Real-World Data-based Simulations: Generating Medical Evidence from Clinical Trial and Real-World Data

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RWD-based Simulations: Generating Medical Evidence from Clinical Trial and Real-World Data

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Introduction

Randomized controlled trials (RCTs) represent the primary mechanism for establishing the safety and efficacy of a treatment compared to placebo or a comparator.[1] RCTs achieve unbiased estimates for causal relationships between treatments and endpoints through randomization. However, their narrow enrollment criteria and standardized treatment protocols result in limited interpretation to real-world populations in routine clinical practice, where treatment decisions are made according to patient health characteristics, socioeconomic factors, personal beliefs and values, physician discretion, insurance coverage, and a myriad of other uncontrolled factors. Therefore, stakeholders are increasingly interested in utilizing real-world evidence (RWE) to support decision-making and the development of clinical practice recommendations. As such, guidance is emerging on the use of real-world data (RWD) and simulation modeling in settings where these methodologies may be more appropriate than RCTs.[1,2]

The recent widespread use of electronic health records (EHR) and expanding interest in developing registries has resulted in an increased abundance of RWD available for secondary analysis. However, gaps in the data and short durations of follow-up relative to the entire patient lifetime, as well as limited ability to link patient records between different sources, can present issues in using RWD to predict the effect of therapy on health outcomes, quality of life, and healthcare costs and utilization. Traditional statistical methods, including regression and propensity score matching analyses, have several drawbacks: they are biased by confounding, can only provide results for associations between independent predictors and/or interaction terms and model outcomes, cannot account for time-varying effects or changes in treatment protocol post-index, are subject to reverse causality, and cannot establish true causation between exposure and outcome.[3]

The challenges described above can be overcome with a strong study design and use of Monte Carlo simulation, also known as the Monte Carlo Method or a multiple probability simulation. This method allows for prescriptive and/or counterfactual analytics which can be used to generate meaningful clinical insights from RWD.[4] It is a mathematical technique that relies on repeated random sampling to predict a set of outcomes based on an estimated range of input values. A Monte Carlo simulation will model a given process at the micro-level (e.g., at a patient-level) via explicit handling of uncertainty, and then aggregates the results to summarize the emergent population characteristics at the macro-level.[5] In this way, Monte Carlo simulation can combine evidence from a variety of sources to provide estimates over longer treatment and/or model durations on real-world populations. This can be applied to the investigation of drugs that have not yet been commonly prescribed or are new to market in the clinical practice setting, and for a broader range of outcomes than is typically observed in RWD.

In this white paper we showcase how this method, when implemented on RWD (from here on, we will refer to it as RWD-based simulation), derives patient-level estimates of the effectiveness and safety of treatments in real-world populations by combining evidence on:

1. The observed patient characteristics in RWD
2. The baseline risk of disease-related events
3. The treatment efficacy

Herein we also provide a case study demonstrating how Axtria's real-world evidence/health economics and outcomes research (RWE/HEOR) team has developed a highly flexible RWD-based simulation to study the impact of a new cardiovascular (CV) therapy on cholesterol goal achievement and risk of major CV outcomes. The published manuscript was able to impact 2018 American College of Cardiology/ American Heart Association clinical practice guidelines on the treatment of high-risk atherosclerotic cardiovascular disease (ASCVD) patients.

