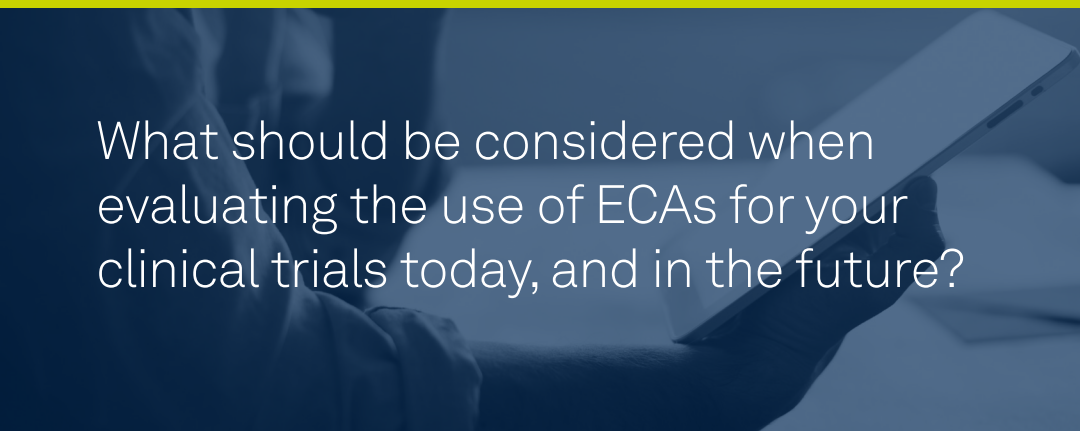
MEDIDATA ai

Synthetic Control Arm®: The Regulatory Grade External Control Arm to Power your Clinical Trials

Randomized Control Trials (RCTs) are the gold standard for evaluating the safety and efficacy of new treatments. However, in some circumstances, maintaining a concurrent control arm is not feasible.

External Control Arms (ECAs) can help sponsors overcome recruitment challenges in trials with small patient populations. They can also provide supplementary data, beyond what a clinical trial itself can produce, to bolster trial results when necessary.

This eBook provides guidance on the increasing role of ECAs, the differences between control groups built using real world data (RWD) and a Synthetic Control Arm (SCA®) containing historical clinical trial data (HCTD), and the successful impact of SCA on clinical trial design decisions and regulatory conversations.



What should be considered when evaluating the use of ECAs for your clinical trials today, and in the future?

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THE EMERGENCE AND IMPACT OF EXTERNAL CONTROL ARMS (ECAs)

The Role of ECAs in Randomized Control Trials

The path from study design to approval is long, complex, and costly. Nine out of 10 clinical trials worldwide can't recruit enough patients within their target timeframes.[1] In an effort to continue trials and overcome this issue, researchers are incorporating ECAs backed by the underused but growing resource of historical clinical trial data.

Data from patients in past trials are used to create external control arms (ECA), essentially mimicking an ideal randomized control trial (RCT). This is especially valuable for single-arm or rare disease trials with small patient populations and clear treatment preferences. ECAs can also be useful when the drug under investigation is available outside of the trial.

What are Typical Applications of an ECA?

Rare Disease and/or Single-Arm Trials

In the case of an early phase single-arm without a control arm, Celsion found a solution by leveraging an ECA.

Celsion is a biotechnology company that develops next generation chemotherapy and immunotherapy agents for liver and ovarian cancers. The company needed to assess a new compound intended for patients with late-stage ovarian cancer.

1 Clinical trials are better, faster, cheaper with big data, MIT Technology Review Insights, 2021

Although the drug seemed to work well in a test group, the study did not have a control arm. Celsion partnered with Medidata AI to create an SCA composed of historic clinical trial patients that were near-perfect matches for the characteristics of the test group.

A comparison of the two groups found that the treatment effect was substantial enough to justify further research in a randomized Phase II trial and could be used to inform the design of the subsequent trial. The trial required approximately 20 fewer patients than was previously estimated, reducing trial costs and accelerating timelines.

