MEDIDATA | WHITE PAPER

Translating Regulatory Insights into Practice with Medidata Synthetic Control Arm®

Japan's Pharmaceuticals and Medical Devices Agency (PMDA) Early Consideration on External Control Arms

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Disclaimer on PMDA Guidance Interpretation

This document summarizes and interprets Japan's PMDA guidance on Externally Controlled Trials. It is not an official or comprehensive translation of the guidance. The content is provided solely to support industry understanding and discussion; readers should consult the original Japanese PMDA documents for authoritative information. This document has not been reviewed by the PMDA and any references to the PMDA should not be construed as an endorsement by the PMDA of its contents.

Introduction

Regulatory agencies around the world have expressed support for the use of external control arms (ECAs) under specific conditions, including the U.S. Food and Drug Administration (FDA, 2023), the European Medicines Agency (EMA) (Houghton, 2023), and Japan's Pharmaceuticals and Medical Devices Agency (PMDA) (Nishioka, 2022; Asano, 2025).

In early 2025, Japan's PMDA released an Early Consideration on External Control Arms (ECAs), marking an important step toward a more clearly articulated regulatory perspective on their use. This document outlines both the potential value and the inherent challenges of externally controlled trials. Among the key advantages, ECAs can provide meaningful comparative evidence in settings where randomized controlled trials (RCTs) are impractical or unethical. However, the PMDA also highlights several critical limitations, such as the absence of concurrent randomization, difficulty in ensuring comparability between the test and control groups, and the risk of confounding imbalances. Additional considerations include differences in treatment regimens, data collection timing, observation periods, endpoints, intercurrent events, and sample sizes.

Medidata's proprietary Synthetic Control Arm® (SCA) directly addresses the key considerations raised in the PMDA's Early Consideration. Unlike traditional ECAs that rely solely on real-world data (RWD), the SCA is a purpose-built, regulatory-grade solution constructed from multiple high-quality sources, including historical clinical trial data (HCTD) from over 36,000 trials protocol-aligned patient-level data. This approach mitigates bias by enabling standardized endpoints, consistent data collection, and alignment with regulatory expectations.

This white paper explores how Medidata's SCA responds to the PMDA's early considerations, offering a practical framework for sponsors seeking to leverage regulatory-grade ECAs. By doing so, sponsors can optimize trial design, reduce timelines, and improve patient outcomes while maintaining scientific and regulatory rigor.

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The Shift Toward Externally Controlled Trials

The landscape of clinical research is continually evolving to meet the increasing complexity of clinical trials, including scenarios where RCTs are not feasible or pose ethical challenges. While RCTs remain the gold standard for evaluating the safety and efficacy of new medical treatments, maintaining a concurrent control arm is not always practical, particularly in the context of rare diseases. Under these circumstances, sponsors may rely on study designs that deviate from the traditional RCT, such as single-arm trials to demonstrate safety and efficacy data to support a regulatory submission (Grayling, 2016).

While single-arm uncontrolled studies can provide advantages, they are prone to several limitations that can lead to biases in interpreting the results stemming from the absence of randomization (Wang, 2024; Mishra-Kalyani, 2022). To address these limitations, externally controlled clinical trials are increasingly being used to provide important contextual evidence that would otherwise be missing, thereby improving the reliability of the study results by allowing for a comparative analysis (Thorlund, 2020; Nuno, 2025). The figure below highlights the main applications of ECAs during different phases of the drug development process.

APPLICATIONS OF EXTERNAL CONTROL ARMS

EARLY IN DEVELOPMENT

- Enhanced interpretation of single arm trial, or increased efficiency of RCT with a hybrid ECA
- Evidence for breakthrough therapy designations Late Stage and Regulatory Use

LATE STAGE AND REGULATORY USE

- Confirmatory single arm trials in life-threatening or rare diseases with futile state of care
- Rescue RCT compromised by availability of experimental product outside of study due to accelerated approvals

PAYOR & HEALTH AUTHORITY DISCUSSION

- Demonstrate therapy value with comparative or real world effectiveness, burden of illness, and value-based contracting

DEFINITION: EXTERNALLY CONTROLLED TRIAL

> An externally controlled trial is one in which the control group consists of patients who are not part of the same randomized study as the group receiving the investigational agent; i.e., there is no concurrently randomized control group. The control group is thus not derived from exactly the same population as the treated population. Usually, the control group is a well-documented population of patients observed at an earlier time (historical control), but it could be a group at another institution observed contemporaneously, or even a group at the same institution but outside the study.

