

Novel Applications of Real World Data (RWD) in External Control Arms

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ABSTRACT

INTRODUCTION: Regulatory agencies have issued guidance on selection and evaluation of Control Groups in clinical trials. External control arms (ECA) may be sourced from prior clinical trial data (individual or pooled), or observational, real-world data (RWD), such as registries, electronic health records, and medical or pharmacy claims. By reducing or eliminating the need to enroll control participants, a synthetic or external control arm can increase efficiency, reduce delays, lower trial costs, and speed lifesaving therapies to market.

ECAs should ideally be temporally and clinically relevant to the treatment arm to minimize bias and require sufficient patient-level data to ensure a statistically robust comparison.

We address key considerations, risks and possible mitigation strategies when employing ECAs in their trial designs. In general, the use of ECAs to determine comparative treatment effect is not widely applicable or appropriate for most clinical studies due to the potential for bias, such as confounding, selection bias, temporal bias, or immortal time bias. Even in a well-understood disease, lack of appropriate measurement of exposure or outcome, misaligned contemporality, or poor selection of an appropriate control can create an artificially significant demonstrated treatment effect that is not related to therapeutic intervention.

CONCLUSION: While ECAs can be the future of drug development if scientific rigor is ensured through analytical methods to compensate for the compromise in study design. Key considerations in data source, ECA definition and analytic methods are crucial to ensuring a valid ECA that will withstand scrutiny by health authorities.

INTRODUCTION

Regulatory agencies have issued guidance on selection and evaluation of Control Groups in clinical trials. External control arms (ECA) may be sourced from prior clinical trial data (individual or pooled), or observational, real-world data (RWD), such as registries, electronic health records, and medical or pharmacy claims. By reducing or eliminating the need to enroll control participants, a synthetic or external control arm can increase efficiency, reduce delays, lower trial costs, and speed lifesaving therapies to market.

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METHODS

A contemporaneous external control arm was defined and executed using SAS® Viya®, SAS® Cohort Builder, R and Python. Exploratory analyses were performed to identify the best fit statistic for this work.

SAS® Viya was used to develop and execute code in SAS, R, Python and other open source languages. In addition, visualizations were executed using SAS® Visual Analytics, Visual Statistics and Visual Machine Learning.






EXAMPLES OF EXTERNAL/SYNTHETIC CONTROL ARMS

The Food and Drug Administration (FDA) cites two examples where RWD were used to accelerate approval of drug products. The first was Alecensa in 2015 submitted by Roche which led to advanced coverage by 18 months in 20 European countries. The second was Amgen's Blincyto for the treatment of a rare form of leukemia.

TYPES OF EXTERNAL/SYNTHETIC CONTROL ARMS

Table 1 illustrates the three main types of external control arms used today. Contemporaneous control arms are those patients whose records are accessed during the recruitment of the treatment arm as their own medical records are populated within the same timeframe. Historical external control arms are usually defined as patients whose medical records are accessed for a study but their medical records are populated prior to the enrollment of the first treatment patient. Hybrid external control arms are a mix of contemporaneous and historical control arms.

Table 1 Types of External Control Arms

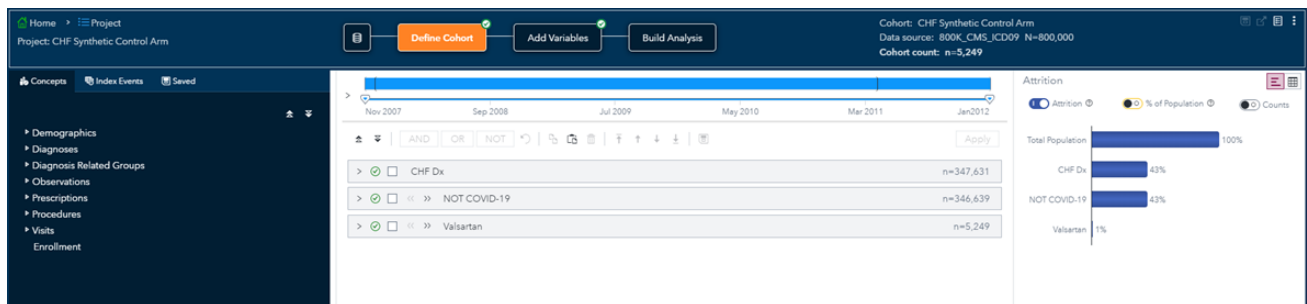
	External Control Cohort	Possible Types of Data Collection	
	Inception Date	Retrospective RWD Collection	Prospective RWD Collection
Contemporaneous External Control	On or after the first patient enrollment in the clinical trial		
Historical External Control	Before the first patient enrollment in the clinical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