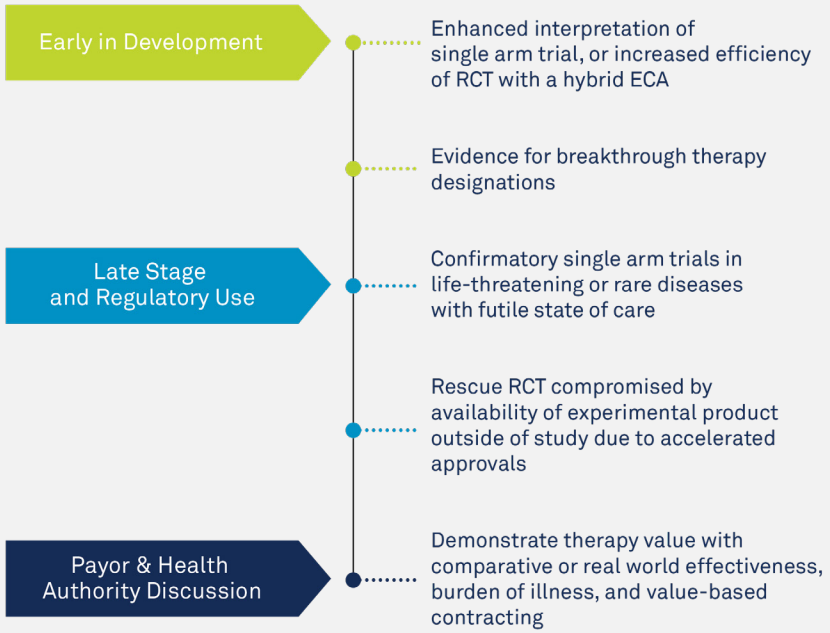
Supplement to Randomized Controlled Trials

ECAs are also beneficial as a supplement or augmentation to an RCT. They can provide invaluable information at all stages of a trial, from go/no-go decision-making to approvals and regulatory submissions.

The substantial influence of ECAs is being realized here and now, with a dramatic reduction in required enrollees when incorporating them into an RCT's methodology.[2] As they are more fully integrated into all types of comparative clinical trials, the impact on bottom lines, timelines, and patient enrollment and retention will grow. ECAs will not only help patients get acccess to life-saving therapies sooner, but also allow organizations to reinvest the time and money saved into further innovation to help future patients.

2 BCG, 2021

APPLICATIONS OF EXTERNAL CONTROL ARMS



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A BETTER ECA: LEVERAGING MORE THAN JUST RWD

The Case for HCTD

ECAs can be generated by referencing one or more data sources, such as the results of a clinical trial or case studies/ clinical experience in literature, data in patient registries, or real-world data. However, when considering ECAs for clinical trials, there are key components that must be included in its build to ensure an acceptable end use. These include:

- Data source
- Data processing
- Data matching

There are precedents for using real-world data, and the FDA has provided guidance to determine whether data is "fit" for regulatory purposes (e.g. the FDA's framework for RWD).[3] However, there are challenges that must be taken into account when using RWD, such as biases and lack of standardization.

Historical clinical trial data (HCTD), on the other hand, contains clinical trial endpoints and complete covariate information. This data is designed in the clinical protocol then captured, monitored, and validated to increase quality and reduce bias.

HCTD is essential when highly specialized and specific criteria are required to inform an ECA. It enables data-driven decision-making by providing complete patient-level data in common domains that are standardized and systematic.

3 FDA, 2018

In the case of Celsion, Medidata combed its database of HCTD to find patients who served as controls in past trials of treatments for a certain condition to create its proprietary version of an external control arm. By matching endpoints and type of data collected, Celsion was able to match possible control patients with the patients in the test arm.

DIFFERENCES IN DATA SOURCES FOR CONSTRUCTING AN ECA

RWD

- **High volume** data from disparate sources
- **Limited standardization** of data sources
- **Biases** originating from several areas
- **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)
- Rich data is often captured in **unstructured formats** such as physician notes

VS.