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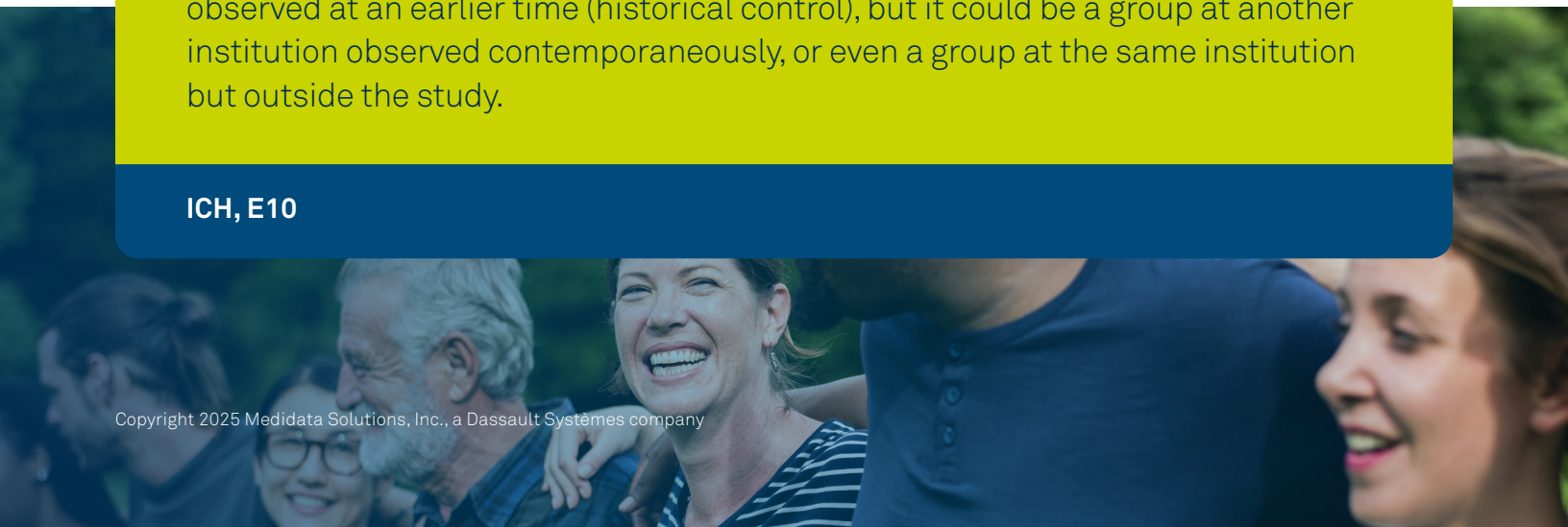

