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WHITE PAPER
SYNTHETIC CONTROL ARM® IN CLINICAL TRIALS

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

The US Food and Drug Administration (FDA) has accepted the use of external controls when it is justified (FDA, 2001) to support regulatory decisions, including the possibility of hybrid approaches where a trial control group is augmented with external data (FDA, 2019). For instance, external controls were successfully used to support the accelerated approvals of blinatumomab and avelumab (Gökbuget, 2016; Cowey, 2017).

Historically, the term “external control” has been used to describe any control group that is not a part of the same randomized study as the group receiving the investigational therapy, and it can be generated by referencing one or more data sources, such as the results of a clinical trial or case studies/clinical experience in the literature, data in a patient registries, or real-world data (RWD) (FDA, 2001).

In contrast to other external controls, which are static summary measures that do not adequately account for patient baseline difference, an SCA® is unique: they are constructed using statistically selected patient-level data (from patients external to the trial) to achieve a balance in the baseline composition of the SCA® with the investigational arm. The source data for generating an SCA® is derived from multiple possible sources, including large datasets of historical clinical trials and RWD. The following table provides a summary of commonly used terms associated with external controls (Table 1).

1 Synthetic Control Arm is a registered trademark of Medidata Solutions, Inc.

Table 1: Definitions of Commonly Used Terms Associated with Control Groups*

Definitions of Commonly Used Terms
Control Arm The group of participants not provided with the investigational therapy. The control arm may receive an intervention that is considered effective (the standard of care), a placebo, or no intervention.
External Control Arm General term that refers to any control group that is not part of the same randomization study as the group receiving the investigational therapy. This can be used as a reference for interpretation of a set of experimental data, especially when randomization is unethical or unfeasible.
Concurrent Control Arm A group selected from the same or a similar population as the experimental intervention group and treated over the same period as the experimentally treated patients. The experimental intervention and control groups should be similar with regard to all baseline and on-treatment variables that could influence the outcome, except for the study treatment.
Historical Control A type of external control. This is a non-concurrent comparator group of patients who received treatment (placebo or active treatments) in the past or for whom data are available through records. This may be patient-level data or summary information gained from medical literature or other sources.
Synthetic Control Arm® A type of external control consisting of patient-level data from patients external to the trial and selected with statistical methods, such as propensity scores, to provide confidence that these patients' baseline characteristics are balanced and comparable with the baseline characteristics of the experimentally treated patients. This can be formed from external clinical trials data, RWD, or other data sources.

*adapted from Friends of Cancer Research, 2019

An SCA® has validated by showing they effectively mimic randomized controls. They can therefore be used to interpret the treatment effects of an investigational product in trials lacking a concurrent control group, such as single-arm trials. Therefore, an SCA® help enhance the scientific validity of single-arm trials; in certain indications, they can also reduce the amount of time and costs associated with trials and expose fewer patients to placebos or existing standard-of-care treatments that might not be effective for them.

CONSTRUCTING A SYNTHETIC CONTROL ARM®

Medidata has been a pioneer in defining adequate external contols and creating a fit-for-purpose SCA® because Medidata has amassed a unique pool of more than six million anonymized patients

> "With the skyrocketing cost of clinical trials, the proliferation of digital data, and a new FDA commitment to considering real-world data in regulatory decision making, it's the right time to begin using synthetic control arms. Medical product development is at the brink of a new age of evidence generation, an environment that's ripe for disruption. The next step requires risk taking, not something this industry is known for." (STAT, 2019)

from nearly 20,000 previous clinical trials, all of which have been cleaned, standardized, de-identified, and aggregated.

An SCA® is constructed by carefully selecting patients for comparison to current experimentally treated patients. The cohorts are built using patients drawn from previous clinical trials, such as Medidata Enterprise Data Store (MEDS), which contains over 20,000 historical clinical trials, or RWD from electronic medical records or claims data. Patients are first selected by extracting patient-level data from the same indication and for those who had met key eligibility criteria and were assigned to receive the standard of care. Statistical methods are then applied in a dynamic matching process that uses the baseline demographics and disease characteristics for each patient in the experimental trial to generate a historical patient group (the SCA®) that closely matches the experimentally treated patients.

