

Entering a new age of evidence generation: synthetic control models

Leanne Larson, Senior Vice President and WW Head, Real-World Evidence & Access
Parexel®

The industry is primed to take real-world evidence (RWE) to a whole new level through the use of external data to create synthetic controls for clinical evaluations. Some say this shift might be considered radical, but for others such as Leanne Larson, Senior Vice President and WW Head, Real-World Evidence & Access at Parexel, she and her team are ready to meet the growing interest in RWE from sponsors, regulators, and payors, by developing innovative data models and technologies, to transform clinical research.

Synthetic control models, which are not new to clinical research, can be used to evaluate the comparative effectiveness of an intervention using external control data. What is revolutionary though, is the opportunity to use existing data and to link patients across multiple datasets, in concert with proven prospective research models within non-

traditional infrastructure settings. According to Leanne, this approach offers important opportunities both to streamline the research process and to bring needed real-world perspective and data to the table. “We have greater access to better data than we did a number of years ago, so our ability to gather the data that we need for the synthetic control arm has significantly improved – and without these advancements, synthetic modelling at this level would never be possible,” she says.

Real-world data also can provide important information in the post-marketing setting, especially from a safety perspective, to answer both regulatory and payor questions. The US Food and Drug Administration (FDA) and European Medicines Agency (EMA) have taken several initiatives to allow for these novel approaches to external control data.

This article was adapted from a *PharmaVOICE* eBook titled “Innovating for the Future in Drug Development,” October, 2020.

A summary of commonly used models and methods for generating synthetic control arms

| Model Complexity | Examples | Pros | Cons |
|----------------------------------|---|--|--|
| Naïve | Simple mean, median or fixed-effect pooling | Easy to perform. Easy to interpret. | Requires high congruence between external and internal data. Often only valid for restrictively small subgroup populations. Thus, falls short on precision. |
| Imbalance Adjustments | Multivariate regression, propensity scoring | Adjusts for imbalance to the extent explanatory factors are available in data. Relatively easy to perform. Relatively easy to interpret. Generally considered valid with good data and sufficient plausible confounding variables. | Methods can be complex or relatively time consuming to implement and test. There is a plethora of approaches with various performance advantages and shortcomings. Thus it may be challenging to choose the “best” approach. Examples of applications with counter-intuitive findings exists, thus underscoring the need to have available and consider as many possible confounders as possible |
| Complex adjustment and weighting | Bayesian mixed-model commensurate power priors. | Can restore patient balance and weigh the contribution of multiple sources of data adequately. | Difficult and complex to implement. Often computationally heavy. |
| Advanced exploratory solutions | Random forests, Neural Networks, Cluster analysis (Gaussian mixture models) | Can identify homogeneous sources of data for enhanced validity. | Mostly exploratory in nature and requires separate statistical analysis to produce synthetic control. No guarantee findings will be interpretable or useful for further analysis. |

Source: National Center for Biotechnology Information, U.S. National Library of Medicine

In a review of 489 pharmaceutical technologies assessed by the National Institute for Health and Care Excellence (NICE), according to the National Center for Biotechnology Information, US National Library of Medicine, as of May 2020, 22 submissions used external data and synthetic control methods to establish clinical efficacy. Of these, 13 (59%) used published RCT data for their external control, and six (27%) used observational data. More than half of the applications were made in the last two years alone, further confirming the increasing attention paid by both drug manufacturers and health technology assessment agencies on this topic.

These numbers support Leanne's read on the biotech and pharmaceutical industries' excitement around the potential of external controls, and their benefits in accelerating clinical timelines, reducing costs, and decreasing the number of patients required for clinical studies. "Today, we have a greater understanding of the robust statistical methodologies that are required, as well as an overarching comfort level and the experience in working with the real-world evidence that supports this new approach," Leanne says.

Even with all of the benefits, however, a synthetic-control model is not appropriate for every study, or every product. "Currently, we see the greatest potential in the areas of rare and life-threatening diseases, where finding study participants is particularly challenging," she says.

Patients, particularly those facing a complex illness, are often hesitant to enroll in a clinical

trial where they run the risk of being randomized to either a placebo control or a control that they fear may be less effective. In this model, though, they are assured they are receiving the innovative, experimental treatment that they hope will offer some relief. "There are also some cases when it's not considered particularly ethical to enroll randomized patients in a placebo control, for instance," she says. "Patients need to be treated, especially in areas of unmet medical need, where there might not be an accepted or effective treatment for that condition."

Leanne and her team are at the forefront of this burgeoning area of research and are well-primed to assist sponsors to determine whether a synthetic-control arm is appropriate for their clinical protocol. Parexel's innovative and consultative approach, based on years of experience, starts with a tremendous amount of due diligence. "We have a well-structured model that we follow," she says. "Based upon our experience in this model, we have a list of questions that we ask, and we know what we need to consider in order to determine whether or not the sponsor's project is appropriate for this approach."

Her goal is to make sure at the outset that the correct study design is in place with the right covariates and endpoints, and that the external patient cohort is comparable to the patient population in the clinical trial treatment arm. "We want to ensure that the synthetic control population mimics the experimental population as closely as possible," Leanne says. "And, justifiably, in some

While the concept of synthetic control arms may be new to many, they have already been successfully used in regulatory decision-making. Roche, for example, met European Union coverage requirements for marketing Alecensa (alectinib) in 20 European markets using a synthetic control arm. In December 2015, Alecensa received accelerated FDA approval as a treatment for a specific form of lung cancer, and in February 2017 it was conditionally approved in the EU. To make a pricing decision, EU authorities requested additional evidence of Alecensa's effectiveness relative to the standard of care (ceritinib). Rather than waiting for Phase 3 results, Roche used a synthetic control arm of 67 patients to provide the necessary evidence of relative performance. The decision to use a synthetic control arm advanced coverage of Alecensa by 18 months in 20 European countries. Another example is Amgen's use of a synthetic control arm to accelerate the approval of Blincyto (blinatumomab) for the treatment of a rare form of leukemia.

cases the criteria that the agencies are utilizing are even more stringent than if we were conducting a randomized study. We want to ensure that we have the best, most-robust and most-representative dataset possible. We match the patients in the synthetic control arm to the patients in the experimental arm as closely as possible so that we can draw the right conclusions from the data.”

With the growing need to achieve better value for healthcare, RWE as a decision-making tool is more important than ever as part of the drug development and commercialization process. Amid the various factors that contribute to costly trials and long development timelines, there is increasing recognition that through synthetic controls and other real-world approaches, it is possible to achieve a better understanding and stronger evidence of product performance, clinical value, and cost effectiveness outside the controlled environment and homogeneous setting of the randomized clinical trial - in the end, allowing us to better inform the healthcare decision-making process.

“As all of the stakeholders gain more and more experience with synthetic control arms, and as our data science and statistical approaches continue to evolve, we will see greater use of this very patient-centric model,” Leanne says. “Not only does it help make the research process easier on patients, but it also helps us, hopefully, accelerate our ability to bring important new therapies to patients who in many cases don't have other effective treatment options.”

With Heart

Parexel International Corporation

275 Grove Street, Suite 101C, Newton, MA 02466, USA

+1 617 454 9300

info@parexel.com

Offices across Europe, Asia, and the Americas

www.parexel.com

© 2021 Parexel International Corporation.

parexel[®]