Advantages of RWD-based Simulation

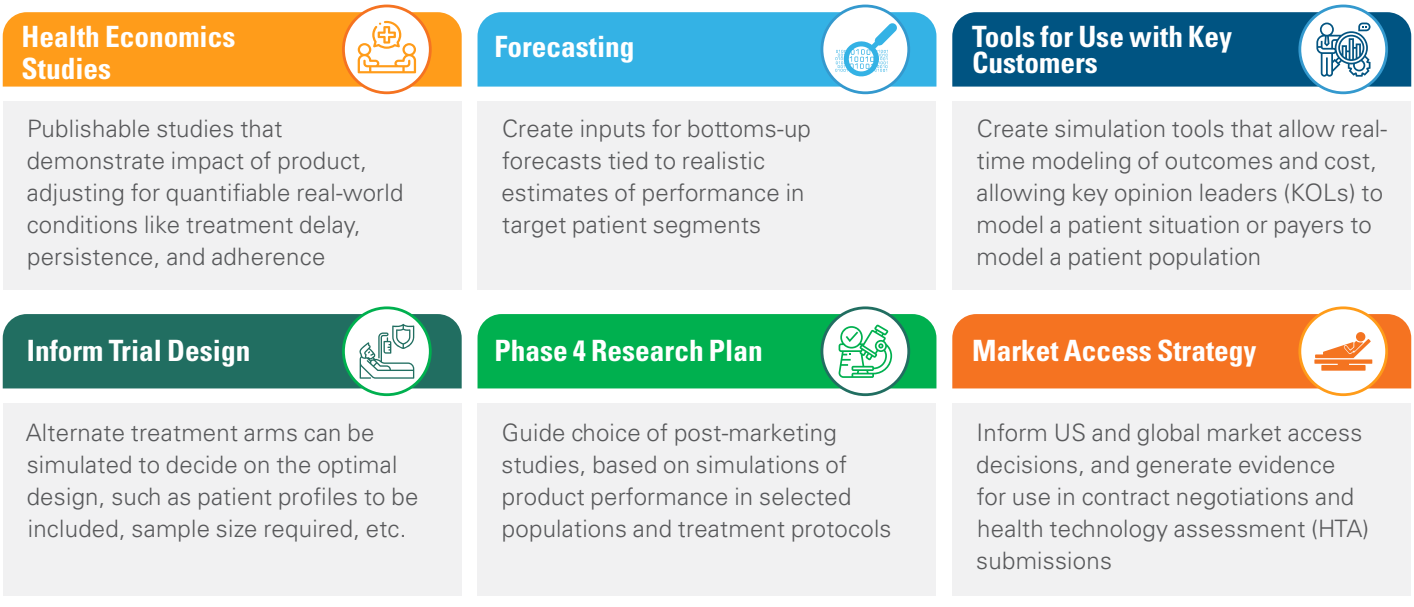
The idea of simulating population outcomes is not new to economic modeling. Discrete event simulation, Markov chains, and Monte Carlo simulation have often been used in healthcare to improve operational efficiencies in hospital systems, assess the impact of drugs on patient outcomes, and estimate disease-related costs to healthcare systems, among other applications.[6] Discrete event simulation is employed to simulate dynamic behaviors of complex systems and a sequence of interactions between individuals, populations, and their environments. However, the inputs are deterministic and outputs are discrete, thus it is not possible to generate uncertainty intervals for outputs of interest from a single sequence. Markov chains used in cost-effectiveness analyses simulate patient progression between health states using a homogenous population without patient-level outcomes. Yet, outcomes captured in a Markov chain model are mutually exclusive and simplified compared with real-world situations; i.e., health state transition probabilities do not depend on patient history.

RWD-based simulations can overcome the challenges faced by other simulation techniques to estimate the impact of treatment in a real-world setting, specifically by:

- Evaluation over longer durations of treatment and follow-up vs. both RCTs and RWD (e.g., new to market drugs or early vs. delayed treatment initiation being a crucial application)
- Assessment of treatment impact by patient subgroups, even those not typically represented in RCTs or who are in a minority of patients receiving care in the real-world setting
- Modeling of alternate complex treatment algorithms according to current guideline-recommended strategies, allowing patients to change treatments throughout the simulation and inform gaps in clinical practice vs. guidelines
- Accounting for uncertainty and heterogeneous response to treatment by specifying a distribution for the treatment effect based on RCT evidence or clinical expert opinion