COMPONENTS FOR BUILDING A SYNTHETIC CONTROL ARM®

Prior to building an SCA®, consideration should be given to the necessary components to ensure the best opportunity to create a rigorous SCA® that will be acceptable for the end use. Key components for an SCA® include the following:

1. **Data Source:** After defining the specific indication and/or therapeutic area, it is important to specify the criteria to select the patients from a set of candidate studies (or datasets) so as to minimize confounding or selection bias. The criteria should also be considered in the context of the end use, such as a regulatory application or market access strategy. Clinical trial data have some advantages when it comes to building an SCA®, such as study designs that are typically highly controlled and monitored, whereas RWD has some challenges that must be taken into account. However, there is precedent for using RWD in the context of an external control, and FDA has provided guidance for making determinations for data that is "fit" for regulatory purposes (e.g., FDA's framework for RWD [FDA, 2018]). Table 2 shows some main differences between clinical trial data and RWD.

Table 2: Differences in Data Sources for Constructing an SCA®

Clinical Trial Data	Real-World Data
Lower volume but high relevance to clinical research, inclusion of usual clinical trial endpoints	High-volume data from disparate sources
Standardized and systematic collection of data for all patients	Some industry standardization of data
Reduced bias due to controlled study designs and better-quality data, since it is monitored and reviewed	Biases originating from several areas

2. **Data Processing:** Data from the historical sources must be standardized, aggregated, cleaned, and de-identified to attain a robust control patient cohort. The highly standardized and systematic collection of clinical trial patient data facilitates efficient data processing, whereas RWD can arrive from a variety of disparate sources with relatively low standardization. This often entails additional time and resources expended to clean and standardize the data.

3. **Data Matching:** A range of possible patient-level data matching and propensity score methods can be used to arrive at a cohort that has the desired features, such as specific population characteristics that match the clinical trial of interest. It is important that the biostatistical methods are rigorous and ultimately acceptable by regulatory agencies. Further, more precise estimates of the comparison group outcome and exploration of subgroup effects can be achieved by combining datasets across multiple trials, which is not possible with historical literature comparisons.

Benefits to Patients and Sponsors

An SCA® offers many benefits 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® can improve the interpretation of uncontrolled trials and provide adequate evidence of treatment effectiveness. An SCA® also offer several advantages over other types of external controls, including reliance on published literature and clinical intuition, and circumvent some of the RWD limitations discussed earlier, although effective use of RWD is possible in the right context.

The surge in rare disease research, coupled with dwindling patient pools due to higher competition for patients and more biomarker-defined cohorts, likely means that single-arm trials will increasingly become the norm, given that they are more commonly used in rare disease trials to begin with and that sites and sponsors may have an increasingly difficult time with timely enrollment of a sufficient number of patients (Bell, 2014). Using an SCA® improves not only patient recruitment and retention, by allowing for all (or most) patients to be treated with the investigational therapy, but also the trial interpretation by providing the appropriate context for experimentally treated patients (by comparing to a non-treatment group).

> "No one who signs up for a clinical trial wants to be placed in the placebo group. Placebos are like our savings accounts, our daily workout, why we wash dishes: the end result justifies the means. That doesn't mean we have to love the process. In fact, the fear of being placed in a placebo group is why some people avoid clinical trials all together." (Abbvie, 2019)

An SCA® can also be used to estimate treatment effects when the control arm may have been compromised. For example, FDA's accelerated approval pathway provides conditional approval for an investigational product after positive effect on a surrogate endpoint has been provided, allowing patients earlier access to the therapy. Confirming a positive effect on the clinical endpoint after conditional approval is required and usually includes a randomized trial. However, such a trial is challenged by availability of the investigational product outside the trial, which means that recruitment becomes more difficult. In addition, patients assigned to the control are more likely to drop out and use the non-assigned investigational product, which may bias the observed treatment effect. An SCA® can replace or augment the randomized control of confirmatory trials of drugs made available through the accelerated approval pathway, where the control arm may be compromised by early withdrawal, noncompliance, or treatment crossover to the investigational agent made available by the accelerated approval (Friends of Cancer Research, 2018; Davi, 2019).

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 satisfied 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.

The results demonstrated that a comparable balance in observed baseline characteristics of the SCA® and target randomized control was achieved. The SCA® replicated the overall survival (OS) in the control. The Kaplan Meier curves for OS in the SCA® and control were visually overlapping. In addition, the log-rank test ($p = 0.65$) and hazard ratio of 1.04 (95% CI: (0.88, 1.23)) were not statistically significant.

