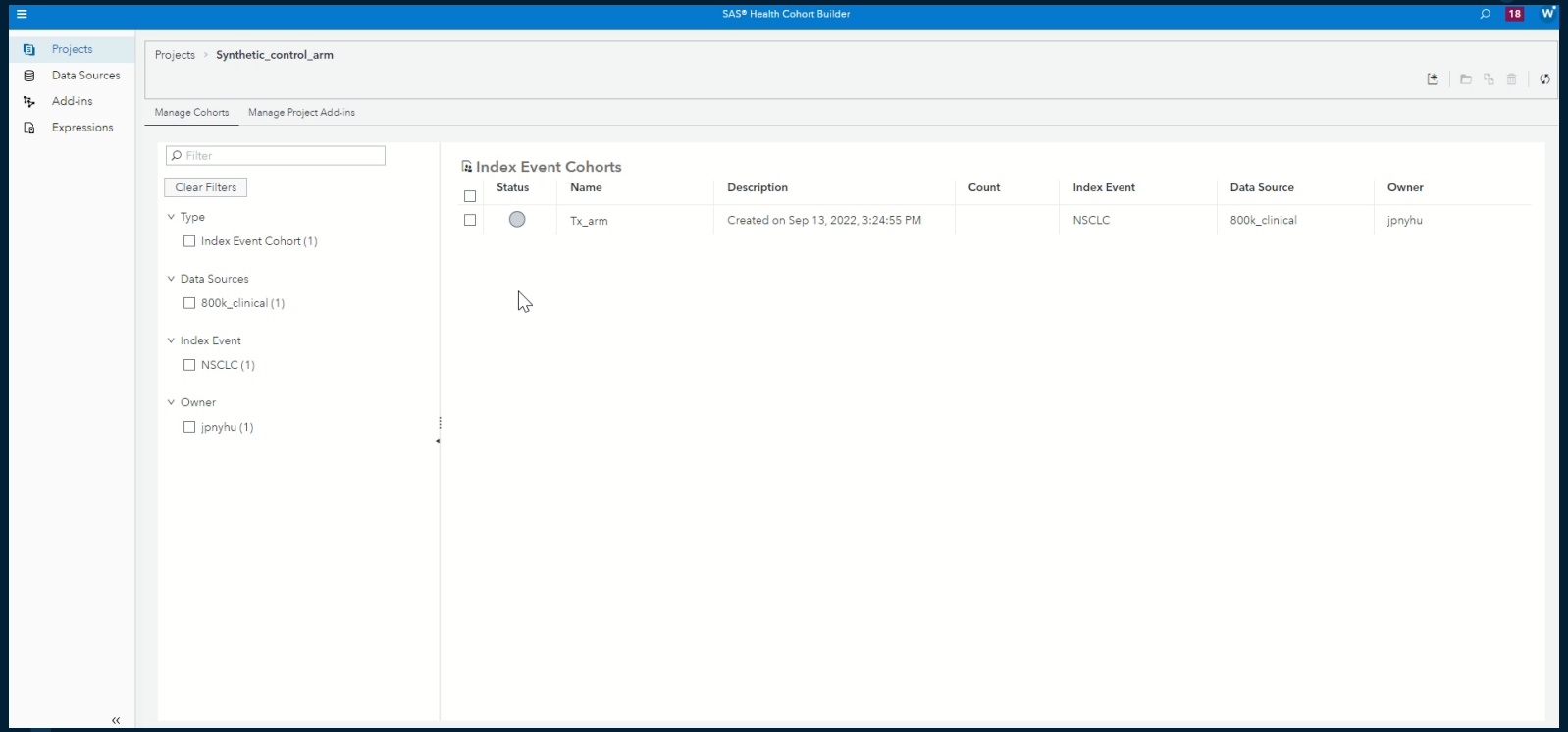
Creation of the treatment arm



Copyright © SAS Institute Inc. All rights reserved.