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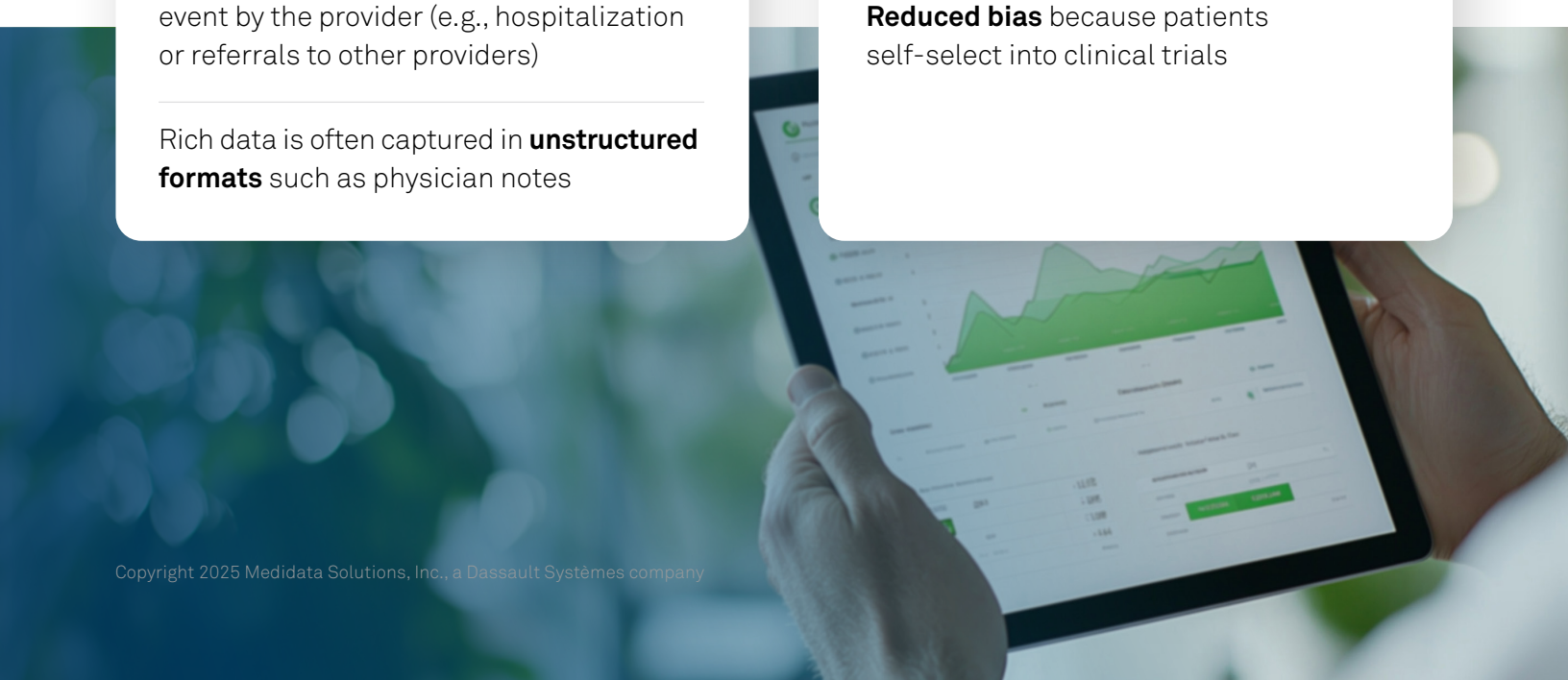
ECAs can be constructed from a variety of possible data sources, including clinical trials (e.g., placebo and active treatment groups from other clinical trials for the same disease) and RWD sources such as electronic health records (EHRs), patient registries, and medical claims databases. Sponsors should be aware of the strengths and limitations inherent in each data source, with the ultimate objective of constructing an ECA that provides contextual evidence that most resembles a RCT.

In the context of creating external control groups, Historical Clinical Trial Data (HCTD) is generally regarded as being more reliable and of higher quality compared to RWD; a perspective that is echoed by the FDA in its guidance documents (FDA draft guidance 2023), underscoring the advantages of using clinical trial data. Several factors contribute to the superiority of historical clinical trial data:

DIFFERENCES IN DATA SOURCES FOR CONSTRUCTING AN ECA

RWD	VS	HCTD
High volume data from disparate sources		**Lower volume but high relevance** to clinical research
Limited standardization of data sources		**Inclusion** of usual clinical trial endpoints, covariates, and prognostic factors
Biases originating from several areas		**Better data quality and completeness** due to rigorous monitoring and review
Incomplete patient reported outcomes or non-serious adverse events may not be captured unless it's observed as a clinical event by the provider (e.g., hospitalization or referrals to other providers)		**Reduced bias** because patients self-select into clinical trials
Rich data is often captured in **unstructured formats** such as physician notes		



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Advantages of Externally Controlled Trials (ECA)

Externally controlled trials can significantly reduce the trial costs. One estimate suggests they may decrease cohort size by 20% to 50% by eliminating the need for a separate control group, potentially saving $10-20 million per trial (BCG, 2021). In oncology, where the per-patient cost averages around $100,000, ECAs help optimize and right-size subsequent trials, resulting in significant cost savings of roughly $100,000 per patient not enrolled. This approach also improves the chances of meeting enrollment and timeline targets, an important benefit given that 80% of clinical trials fail to meet these goals (Desai, 2020).