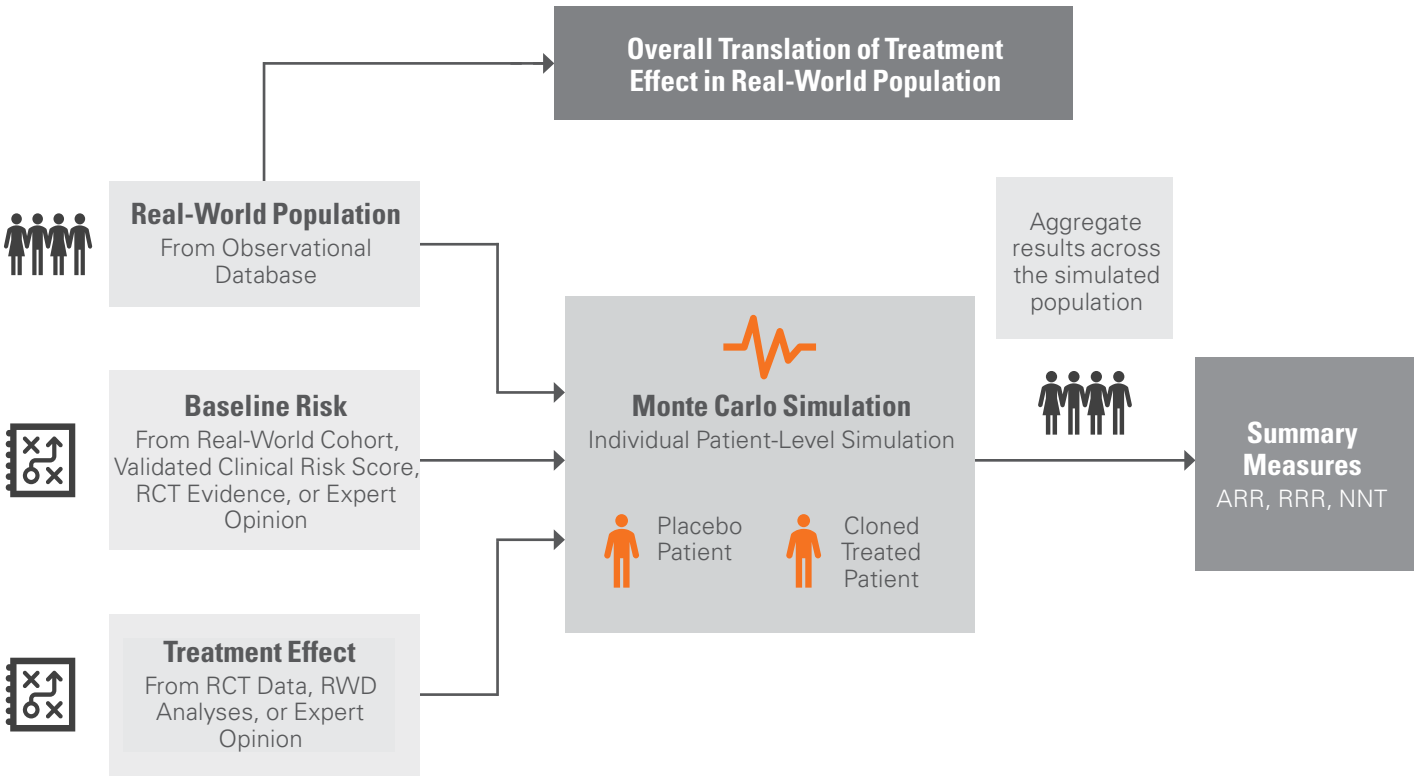
These features make RWD-based simulation a useful tool for generating brand insights and supporting a wide range of applications, as shown in Figure 1.

Figure 1. Applications of RWD-based Simulation



Source: Axtria Inc.

Figure 2. Proposed Framework for RWD-based Simulations



Abbreviations: ARR = absolute risk reduction; NNT = number needed to treat; RCT = randomized controlled trial; RRR = relative risk reduction

