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Novel Ways to Leverage Your Real-World Data Investment in Integrated Evidence

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ABSTRACT

Traditionally, Real World Data (RWD) has been used in health economics and outcomes research, market access evidence generation and post-marketing commitments. The FDA has released the final guidance, and these data can now serve multiple functions across the product value chain including integrated evidence package submissions. This work covers novel applications of RWD to support activities such as clinical trial optimization, external control arms, integrated evidence package submissions, diversity plans and patient journey to determine unmet need, as well as applications in safety and pharmacovigilance and key considerations in their execution.
Leveraging RWD in accordance with the FDA RWE Guidance warrants new and advanced methods in machine learning, deep learning, artificial intelligence and simulation to manage data and generate the insights needed to execute these novel applications. We highlight key considerations in this work.

INTRODUCTION

Traditionally, Real World Data (RWD) has been used in health economics and outcomes research, market access evidence generation and post-marketing commitments. The FDA has released the final guidance, and these data can now serve multiple functions across the product value chain including integrated evidence package submissions. The FDA has provided the following guidance on key applications of Real World Evidence (RWE)

I. For the purposes of pharmacovigilance and safety surveillance following the release of a drug, medical device, or intervention.
II. Drug, device, and diagnostic test evaluations all benefit greatly as part of health technology assessment.
III. Patient subgroups who may respond differently to treatments or interventions are identified through RWE, which contributes to the development of personalized medicine approaches.
IV. Better design and execute studies that answer unmet clinical needs, which in turn facilitates the recruitment of clinical cohorts likely to respond favorably to novel treatments.
V. The development of healthcare policies, clinical guidelines, and treatment pathways.

We explore novel applications of RWD across the value chain and specific considerations for responsible innovation in three use cases.