HCTD

- **Lower volume but high relevance to** clinical research
- **Inclusion** of usual clinical trial endpoints, covariates, and prognostic factors
- **Better data quality** due to rigorous monitoring and review
- **Reduced bias** because patients self-select into clinical trials

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MEDIDATA AI SYNTHETIC CONTROL ARM

Built to Enhance Your Trial's Regulatory Viability

Pioneered by Medidata AI, Synthetic Control Arm (SCA) offers the only external control arm derived from multiple sources including both cross-industry HCTD and RWD. A rigorous ECA will incorporate both RWD and HCTD, following FDA guidance and offering depth unmet by RWD alone.

Medidata's enormous HCTD repository of 7 million+ patients and 25,000+ trials from over 20 years of helping sponsors and CROs run clinical trials, providing the depth needed to meet regulatory requirements.

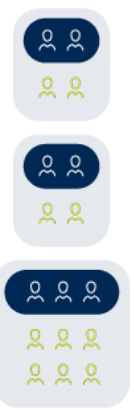
In contrast to other external controls, which are static summary measures that do not adequately account for patient baseline difference, Medidata's SCA is constructed using carefully selected patient level data to yield a baseline composition that is statistically well balanced with the experimental arm to create an accurate synthetic control group.

Case Study: FDA Agrees to Trial Design Utilizing an ECA

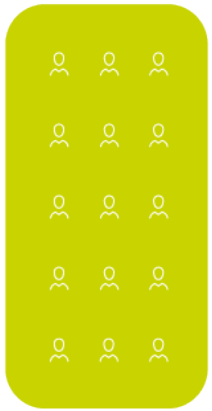
Medicenna Therapeutics, a clinical stage immunotherapy company, successfully gained the support of the FDA to use Medidata's SCA in a Phase 3 registrational trial in recurrent glioblastoma (rGBM), a disease with poor prognosis and high unmet need. By utilizing SCA, Medicenna will reduce the number of patients required to be assigned to the control therapy in the trial and will provide rigorous scientific data, as well as enable speedier development of the product. The Phase 2 single arm trial was also enhanced by SCA and estimates of the treatment effects were part of the briefing information provided to the FDA for justification of the use of a hybrid-SCA in Phase 3.

HISTORICAL CLINICAL TRIAL PATIENTS FROM THE MEDIDATA CLINICAL CLOUD HAVE DISTINCT ADVANTAGES

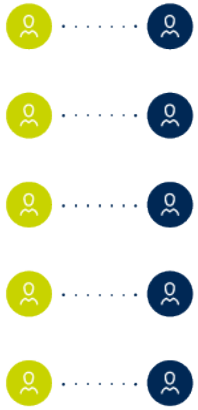
- Traditional clinical trial endpoints, covariates, and prognostic factors
- Global data covering a heterogeneous mix of over 94 countries
- High quality data (e.g. academic medical centers, monitored, locked)
- Patients that have self selected for participation in clinical trialsreducing potential bias



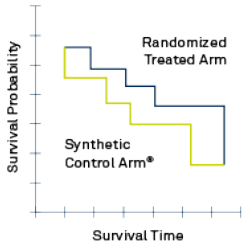
Candidate Studies Based on Eligibility Criteria