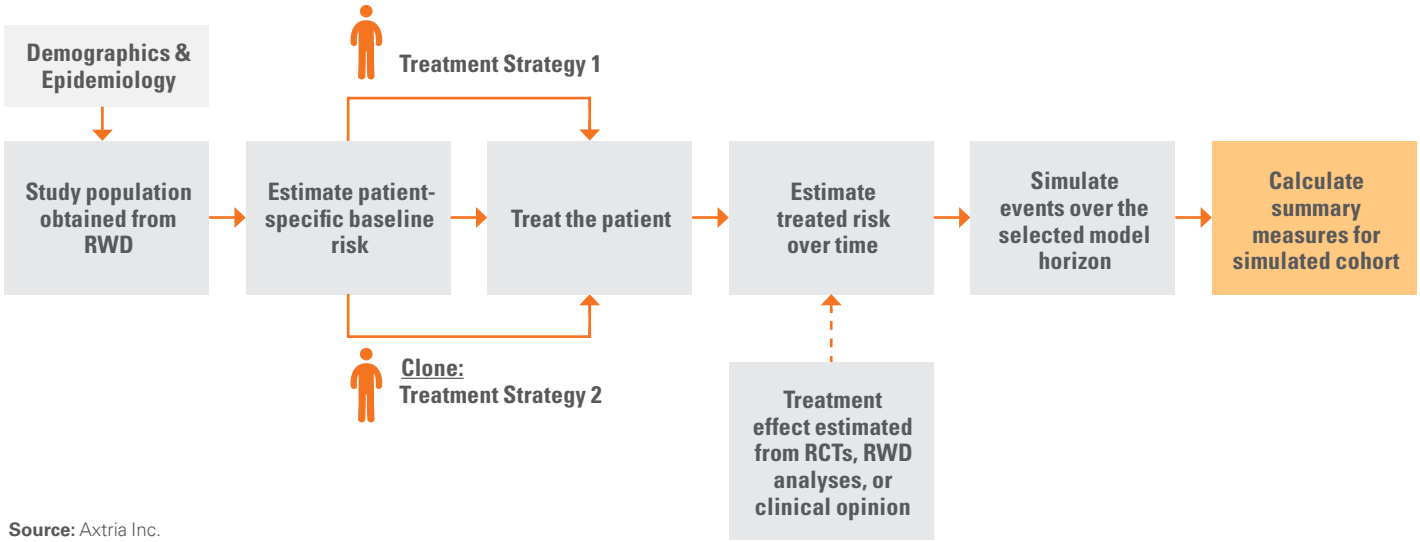
Source: Axtria Inc.

The core framework of RWD-based simulation studies (Figure 2) includes input identification, model development, and generation of summary measures. Specific inputs to the models are identified as follows:

1. **Observed Patient Characteristics in RWD.** This represents the population for which outcome estimates are desired, and key patient attributes and events should be specified. Potential data sources include EHRs, claims, and registry databases. The main considerations for selecting RWD sources include:
   - Availability of patient-level data and a broad collection of key patient attributes that influence the baseline risk
   - If used to determine baseline risk, the ability to track patients longitudinally for the endpoints of interest
   - The ability to ensure the simulation is representative of the population of interest
2. **Baseline Risk of Disease-related Events.** This represents patients' risk of experiencing an event (e.g., myocardial infarction) over a given period, depending on patient characteristics, and can come from RWD or validated risk scores, like the Thrombolysis in Myocardial Infarction (TIMI) Risk Score for Secondary Prevention (TRS 2^{0}P).
3. **Treatment Efficacy.** This represents the patients' risk with treatment. As treatment effect estimates include causal associations, these are preferably based on RCTs or well-designed RWD studies that employ robust statistical methods[3]. Alternatively, this can be informed by expert clinical knowledge.

The workflow of an RWD-based simulation model is outlined in Figure 3. In alignment with the Monte Carlo approach, patients are randomly sampled with replacements from the original real-world population one at a time. The patient's baseline risk is estimated,

Figure 3. Overall Workflow for RWD-based Simulations



Source: Axtria Inc.