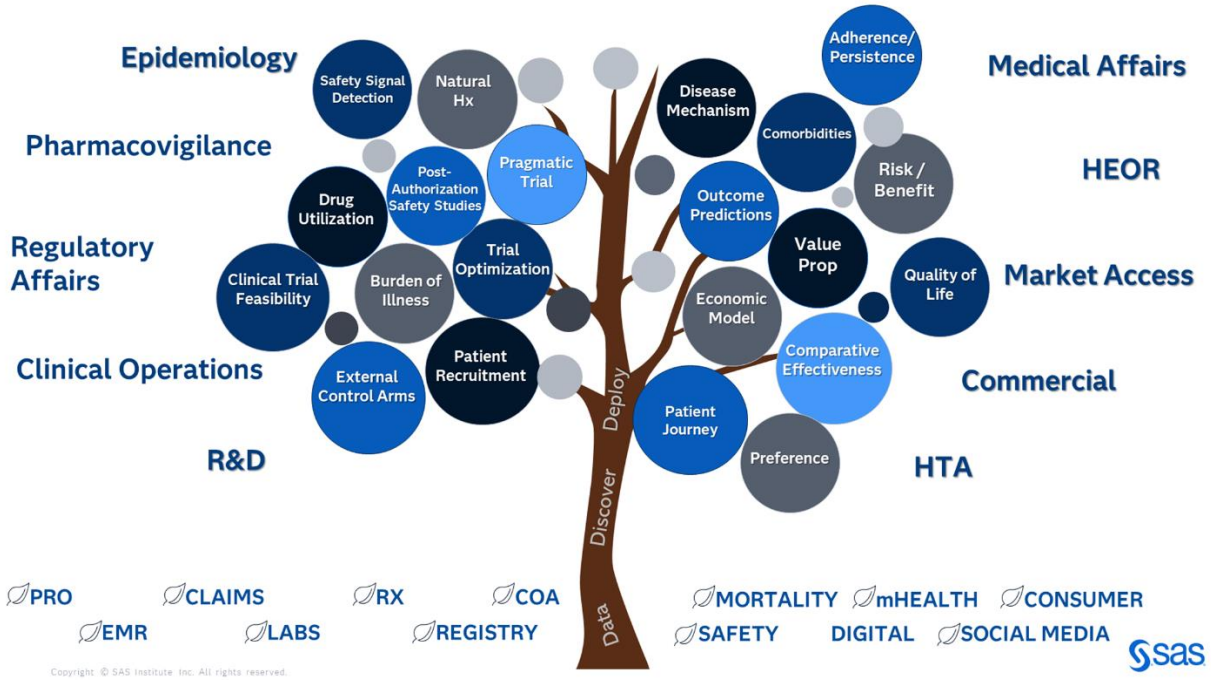

Figure 1: Developing RWE from RWD in Novel Ways Across the Product Value Chain

CLINICAL TRIAL OPTIMIZATION

The goal in leveraging RWD in this use case is to define the optimal Target Patient Population (TPP) and simulate clinical trial enrollment. This allows clinical researchers to identify geographic distributions of patients who meet the clinical trial eligibility criteria and more efficiently target trial sites to recruit and enroll patients. RWD utilization in this case can allow for greater numbers of eligible patients as well as more precisely defined TPP which will reduce the burden on and risk to the patient and to the processes of the clinical trial operations. Thus, attrition and number of protocol amendments are significantly reduced, contributing to a more efficiently run clinical trial. Finally, another benefit is site performance can be monitored during the execution of a trial using simulation and real time data.

In our example, we defined TPP using conventional means, subject matter expertise (SME) to remove an exclusion criteria and, finally, a machine learning analysis of variables of importance to identify eligibility criteria with SME input. Variables of importance was determined using random Forest trees. Spatial analyses were performed to determine geographic distribution of patients and overlay potential trial sites. Univariate analyses of baseline characteristics were performed to determine statistical significance of potential impact of each method.
To determine the impact on scientific robustness, we tested the hypotheses using logistic regression, gradient boosting, neural networks and decision tree analyses, followed by a model comparison using KS (Youden) fit statistic. Final output could be used as prior estimates for simulations of enrollment and each site then monitored and evaluated for performance.

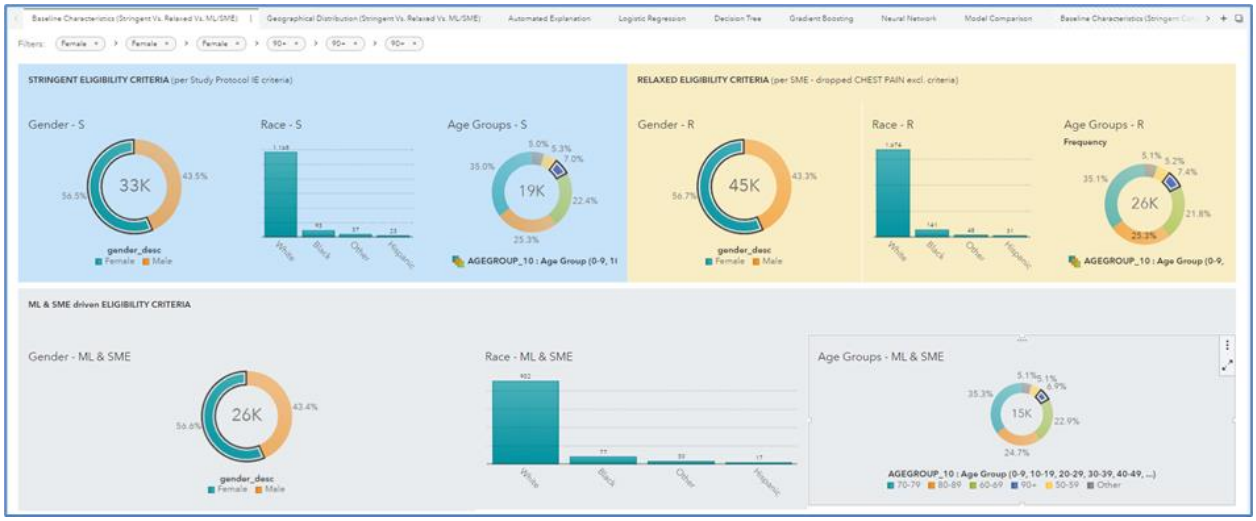

Figure 2: Baseline Comparisons of Each TTP Using SAS Visual Analytics.

EXTERNAL CONTROL ARMS

The goal in leveraging RWD in this use case is to provide sufficiently robust evidence with diverse sources of data to expedite regulatory approval. This allows clinical researchers to identify patients who meet the clinical trial eligibility criteria and more efficiently target patients while reducing the burden and risk to the patient. RWD utilization in this case can contributing shortened timelines and lower costs of clinical trials.

In our example, we defined external control arms (ECA) using synthetic data to determine if we could adequately establish a robust comparator arm for a clinical trial. We selected patients who would be considered historical and contemporaneous controls to treatment arm. Baseline characteristics were analyzed and reported and primary and secondary endpoints were compared between both arms.