USE CASE: PARAGLIDE-HF

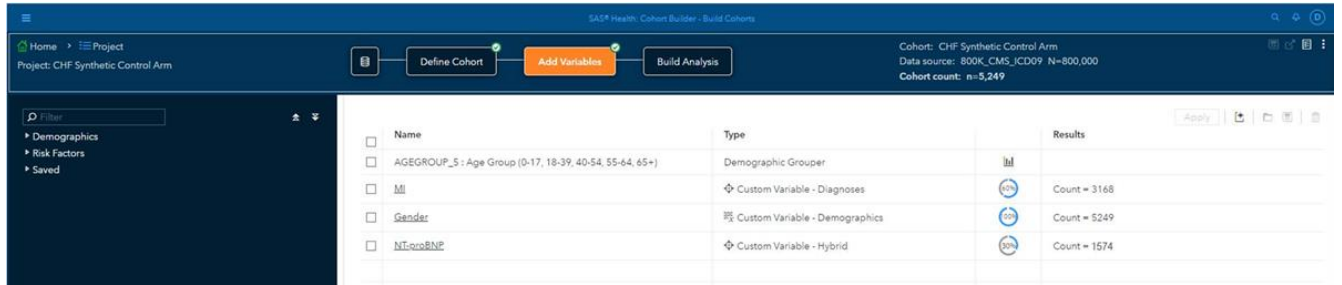
COVID-19 had a drastic impact on numerous ongoing clinical trials. This team identified a named clinical trial that had paused recruitment as a result of COVID-19. As of May 2020, PARAGLIDE-HF had paused recruitment of patients which could have lead to a termination of the trial or extension of the trial duration which would, in turn, drive higher costs

DEFINE EXTERNAL/SYNTHETIC CONTROL ARMS

We used the SAS® Cohort Builder to define the external control arms to meet the trial's eligibility criteria as seen in Display 1. In Display 2, covariates and endpoints as defined in the study protocol are included for the cohort.