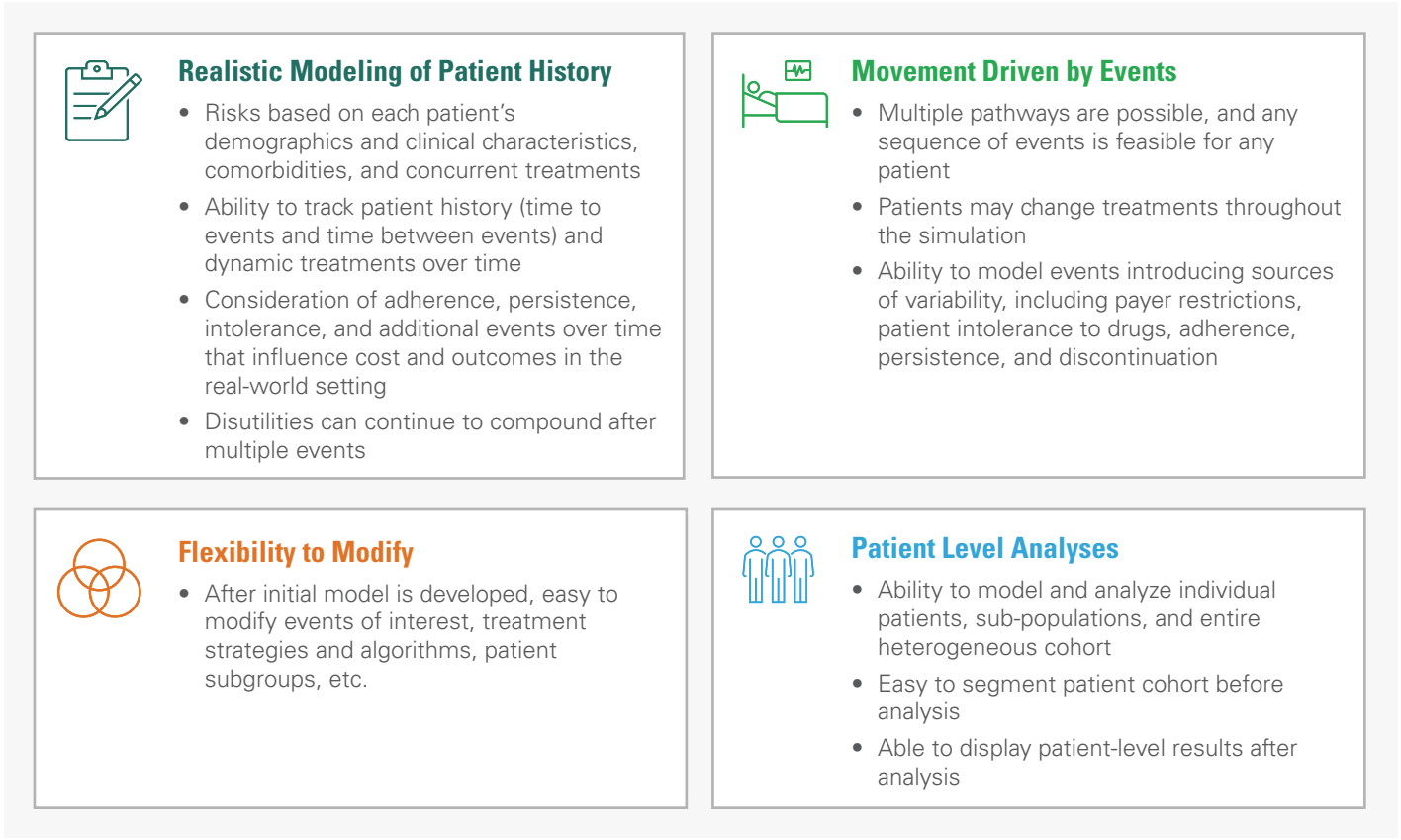
and each patient is cloned such that the patient receives one treatment strategy (i.e., the placebo or comparator) and the clone receives a second treatment strategy (i.e., treated). Baseline risk is modified according to the treatment received, and events are simulated over time. This process is repeated until a sufficiently large sample is reached (e.g., one million patients), and results are aggregated across the entire simulated population.

Figure 4. Structured Approach to Developing RWD-based Simulations

Specifications	Data Gathering	Model Development	Output Development	Application Across Stakeholders
• Define patient cohort • Agree on key patient attributes, e.g., demographics, comorbidities, etc. • Assess key events to be modeled • Identify treatments and treatment protocols of interest • Agree on key features needed, e.g., level of flexibility	• Define data requirements based on specifications • Assess availability of data: patient level, aggregate • Evaluate data sources and select sources for each required input • Agree on analytical approach where patient-level estimates need to be generated	• Assemble patient level estimates from data sources • Create patient cohort, applying inclusion and exclusion criteria, stratification rules • Program logic for patient cohort selection • Program logic for user inputs (treatment algorithms, constraints, time periods) • Program logic for Monte Carlo simulation	• Display of modeling scenario • Summaries of model results • Ability to define and compare population segments • Sensitivity analyses regarding clinical intervention, model structure, etc. • Animations to show patient behavior over time	• Leverage platform to support brand • Internal applications, e.g., forecasting, research plans • Publications, e.g., use in health economic studies • Customer facing, e.g., payer discussions

Source: Axtria Inc.