Over 100 Covariates Standardized Across Eligible Trials



Carefully Designed Propensity Score Match/Weight to the Treatment Group

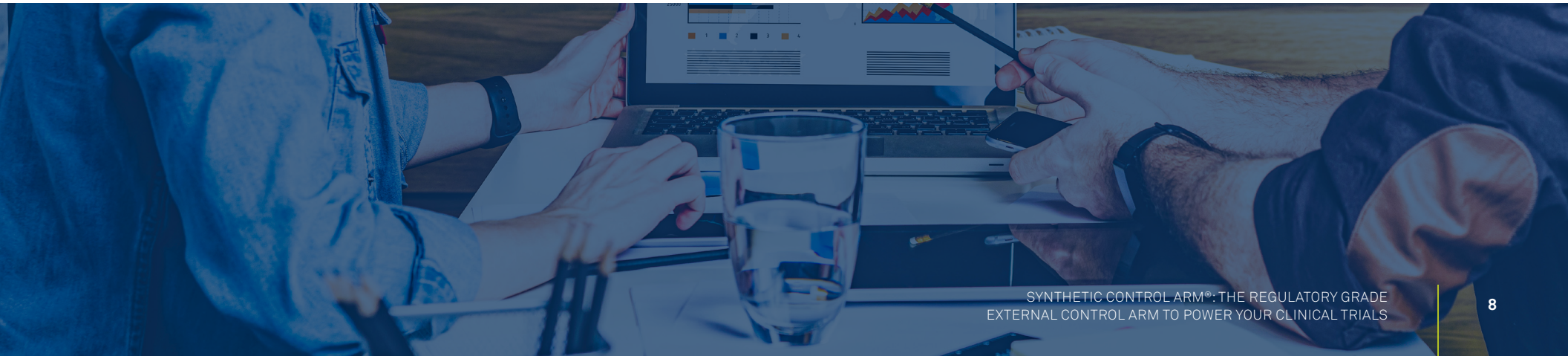


Baseline Characteristics

Comparative Analyses of Efficacy

- Reponse Rates
- Survival Rates

Adverse Event Frequencies



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MEDIDATA AI: SCA IN ACTION

Why Choose Medidata AI Synthetic Control Arm as Your ECA?

The advantages of incorporating an ECA are far-reaching. With successful, regulatory grade case studies and clear patient experience and financial return, the value of Medidata AI Synthetic Control Arm remains unmatched, offering:

Robust Data

- Unsurpassed repository of cross-sponsor regulatory grade historical clinical trial data providing greater confidence in the data
- Uniquely positioned to generate evidence by offering both Historical Clinical Trial Data and Real World Data

Efficiency

- Accelerated clinical development timelines, while potentially reducing costs
- Ease patient recruitment and retention challenges, while still generating scientifically rigorous data

Scientific Certainty

- Fuller understanding of treatment effect to confidently continue product development from single arm early phase trials to the next phase
- Better data interpretation and decision-making in go/no-go decisions

CASE STUDIES

MEDICENNA™

"The Medidata AI team's expertise and collaborative effort with thought leaders was instrumental in demonstrating to the FDA the validity of a well designed external control in a registration trial."

Dr. Fahar Merchant
President and CEO

Celsion Corporation

"We are extremely impressed with the high quality of the matched data from the Medidata SCA. Using an 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."

Michael H. Tardugno
Chairman, President and Chief

FRIENDS of CANCER RESEARCH

"The vast amount of data available in the life sciences today offers an opportunity to transform the clinical trial process. Partnering with the Medidata Institute to make these data actionable is a game-changing effort that will enhance the clinical trial experience for patients."

Mark Stewart
Vice President, Science Policy

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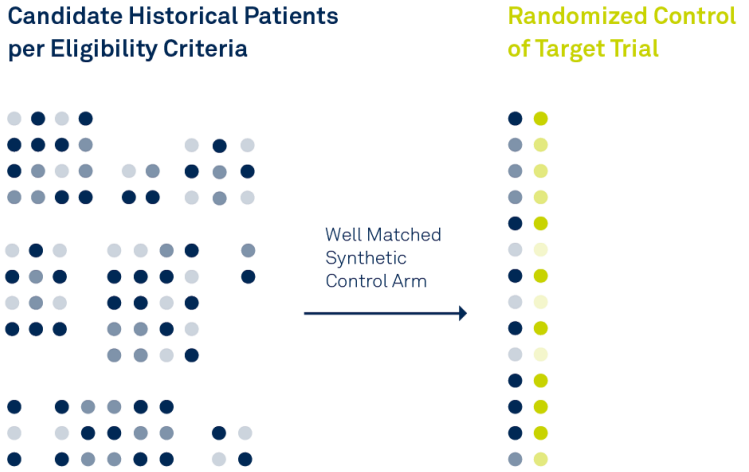
THE ADVANTAGES FOR PATIENTS

Patients often view an investigational drug as an opportunity for a novel treatment, particularly in rare diseases where a control arm may be perceived as a suboptimal treatment option. Using an SCA may make a study more appealing to potential participants, expediting recruitment.