Improved patient recruitment and retention represent additional advantages of externally controlled trials, as the possibility of being assigned to a control group in an RCT, including placebo or suboptimal standard-of-care treatment, can discourage individuals from participating in clinical trials (American Cancer Society Cancer Action Network, 2018). Additionally, when patients become aware of their placement in a non-treatment control group, they may withdraw from the study or pursue alternative therapies outside the trial protocol. Thus, externally controlled trials enhance both recruitment and retention through study designs that allow all participants to receive the investigational treatment.

There is growing interest in augmented and hybrid trial designs, which have demonstrated the potential to reduce cohort sizes and accelerate development timelines in certain cases. Since these designs have both a small randomized control arm and an ECA, they preserve key elements of RCTs such as randomization, while capitalizing on the benefits of ECAs through supplementation rather than substitution of randomized controls. In short, the randomized control arm is supplemented with the external control patients to bring the control size back up to the size of the investigation arm, and if the outcomes of these two groups are similar, it increases the confidence that there is no unknown confounding (Barrie, 2025; Mishra-Kalyani, 2022). This approach has received FDA agreement, as was the case for Medicenna (see Case Studies section), where Medicenna's planned hybrid SCA reduces the number of patients assigned to the control therapy, while providing robust data and a faster development timeline.

Regulatory Acceptance of External Control Arms (ECAs)

Globally, regulatory agencies have increasingly recognized the use of ECAs, not just in the context of the post-marketing setting, but also as a source of safety and efficacy data to support new drug applications. This shift is driven by the view that externally controlled trials can make drug development more efficient, expedite the approval of novel medicines, and ultimately give patients faster access to new therapies by generating more robust scientific evidence. This is exemplified by the US FDA's 2023 draft guidance document outlining its recommendations for the use of externally controlled clinical trials to provide evidence of the safety and effectiveness of a drug product (FDA, 2023).

Regulatory authorities including the FDA and EMA have already accepted externally controlled clinical trials for drug approvals, integrating such evidence into their benefit-risk evaluations, while considering multiple factors such as disease rarity and ethical concerns associated with the use of a placebo arm (Mishra-Kalyani, 2022; Nishioka, 2022; Asano, 2025; Jahanshahi, 2021; Gökbuget, 2016; Cowey, 2017).

PMDA's Regulatory Perspective on Externally Controlled Clinical Trials

In early 2025, Japan's PMDA released an Early Consideration specifically focused on externally controlled clinical trials (ECTs). According to the agency, ECTs may be appropriate in situations where conducting randomized controlled trials (RCTs) is not feasible—such as in rare diseases with limited patient populations or where a substantial treatment effect can reasonably be expected based on existing scientific knowledge.

That said, the PMDA underscores that ECTs have inherent limitations arising from the absence of randomization and blinding. These design characteristics increase the potential for bias, confounding, and reduced comparability between the investigational group and the external control. As a result, small differences in outcomes may be difficult to interpret with confidence.

The Early Consideration emphasizes the importance of rigorous planning and methodological transparency. Before initiating an ECT, sponsors should predefine how the external control group will be selected, the statistical methods to be applied, and the treatment effects (estimands) to be evaluated. Patient-level data are critical to ensure comparability and to assess potential confounding factors, while the rationale for data sources must be transparently justified to avoid selective use. Wherever possible, patient characteristics, treatments, observation periods, and evaluation methods should be harmonized between groups.

The PMDA also encourages feasibility assessments to confirm adequate sample size and to anticipate challenges such as missing data, particularly when using real-world data (RWD).

In the following section, we will demonstrate how Medidata's Synthetic Control Arm® (SCA) is designed to align with the considerations raised in the PMDA's Early Consideration on external controls.