Display 1 Define Cohort for External Control Arm



Display 2 Define Covariates and Endpoints

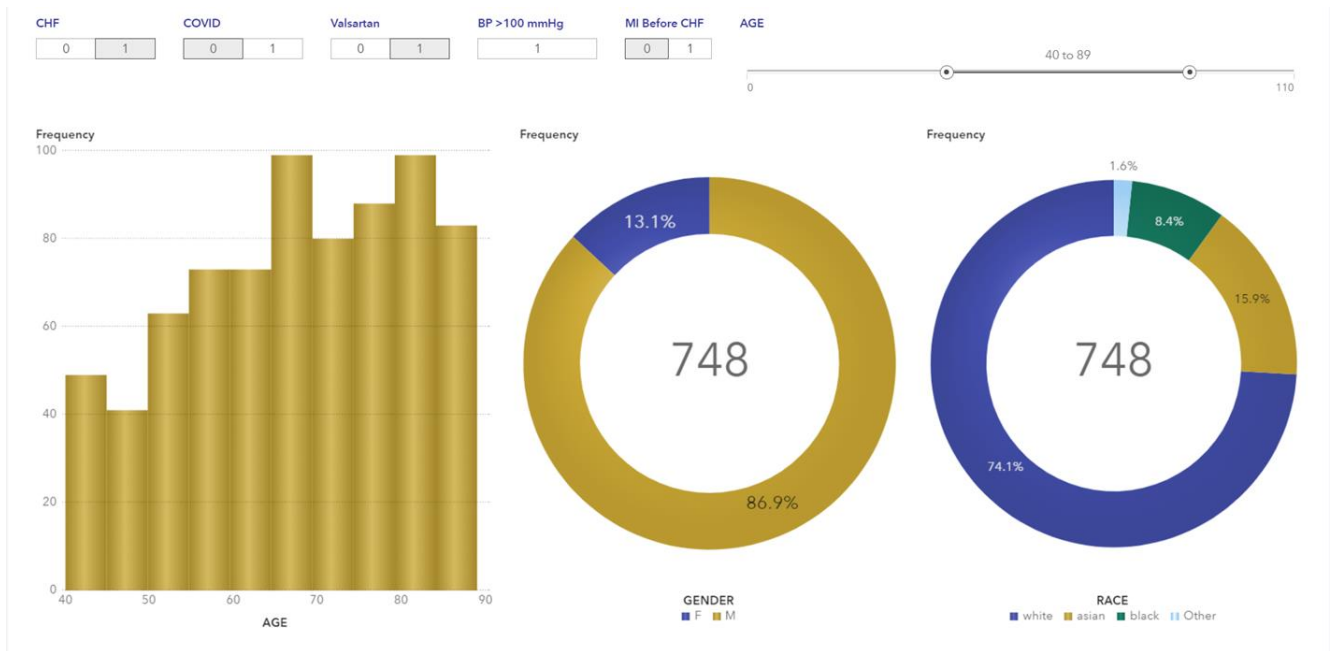
VISUALIZATIONS AND SCIENTIFIC ROBUSTNESS

It is critical that the flow of patients over time demonstrate a viable source of recruitment as shown in Display 3. Using SAS® Visual Analytics, the count of patients who meet eligibility criteria is assessed and rapid sensitivity analyses can be executed.

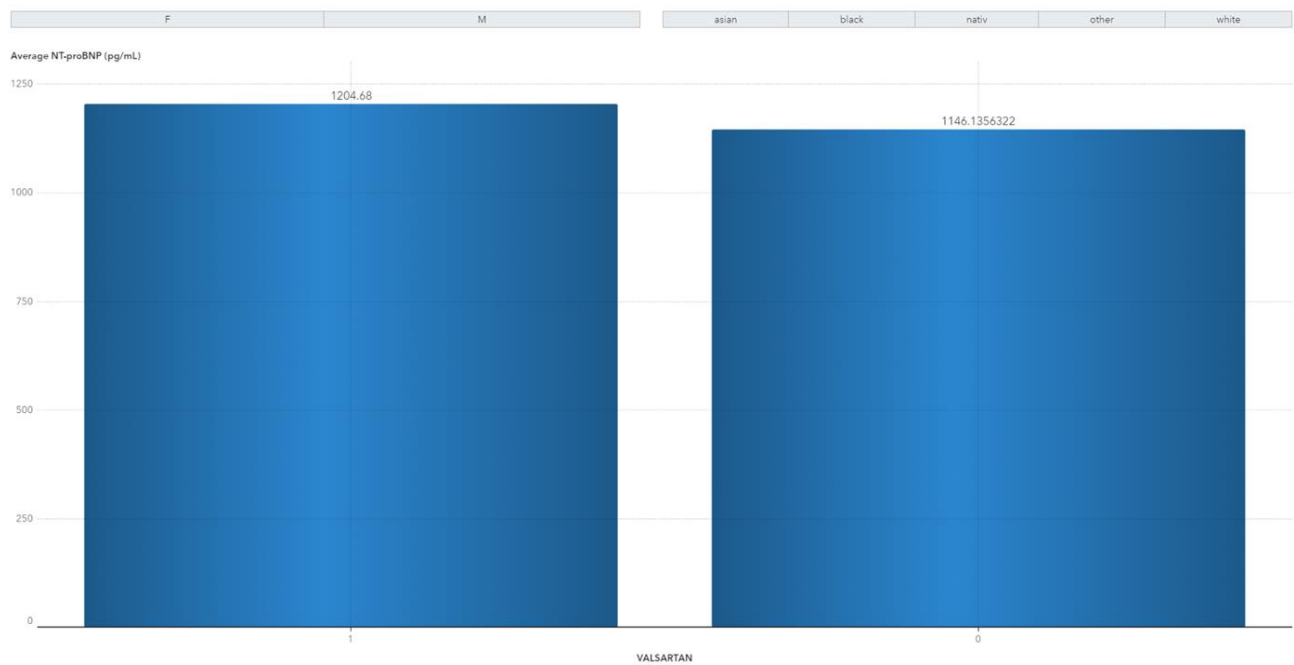


Display 3 Visualize External Control Arm Patient Counts

Display 4 illustrates the ease by which baseline demographics and sensitivity analyses can be executed on the ECA. Researchers can interact with the data directly and leverage controls and toggles to explore the data and various scenarios. We followed this with a visualization of the primary endpoint mean comparison between both groups shown in Display 5