Figure 3: Visual Analysis of ECA Enrollment with Eligibility Criteria Using SAS Visual Analytics.

Key considerations for researchers regarding the data and methods include the following:

Data

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?

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?

DIVERSITY PLAN

The goal in leveraging RWD in this use case is to provide sufficiently more representative and inclusive patient populations in clinical trials. This allows clinical researchers to establish a more inclusive and representative patient population.

In our example, we assess bias in RWD compared to a true epidemiologic profile using built in bias and fairness reports of models. Using SAS Enrollment Simulator, enrollment plans could be established for each site and assessed for diversity targets. Using SAS Health, researchers could connect directly to Electronic Medical Records (EMR) using interoperability adaptors (i.e. FHIR, OMOP, etc.).

given	family	Medical Record Number	Driver's License	Social Security Number	Passport Number
Adaline602	Koch169	aca39bdc-0d62-4e6b-8b6e-9a451dab6231	S99936519	999-14-4205	X7209357X
Al123	Daugherty69	af324ccb-9837-45cc-b39f-2f77f99429eb	S99980980	999-93-2747	X70569062X
Allegra202	O'Connell601	4fcc744e-7191-4f81-8717-b910837f5ae2		999-94-3248	
Angla303	Homenick806	643d00f0-c49a-43df-839b-b7e8d4cf0fd8		999-14-5453	
Astrid395	Koch169	15cd4083-8a2c-4a0c-be30-ccbf860ce8b2	S99977603	999-76-5212	X23669981X
Burl285	Feil794	b99333dd-dc81-43eb-8aee-a3147a0e6b74	S99911736	999-11-9181	X87664340X
Carmelo33	Kirlin939	959b05e1-f5c7-4dbd-8e04-bde111be0d21		999-50-2988	
Cruz300	Wyman904	f87ebd0e-359d-4d78-a58e-bb914dddecee	S99988755	999-46-3430	X8435178BX
Danny396	Mraz590	632b48b2-06d5-44e5-b518-c5eca0fe4765	S99927572	999-86-8119	X22332887X
Daren950	Spencer878	60829189-4a97-47b1-9b63-74bb5a2f9ff4	S99936630	999-64-3262	X2149378X
Dewayne363	Orn563	b69db372-a049-4af5-ac3f-35c11a455b8a		999-75-9587	
Dominque770	Schumm995	ac0d224d-beb6-4f00-aae1-77492372430e	S99963375	999-33-2191	X2074231X
Gregg522	Hettinger594	a238ebf2-392b-44be-9a17-da07a15220e2	S99942098	999-99-7515	X19416767X
Izetta651	Hintz995	f39d0979-c774-4109-bcca-8fd54d37577c	S99914066	999-95-5645	X80347960X

Figure 4: Diversity Reports on FHIR Connected EMR Patient Data using FHIR Adaptor on SAS Viya.

RESPONSIBLE AND ETHICAL INTEGRATED EVIDENCE PACKAGES

According to the FDA Guidance on RWE, a primary point of focus will be assessing the fitness of RWD after assessing the Clinical Study Methodology. This is constituted in the following steps:

- Reliability of **Data**
  - Data accrual
  - Data quality control
  - Data assurance
  - Data relevance
- Standardized **Ontologies**
  - ICD-9/10
  - LOINC
- Standardized Definitions
  - Do codes adequately represent underlying medical concepts
  - Are data relevant on exposure, outcomes, and covariates.
- Global regional differences in population and policy

SAS is committed to responsible innovation and has contributed to FDA Requests for Information on RWE and

ML/AI. SAS is dedicated to an AI Risk Management Framework based on the National Institute of Standards and Technology (NIST). These include the following components:

- Framing risk
  - Framing risk includes information on:
    - Understanding and Addressing Risks, Impacts, and Harms
    - Challenges for AI Risk Management
- Audience
  - Identifying and managing AI risks and potential impacts requires a broad set of perspectives and actors across the AI lifecycle. The Audience section describes AI actors and the AI lifecycle.
- AI Risks and Trustworthiness
  - For AI systems to be trustworthy, they often need to be responsive to a multiplicity of criteria that are of value to interested parties. Approaches which enhance AI trustworthiness can reduce negative AI risks. The AI Risks and Trustworthiness section articulates the characteristics of trustworthy AI and offers guidance for addressing them.
- Effectiveness of the AI RMF
  - The Effectiveness section describes expected benefits for users of the framework.
- AI RMF Core
  - The AI RMF Core provides outcomes and actions that enable dialogue, understanding, and activities to manage AI risks and responsibility develop trustworthy AI systems. This is operationalized through four functions: Govern, Map, Measure, and Manage.
- AI RMF Profiles
  - The use-case Profiles are implementations of the AI RMF functions, categories, and subcategories for a specific setting or application based on the requirements, risk tolerance, and resources of the Framework user.