While hybrid designs that combine external and randomized controls are not the primary focus of the document, the same principles regarding comparability and bias still apply. The PMDA also notes that this document reflects an early-stage regulatory perspective intended to communicate the agency's current thinking rather than formal guidance.

Medidata's Synthetic Control Arm®:

A Regulatory-Grade Solution

Medidata Synthetic Control Arm (SCA®) is an ECA built from an extensive database of patient-level, cross-industry, historical clinical trial data from over 36,000 clinical trials and 11 million patients, complete with endpoints and covariates as they were captured and validated in their original trial.

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HOW IT WORKS

To build a Synthetic Control Arm (SCA), Medidata researchers draw from a large database of past clinical trials conducted on the Medidata Rave Electronic Data Capture (EDC) platform to identify control patients who align with the target trial's key eligibility criteria. Data from eligible trials are standardized for consistency, and patients in the target trial are matched to historical controls using propensity score models on prognostic variables such as age, sex, and performance status. This process maximizes comparability, enabling robust comparative analyses between the SCA and the target trial.

BENEFITS

Medidata's SCA can bolster evidence and increase scientific certainty across clinical and commercial development.

Provides a standardized reference against a current study

Offers the most relevant comparator data, inherently aligned with current trials in patient populations, variables, and endpoints, while propensity score models further enhance comparability and yield more precise treatment effect estimates than literature or criteria-matched cohorts.

Helps accelerate timelines

Increases early scientific certainty and confidence to continue clinical development or fail fast, minimizing wasted time and resources.

May reduce the number of patients required to enroll in a control arm and improve retention, bringing a product to market faster.

Patient-Centric

Offers a more patient-centric solution that maximizes the proportion of patients receiving a potentially promising therapy in diseases with high unmet need and/or inadequate standard of care.

Aligning with PMDA's Early Consideration:

How Medidata's Synthetic Control Arm® Enables Robust Externally Controlled Trials

The following sections describe how Medidata's Synthetic Control Arm® (SCA®) aligns with PMDA regulatory considerations for externally controlled trials, supporting scientifically rigorous and regulatory-ready approaches to modern clinical research.

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1 Fundamental Principles

Medidata's Synthetic Control Arm (SCA®) is designed in full alignment with PMDA's foundational principles for externally controlled trials. For regulatory submissions, SCAs are primarily applied to rare and severe diseases where randomized trials are often impractical or unethical, and standard of care is limited. Built from a uniquely large, patient-level, cross-industry clinical trial database, Medidata SCA enhances comparability through standardized covariates, advanced patient-level matching, and pre-specified statistical methodologies. These elements directly address PMDA's concerns regarding bias and confounding in non-randomized, unblinded settings. This foundational approach informs the subsequent stages of trial planning, data selection, and statistical analysis, ensuring that each SCA is scientifically rigorous and fit for regulatory use.

2 Data Sources

Medidata Synthetic Control Arm (SCA®) is an external control arm built from our unique, patient-level, cross-industry database of more than 36,000 clinical trials and 11 million patients, complete with endpoints and covariates captured and validated in their original protocols. By relying on structured, trial-quality data rather than static literature benchmarks or uncurated real-world data (RWD), Medidata SCA delivers higher reliability, richer endpoint coverage, and populations more comparable to those enrolling in new clinical trials.

To further strengthen comparability, Medidata standardizes covariates across eligible trials and applies advanced patient-level matching methods such as **propensity score modeling**, directly addressing PMDA's considerations regarding potential bias and confounding.

Propensity score modeling serves to recreate the balance normally achieved through randomization. By estimating each patient's likelihood of belonging to a given trial arm based on observed baseline factors (such as age, disease stage, or ECOG score) and matching patients with similar probabilities across historical trials, this method minimizes systematic differences between the synthetic and actual control arms. The result is an evidence base that is both statistically robust and scientifically comparable, allowing historical data to be used confidently in regulatory-grade analyses.