It was concluded that if the SCA® had been used in place of the randomized control in this study, conclusions about the treatment effect would have been the same. While this may not hold when it is not possible to balance the groups on all confounders, it was noted that the data suggest that an SCA® could augment or replace the randomized control in future trials in some settings, easing recruitment, retention, and crossover challenges without compromising the understanding of the treatment effect (Davi, 2019).

CASE STUDY IN MULTIPLE MYELOMA

This study explored whether the treatment effect (difference between arms) based on an SCA® can mimic the treatment effect from an RCT. The SCA® was constructed using patient-level data from previous clinical trials in relapsed or refractory multiple myeloma. The SCA® patients satisfied key eligibility criteria of the target RCT and were further selected using propensity score methods to balance the baseline characteristics in the SCA® with the target randomized treatment group (TRT) from the original RCT.

Comparable balance was achieved in observed baseline characteristics between the SCA® and the matched patients from the TRT. The treatment effect utilizing SCA® was similar to the original RCT. The Kaplan Meier curve of OS for the SCA® overlapped with that of the randomized control, and the quantified differences between the SCA® and matched patients from TRT were very similar to the original RCT (Table 3).

1 Friends of Cancer Research is a nonprofit that brings together key stakeholders in the scientific, patient, government, and corporate sectors to find solutions to important issues facing cancer research.

Table 3: Treatment Effect Estimates

	HR	95% CI
RCT	0.743	(0.60, 0.92)
SCA® vs. Matched RCT	0.758	(0.63, 0.91)

CASE STUDY FROM CELSION CORPORATION

Celsion is developing their GEN-1 compound, which is an interleukin-12 DNA plasmid vector encased in a nonviral nanoparticle delivery system, for patients with Stage III/IV ovarian cancer. After discussing their preliminary impressive findings from the Phase 1b OVATION I Study with FDA, the agency encouraged Celsion to continue with the development of GEN-1 but noted that a limitation with the trial was the lack of a control group to evaluate GEN-1's independent impact on impressive tumor response, surgical results, and PFS.

> "We are extremely impressed with the high quality of the matched data from the Medidata SCA," said Michael H. Tardugno, Celsion's chairman, president and chief executive officer. "They were able to provide near-perfect matches for patient characteristics in our Phase 1b OVATION I Study. Based on this capability and the remarkable potential demonstrated by GEN-1, we plan to move forward with a partial synthetic control arm for the Phase II portion of our Phase I/II OVATION 2 Study with GEN-1 in advanced ovarian cancer. Using a SCA for a portion of the study will reduce costs and should improve the rate of enrollment as patients will be more likely to receive GEN-1 rather than placebo." (Celsion, 2020)

To overcome this limitation, Celsion worked with Medidata to construct an SCA® using matched patient data provided by Medidata. By employing the SCA®, Celsion was able to show strong signals of efficacy in progression-free survival (an FDA recognized surrogate for OS), with a hazard ratio of 0.53 in the intent-to-treat group (Table 4) (Celsion, 2020).

Table 4: Progression-free survival data comparing GEN-1 with the SCA®

GEN-1 Population	Progression-free survival HR (CI)
Intent-to-treat (n = 15)	0.53 (95% CI 0.16, 1.73); log-rank p = 0.29
Per-protocol (n = 14)	0.33 (95% CI 0.08, 1.37); log-rank p = 0.11

Medidata is also supporting additional commercial projects to facilitate an augmentation approach. For instance, multiple statistical plans have been established for several SCA® offerings, and while they have not yet been built, the plans provide the foundation for doing so should that be requested, such as by FDA during application review.

Summary

As described in this paper, there are numerous clinical scenarios where randomization may be difficult or not feasible, and consequently, the interpretation of the trials can be difficult and uncertain. The use of external controls in such clinical studies offers an opportunity to 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, an SCA® is well-positioned to revolutionize clinical trials in some indications and diseases, given that the availability of vast amounts of patient-level data is enabling these higher-quality and more informative external control arms.

By working collaboratively with Medidata's experts, sponsors can learn how to operationalize an SCA® in their trials and inform the design of future clinical studies.

Endnotes

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