Demo

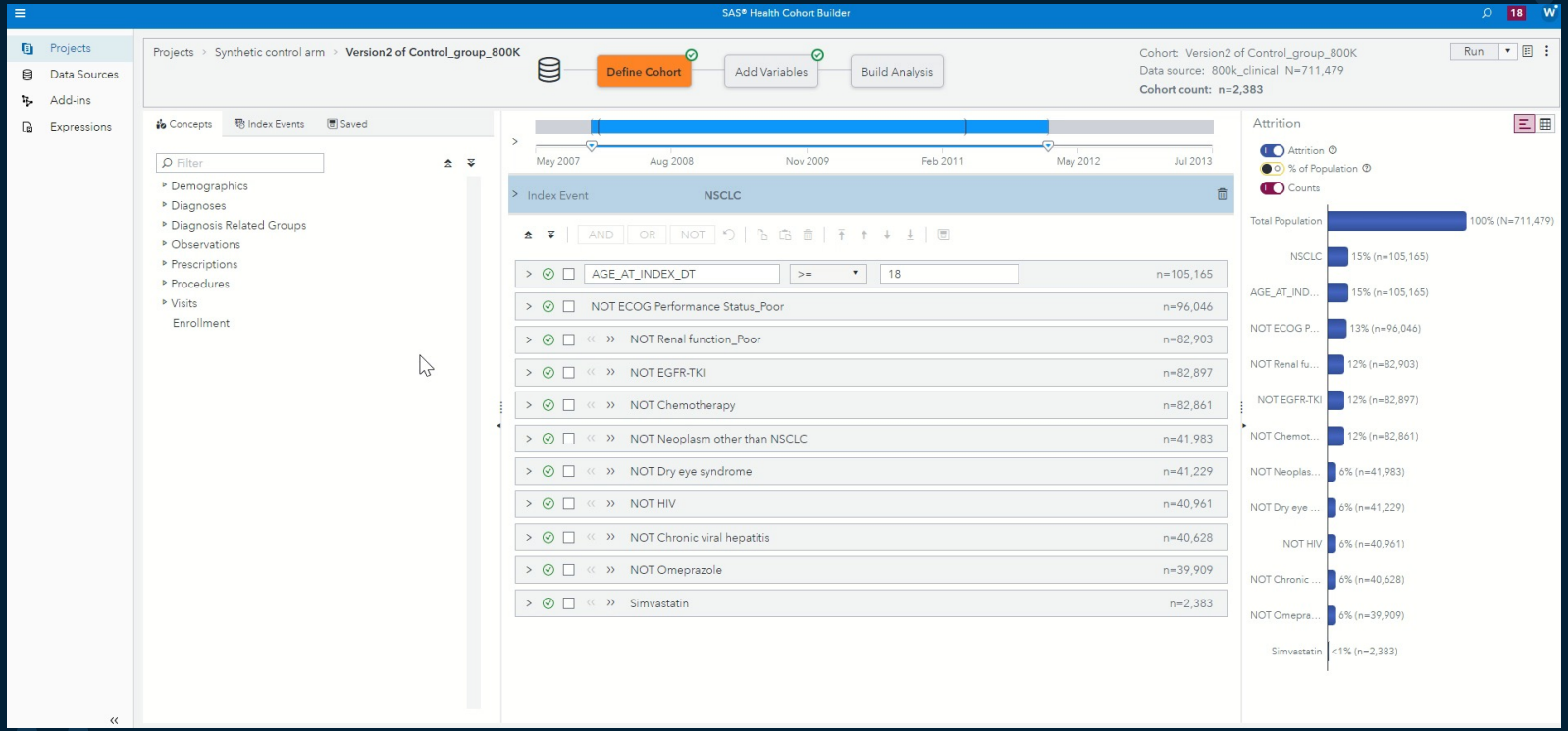
Creation of the synthetic control arm



Copyright © SAS Institute Inc. All rights reserved.