Over the past 4 years, commercially sponsored Phase 3 trials had an average enrollment of 600 patients (BCG, 2021). With a study design allowing for an SCA, all or at least more patients can be treated with the experimental therapy creating a higher chance for positive patient outcomes and an incentive for enrollment and adherence.

Medidata partnered with Friends of Cancer to find a solution to recruitment and retention challenges and reduced the patient burden associated with randomized controls. The working group demonstrated that SCA — leveraging advanced analytics and patient-level data from multiple historical clinical trials — can mimic the results of a traditional randomized control. The results hold promise in finding ways to reduce the number of patients needed for a randomized control arm.



Note: The intensity of color corresponds to various baseline characteristics

THE ADVANTAGES FOR SPONSORS

Using an SCA is especially beneficial in populations that are hard to recruit, such as in rare disease or diseases with a standard of care that is deemed unacceptable. Sponsors can also avoid common issues with randomized control arms, such as early withdrawal, noncompliance, and treatment crossover.

The use of Medidata's SCA by Medicenna in its groundbreaking hybrid design in recurrent Glioblastoma (rGBM) with MDNA55 resulted in the FDA's endorsed use of hybrid (augmented) SCA in a Phase 3 study design in rGBM.

Another valuable immediate use is for conducting rapid preliminary trials, to evaluate whether a treatment is worth pursuing to the point of a full clinical trial, significantly lessening the financial burden on sponsors.

SCA can also drive higher returns. In the case of Celsion, it is estimated that each cancer patient cost Celsion tens of thousands of dollars to enroll in a trial and follow throughout the entire protocol. Using SCA may make a study more appealing to potential participants, expediting recruitment, and reducing costs. Depending on context, they can reduce cohorts by 20-50%, potentially generating $10-20M in savings per trial.[4]

WHEN SCA SUPPLEMENTS THE CONTROL ARM IN ONCOLOGY TRIALS[5]

UP TO **50%** reduction in number of patients

$10-$20M in savings per trial

Faster time to market

4 BCG, 2021
5 BCG, 2021

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SUCCESS OF SCA IN REGULATORY CONVERSATIONS

1. Single-Arm Trials

In cases where a regular control group is impractical, an ECA is a vast improvement over the most common method of searching existing medical literature for comparisons. Investigators can get patient-level data using an SCA created from Medidata's database of past clinical trial patients to precisely choose their control patients to match their test patients and get a more scientifically valid comparison of the two groups.

2. Hybrid Models

Replacing traditional control arms with external data faces more scrutiny—but a hybrid design, in which external controls supplement rather than replace a standard control arm has previously received FDA agreement. This was the case for Medicenna, a mid-sized biopharma company that received FDA agreement to design a Phase 3 trial utilizing a SCA built by Medidata AI. This hybrid SCA will reduce the number of patients assigned to the control therapy, provide rigorous scientific data, and enable speedier development of the product.

3. Accelerated Approval Pathways

In many instances, sponsors may seek evaluation of a product for FDA accelerated approval using a single arm trial and benchmarking with medical literature or clinical intuition. The FDA has shown appetite for comparing these single arm trials with an external control because this approach assures a better balance in baseline condition.

SYNTHETIC CONTROL ARM®: THE REGULATORY GRADE EXTERNAL CONTROL ARM TO POWER YOUR CLINICAL TRIALS

About Medidata

Medidata is leading the digital transformation of life sciences, creating hope for millions of patients. Medidata helps generate the evidence and insights to help pharmaceutical, biotech, medical device and diagnostics companies, and academic researchers accelerate value, minimize risk, and optimize outcomes. More than one million registered users across 1,800+ customers and partners access the world's most trusted platform for clinical development, commercial, and real-world data. Medidata, a Dassault Systèmes company (Euronext Paris: #13065, DSY.PA), is headquartered in New York City and has offices around the world to meet the needs of its customers. Discover more at **www.medidata.com** and follow us **@medidata**.

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