Figure 5. Features of RWD-based Simulation



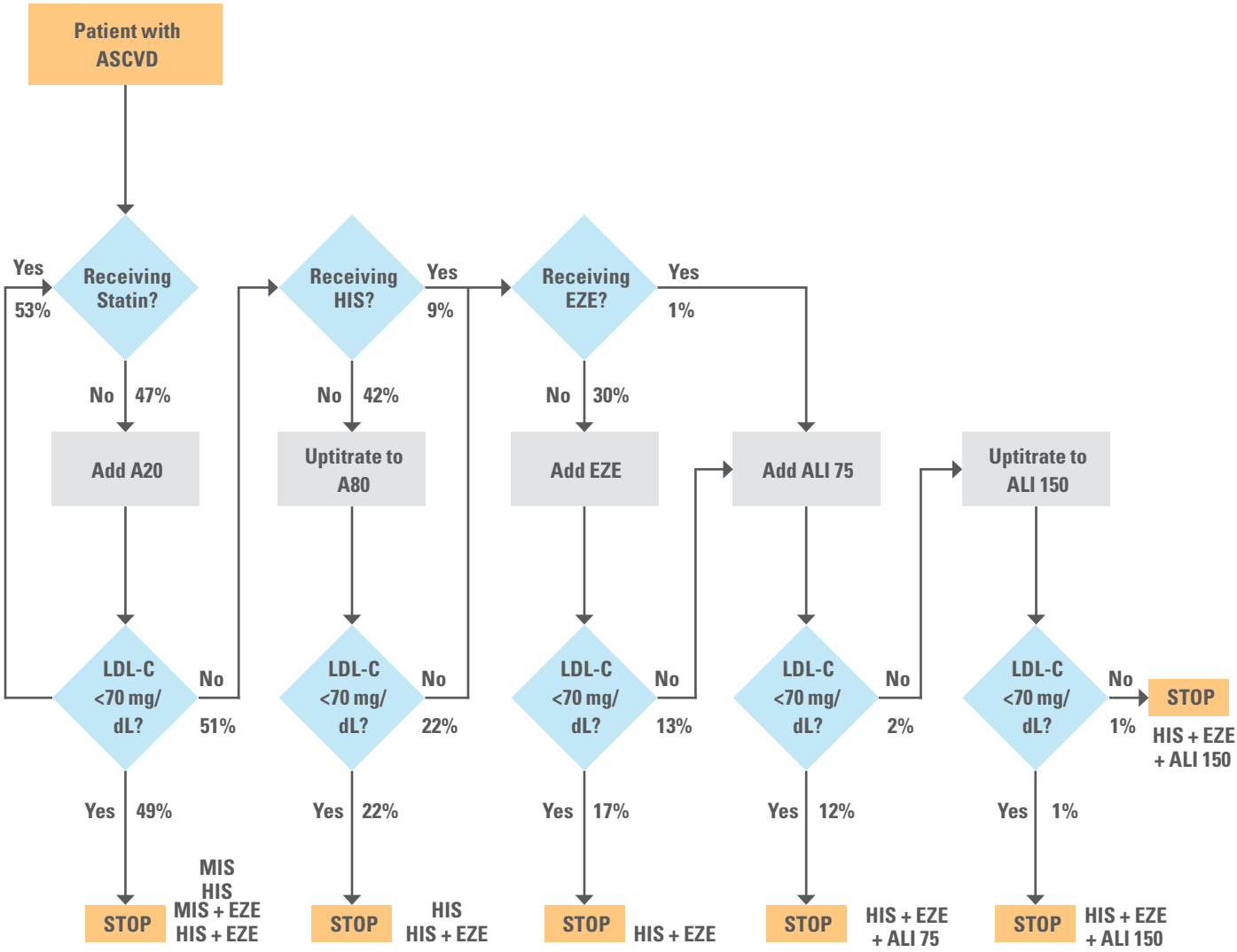
Source: Axtria Inc.