Demo

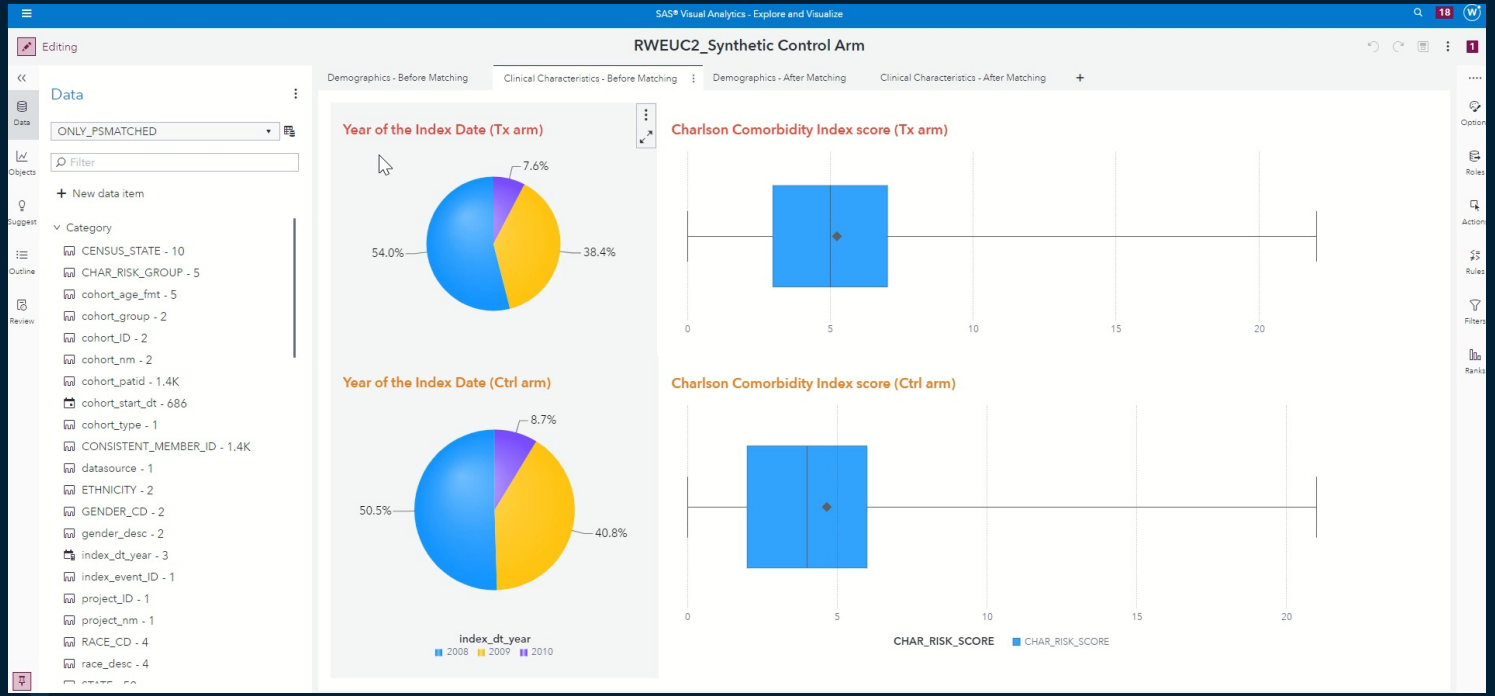
Make a crude comparison (before matching)



Copyright © SAS Institute Inc. All rights reserved.

Demo

Identify a subset of patients in control arm using Propensity Score Matching



Copyright © SAS Institute Inc. All rights reserved.

Key Considerations for the Use of RWE in Submission

Data

Whether the RWD are fit for use

Framework for FDA's RWE Program

Methods

Whether the trial or study design used to generate RWE can provide adequate scientific evidence to answer or help answer the regulatory question

Process

Whether the study conduct meets FDA regulatory requirements

Reliability

Relevance

Transparency & Reproducibility

Copyright © SAS Institute Inc. All rights reserved.

Thank you!
Any Question?

CDERMedicalPolicy-RealWorldEvidence@fda.hhs.gov

sas.com

Copyright © SAS Institute Inc. All rights reserved.