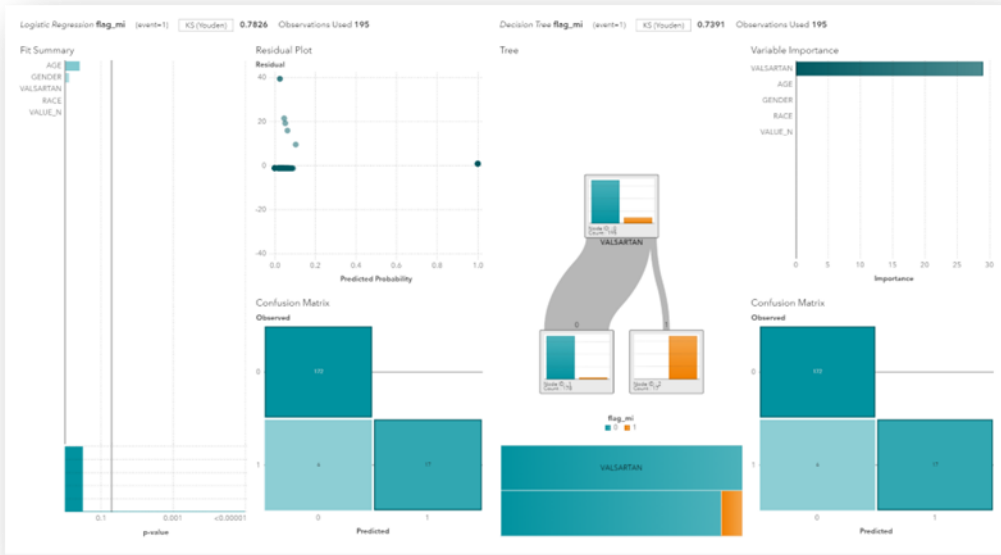


Display 4 Assess Baseline Characteristics

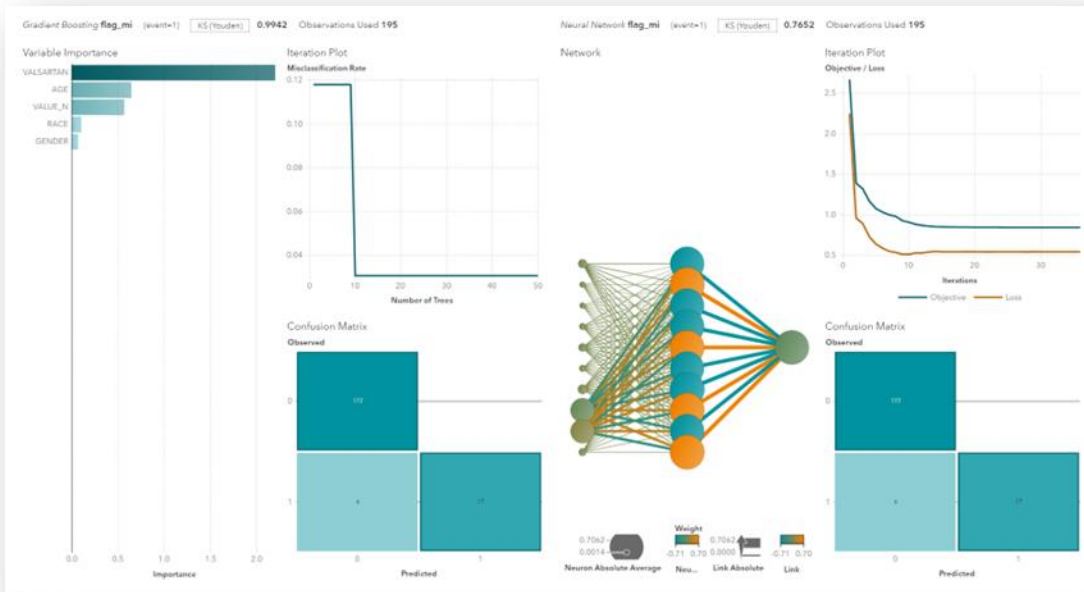


Display 5 Compare Primary Endpoint

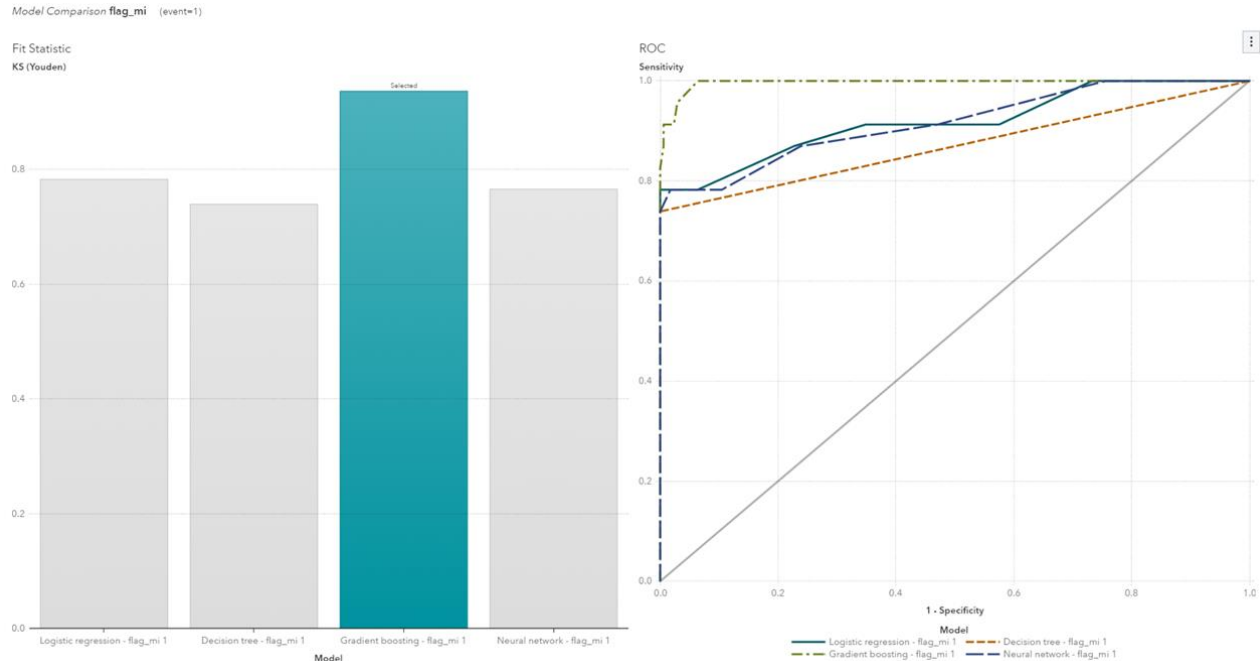
Secondary and exploratory endpoints and *Ad hoc* analyses were executed using logistic regression, decision trees, gradient boosting models and neural networks as demonstrated in Display 6 and Display 7. These predictive and machine learning analytics were compared using the KS Youden fit statistic to determine which was the best fit model for these data. Display 8 shows the results of the model comparison with gradient boosting modeling identified as the champion model.



Display 6 Explore Best Analytics to Fit the Data for Secondary and Exploratory Endpoints



Display 7 Explore Best Analytics to Fit the Data for Secondary and Exploratory Endpoints



Display 8 Compare Models

KEY CONSIDERATIONS

External Control Arms are definitely an opportunity for exploration and innovation. However, we caution that they are not a universal replacement for conventional control arms if applicable. It is well-documented that RWD may be difficult to extract, lack quality or even not be truly comparable. As such, study design and analytics may not fully control for all systematic issues and biases.

Furthermore, as this is an emerging discipline in our industry, new tools and methodologies are needed to consolidate, organize and properly structure RWD to generate research and regulatory-grade evidence. This is primarily the case as it pertains to established ECAs as a legitimate and true comparator arm.

We anticipate that specific analytic approaches and evolving practices may address some challenges posed here. Some approaches could include Natural Language Processing and Machine Learning, Deep Learning and Artificial Intelligence.

CONCLUSION

This body of work reflects the growing importance of the role that RWD and RWE play in clinical trials. While ECAs can be the future of drug development if scientific rigor is ensured through analytical methods to compensate for the compromise in study design. Key considerations in data source, ECA definition and analytic methods are crucial to ensuring a valid ECA that will withstand scrutiny by health authorities.

CONTACT INFORMATION

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