Case Study: Impact of Axtria RWE & HEOR's RWD-based Simulation on the 2018 American College of Cardiology/ American Heart Association Clinical Practice Guidelines

A global pharmaceutical manufacturer launched a highly effective but costly alirocumab (proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9i)) therapy with a new mechanism of action into the competitive low-density lipoprotein-cholesterol (LDL-C)-lowering market. To communicate the value of this new agent and guide evaluations of its place in therapy, a Monte Carlo patient-level simulation model for treatment intensification was developed.[7] The resulting model assessed the potential population-level benefits of cholesterol-lowering interventions and helped the client identify and characterize new populations that may be eligible for PCSK9 inhibitor therapy. Notably, the study was cited in the 2018 American College of Cardiology/American Heart Association clinical practice guidelines as a "well-designed" simulation study providing evidence in support of addition of ezetimibe to statin therapy prior to PCSK9 inhibitor initiation, with the goal of lowering LDL-C to <70 mg/dL (1.8 mmol/L).[12]

To investigate gaps in clinical practice vs. ideal guideline-based intensification, two scenarios were modeled: 1) real-world treatment scenario, representing payer restrictions, non-adherence, and statin intolerance; 2) ideal treatment scenario, representing no payer restrictions, full adherence, and no statin intolerance. The simulation was programmed such that cloned patients received intensified treatment to reach defined LDL-C goals. Figure 6 shows the sequence of treatment intensification used in the model and percentage of RWD cohort receiving treatment at each step. Risk based on patient characteristics and LDL-C level at baseline was modified according to the LDL-C reductions expected from post-index treatment(s) over time, and patient-level CV events were predicted.

Figure 6. Logic of Intensification Treatment Algorithm and Proportion of Patients at Various Intensification Steps for the Ideal Treatment Scenario



Abbreviations: A20 = atorvastatin 20 mg; A80 = atorvastatin 80 mg; ASCVD = atherosclerotic cardiovascular disease; ALI 75 = alirocumab 75 mg; ALI 150 = alirocumab 150 mg; EZE = ezetimibe; HIS = high-intensity statin; LDL-C = low-density lipoprotein cholesterol; MIS = moderate intensity statin

Source: Axtria-affiliated paper[7]

1. **Observed Patient Characteristics from RWD.** The study population represented claims database patients at high CV risk, with known patient characteristics, therapies, CV event history, and LDL-C level. To address bias (e.g., underrepresented patients aged ≥65 years), the population was stratified and reweighted.
2. **Baseline Risk of Disease-related Events.** CV event risk was modeled according to a multivariate Cox proportional hazards model based on patients' baseline characteristics, which enabled patient-specific prediction of time-to-event for CV events.
3. **Treatment Efficacy.** Estimated efficacies of expected LDL-C reduction and subsequent CV risk reduction with treatment for all treatments considered in the model were obtained from meta-analysis and RCT.[8,9,10,11]

In the real-world cohort of patients with ASCVD (i.e., before treatment intensification), 51.5% of patients used statin monotherapy, 1.7% used statins plus ezetimibe, and only 25.2% achieved an LDL-C level of less than 70mg/dL. After treatment intensification within the simulation model, 99.3% of patients in the cohort could achieve an LDL-C level of less than 70mg/dL, including 67.3% with statin monotherapy, 18.7% with statins plus ezetimibe, and 14% with add-on PCSK9 inhibitor. Subsequent model enhancements explored the impact of real-world limiting factors like non-adherence, discontinuation, and payer restrictions.[13]

Conclusions

RWD-based simulations enable the evaluation of proposed treatment interventions on the real-world subpopulations of interest and over longer time horizons than RCT or RWE studies. The case study described above helped identify appropriate target populations for a newly launched therapy, and resultingly, impacted clinical practice guidelines. With growing recognition and appreciation of RWE studies, additional applications of RWD-based simulations can extend to market access, safety and efficacy studies, and regulatory submissions.

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