AT

WHITE PAPER
SYNTHETIC CONTROL ARM® IN CLINICAL TRIALS

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While randomized controlled trials (RCTs) are the gold standard for evaluating the safety and efficacy of new medical treatments, maintaining a concurrent control arm is sometimes not feasible and can lead to increased patient burden and threaten the completion of a trial.

Such uncontrolled trials are commonly conducted in rare, orphan, or very serious drug indications, when there is a shortage of patients or investigational drug, when there are scientific concerns about treatment switching/crossover, or for ethical concerns. In such cases, sponsors rely on study designs that deviate from the traditional RCT, such as single-arm trials, which can yield important safety and efficacy data that can support a regulatory submission and have recognized benefits, such as smaller sample sizes, the ability to end quickly if a drug has low activity, and that all (or at least most) patients receive the investigational drug (Grayling, 2016). However, uncontrolled trials also risk generating biased data because of a lack of randomization.

To overcome these challenges, sponsors sometimes employ external controls; these improve the interpretation of single-arm trials, by providing supportive evidence that is highly contextual and would otherwise be absent, and also allow sponsors to better understand their trial population if patients were not on therapy. While there are several available external control options, the accumulation of vast amounts of patient-level data is enabling higher-quality and more informative external control arms.

This white paper discusses the concept of the Synthetic Control Arm® (SCA®),[1] which is a type of external control that is generated using patient-level data from patients external to the trial with the goal of improving the interpretation of uncontrolled trials, which can enable better product development decisions. A series of case studies are provided to highlight the different ways an SCA has been used.

Introduction to Synthetic Control Arm®

SYNTHETIC CONTROL ARM IS A TYPE OF EXTERNAL CONTROL

An SCA®

Bene f ts to Patients and Sponsors

An SCA® offers many bene□ts to patients and drug sponsors alike, including the following.

FOR PATIENTS

An SCA® can reduce the burden associated with traditional RCTs. While patients often view an investigational drug as an opportunity for a novel treatment, particularly in rare and life-threatening diseases, the possibility of landing in a control arm, such as placebo or ineffective standard-of-care treatment, can dissuade patients from participating in a trial (American Cancer Society Cancer Action Network, 2018). Additionally, if patients detect they are in a non-treatment control arm, they may drop out or seek therapies outside the trial protocol (Kemmler, 2005). Further, an SCA® can improve patient recruitment and retention by allowing for a study design where all or at least more patients can be treated with the experimental therapy.

FOR DRUG SPONSORS

While external controls are not a replacement for RCTs, a well-designed study with an SCA®

Case Studies

The validity of an SCA® has been demonstrated in several studies. This section summarizes these studies (two that were conducted by Medidata in partnership with the **Friends of Cancer Research**[1] and one by the Celsion Corporation).

CASE STUDY IN NON SMALL CELL LUNG CANCER NSCLC

The validity of an SCA® in an accelerated approval setting was evaluated by examining if an SCA® could replicate the outcomes of a target randomized control from a NSCLC trial. The patients for the NSCLC SCA® were required to have satis□ed the key eligibility criteria of the target trial and were further selected using a propensity-score-based approach to balance the baseline characteristics in the SCA® and the target randomized control. All patient selections were made without knowledge of patient outcomes.

Summary

As described in this paper, there are numerous clinical scenarios where randomization may

Endnotes

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