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3 Trial Planning

In alignment with PMDA guidance, Medidata's Synthetic Control Arm (SCA®) follows a structured, transparent, and bias-controlled planning process to ensure scientific rigor and comparability before analysis begins. Each project starts with a **6–8-week Data Validation phase** to confirm feasibility, assess endpoint availability, verify covariate completeness, and ensure sufficient sample size. This early pre-specification of inclusion criteria, statistical methods, and success parameters minimizes bias and post-hoc modifications, directly addressing PMDA's expectation for advance definition and methodological transparency.

1 Understanding Data Source Characteristics

Medidata SCA uses only **GCP-compliant historical clinical trial data** — over 36,000 trials covering 11 million de-identified patients providing structured, protocol-level datasets with defined regimens, observation periods, and endpoints. This enables evaluation of data context, recency, and standard-of-care relevance to the investigational trial.

2 Comparability of Populations

Eligible studies are harmonized using standardized data models and covariate normalization to align baseline characteristics and inclusion/exclusion criteria with the target trial. **Propensity-score modeling** and other pre-specified selection criteria further minimize systematic differences between treatment and external control arms.

3 Estimand and Treatment Definition

Each SCA defines the **estimand**, the precise treatment effect to be estimated and confirms treatment variables (regimen, dose, duration, concomitant therapies) to ensure interpretability and alignment across datasets.

4 Timing and Data Collection Alignment

SCA projects evaluate timing, frequency, and completeness of endpoint data to ensure overlap with the investigational trial. By **prioritizing contemporaneous data** and **harmonizing key covariates**, Medidata mitigates time-related bias and strengthens cross-trial comparability.

5 Endpoint Definition and Assessment Consistency

Endpoints are **objective, clearly defined,** and **harmonized** across datasets. All contributing studies are GCP-compliant; endpoint definitions, timing, and assessments are standardized or re-derived using CDISC-based mappings. Independent or centrally reviewed outcomes are prioritized to reduce evaluation bias and satisfy PMDA's requirement for consistent endpoint assessment.

6 Governance, Documentation, and Transparency

Each SCA engagement document studies inclusion rationale, endpoint mapping, and data provenance in detail. Analytic methods and data decisions are pre-specified in the **Statistical Analysis Plan (SAP),** and **early consultation with PMDA or other authorities** is encouraged to confirm feasibility and methodological soundness.

Through these structured processes, Medidata SCA operationalizes PMDA's trial-planning principles, creating an external control that is **scientifically justified, bias-controlled, and ready for regulatory review before the first subject is enrolled**.

4 Statistical Analysis

Medidata's Synthetic Control Arm (SCA®) framework aligns with PMDA's expectations for **transparent, pre-specified,** and **bias-controlled** statistical analysis in externally controlled trials.

Pre-specification and Transparency of the Statistical Analysis Plan (SAP)

Each SCA operates under a **pre-defined Statistical Analysis Plan (SAP)** established before outcome data are reviewed. The SAP details objectives, analytical populations, covariates, matching methods, balance diagnostics, and sensitivity analyses. To prevent data-driven bias, analysts finalize model specifications without access to external-control results. Any methodological changes, if unavoidable, are time-stamped, justified, and fully documented to maintain traceability and compliance with PMDA's requirements for advance definition and justification.

Statistical Methods and Confounding Adjustment

Medidata applies **propensity-score modeling** and other regression or weighting methods to achieve covariate balance between investigational and control groups. Model parameters such as covariate selection, caliper width, matching ratio, and re-estimation criteria are pre-specified in the Statistical Analysis Plan (SAP). Post-matching comparability is confirmed using standardized mean differences and graphical diagnostics, while residual bias is assessed through stratified or sensitivity analyses. This structured approach ensures that differences in patient characteristics or data collection timing are minimized and quantitatively evaluated.

Handling Data and Comparison Limitations

Each SCA incorporates **sensitivity and supplementary analyses** to test the stability of results under alternative assumptions, such as varying matching thresholds or missing-data mechanisms. Missing data are identified relative to the estimand and handled using pre-specified strategies (e.g. multiple imputation or censoring rules). The influence of missingness or unmeasured confounding is explicitly assessed to ensure analytical robustness and interpretability.

Through rigorous pre-specification, documented analytical governance, and reproducible bias-adjustment methods, Medidata SCA provides a **statistical framework that is transparent, scientifically robust,** and **regulator-ready** for externally controlled trials.