When developing innovative and responsible approaches to drug development that include Integrated Evidence Packages, there are key considerations the authors emphasize due diligence for ethical review:

- **Technology**
  - Select the appropriate technology Implement industry standards
  - Governance capabilities
  - Model interoperability.
  - Connect to and ingest big data and *a priori* standardize it before applying AI/ML techniques
- **Data Governance**
  - Data acquisition, integration, harmonization
  - Assess data quality
  - Track data lineage
  - Version code
- **Model Operations**
  - Develop fit models
  - Govern and monitor model performance
  - Version models
  - Establish a model operations process
- **Model Performance Bias**
  - Identify variable inputs
  - Assess weight of each variable
  - Detect any bias in the models
  - Understand the source and collection of data used
- **Transparency**
  - Lineage of operations (data management and analyses)
  - Explainability of models
  - Understand any system limitations
  - State assumptions in the data chain of custody
  - Assess impact the projected and modeled outcomes of the trial

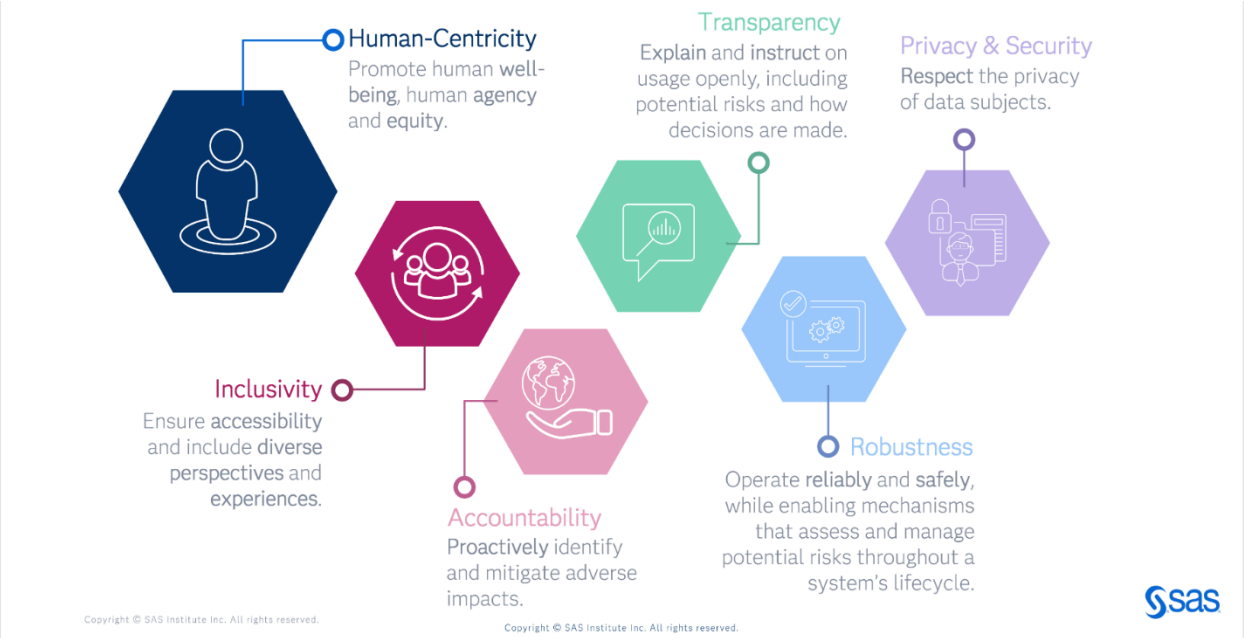

Figure 5: Principles of Responsible Innovation with ML and AI.

CONCLUSION

In conclusion, use cases presented here and others in the figure demonstrate novel applications of RWD/RWE in the value chain of product development. Key considerations in submitting evidence using these data are critical to meet regulatory requirements and responsible drug development. Responsible ML and AI practices and procedures are every organization's responsibility as regulations continue to be developed.

CONTACT INFORMATION

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