Summary and Outlook

For nearly a decade, Medidata has been at the forefront of advancing externally controlled methodologies through its Synthetic Control Arm® (SCA®) program. Beyond delivering high-quality SCAs, Medidata actively supports sponsors throughout their regulatory journey, collaborating to develop clear, regulator-ready documentation and ensuring every methodological decision is transparently justified. Our experts frequently represent sponsors in discussions with major regulatory authorities such as the FDA and EMA, and are fully prepared to do the same with Japan's PMDA.

As an active participant in a Friends of Cancer Research (FoCR) working group, a leading U.S.-based public–private partnership that brings together the FDA, pharmaceutical companies, and academia to advance oncology research, Medidata contributed some of the earliest and most influential analyses demonstrating the validity of external control methods. These studies showed that overall survival estimates generated using the SCA closely replicated the results of randomized controlled trials across multiple case studies, providing foundational evidence for the scientific soundness of external controls.

Today, Medidata continues to drive this innovation through a world-class team of statisticians, data scientists, and clinicians, many with prior experience at the FDA or in the pharmaceutical industry. By combining scientific rigor with hands-on regulatory expertise, Medidata enables sponsors to meet evolving global expectations and confidently advance their clinical development programs.

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Case Studies

The following examples demonstrate the impact that SCAs had on three different drug development programs, including regulatory authority endorsement.

KITE PHARMA

Kite Pharma partnered with Medidata to develop a well-balanced Standard of Care comparator for its ZUMA-3 trial, evaluating brexucabtagene autoleucel in R/R B-ALL (Bijal, 2022). The SCA comparison demonstrated a clinically significant improvement in Overall Complete Response at 24 weeks (OCR24) and OS versus available therapies and provided strong evidence for its use in adult patients with R/R B-ALL. These insights supported EMA regulatory submissions, leading to market approval in 2022, while also informing payer discussions across the European Union.

MEDICENNA THERAPEUTICS

This clinical-stage immunotherapy company successfully gained the support of the FDA to use Medidata's SCA in a Phase 3 registrational trial in recurrent glioblastoma (rGBM), a disease with poor prognosis and high unmet need (Majumdar, 2022; Medidata, 2022). By using the SCA, Medicenna will reduce the number of patients required to be assigned to the control therapy in the trial and will provide rigorous scientific data, while allowing speedier development of the investigational therapy. The Phase 2 single arm trial was also enhanced by a SCA and estimates of the treatment effects were part of the briefing package provided to the FDA for justification of the use of a hybrid-SCA in Phase 3. This reduced the number of patients required in the control arm while maintaining scientific rigor.

FRIENDS OF CANCER RESEARCH

By Partnering with Friends of Cancer Research, the validity of an SCA in an accelerated approval setting was evaluated by examining if an SCA could replicate the outcomes of a targeted randomized control from a Non-Small-Cell Lung Cancer (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).

Conclusions

Externally controlled trials are becoming increasingly important for addressing challenges in clinical research where randomized controlled trials (RCTs) are less feasible. They provide essential comparative evidence that might otherwise be unavailable, while potentially reducing costs, shortening timelines, and enhancing patient engagement.

In early 2025, Japan's PMDA published an Early Consideration that outlines both the promise and the key challenges associated with externally controlled trials, with the chief challenge being the need to ensure comparability between the external control and investigational treatment groups. These considerations reflect the agency's commitment to maintaining scientific rigor while enabling innovation.

Medidata's Synthetic Control Arms® (SCAs®) are uniquely positioned to meet these high standards. Designed to address the very considerations raised by the PMDA, SCAs provide a regulatory-grade solution that also aligns with expectations from the FDA and EMA, serving as a bridge between innovation and compliance.

Before planning an externally controlled trial, early engagement with regulatory authorities and industry experts is strongly encouraged to ensure the greatest likelihood of success. Forward-looking sponsors are urged to embrace externally controlled trials, including SCAs, as a strategic approach to optimize trial design, reduce development costs and timelines, and ultimately accelerate the delivery of new therapies to patients.

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