WHITE PAPER

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A New Frontier in Clinical Trials:
The Promise of Synthetic Control Arms

Introduction

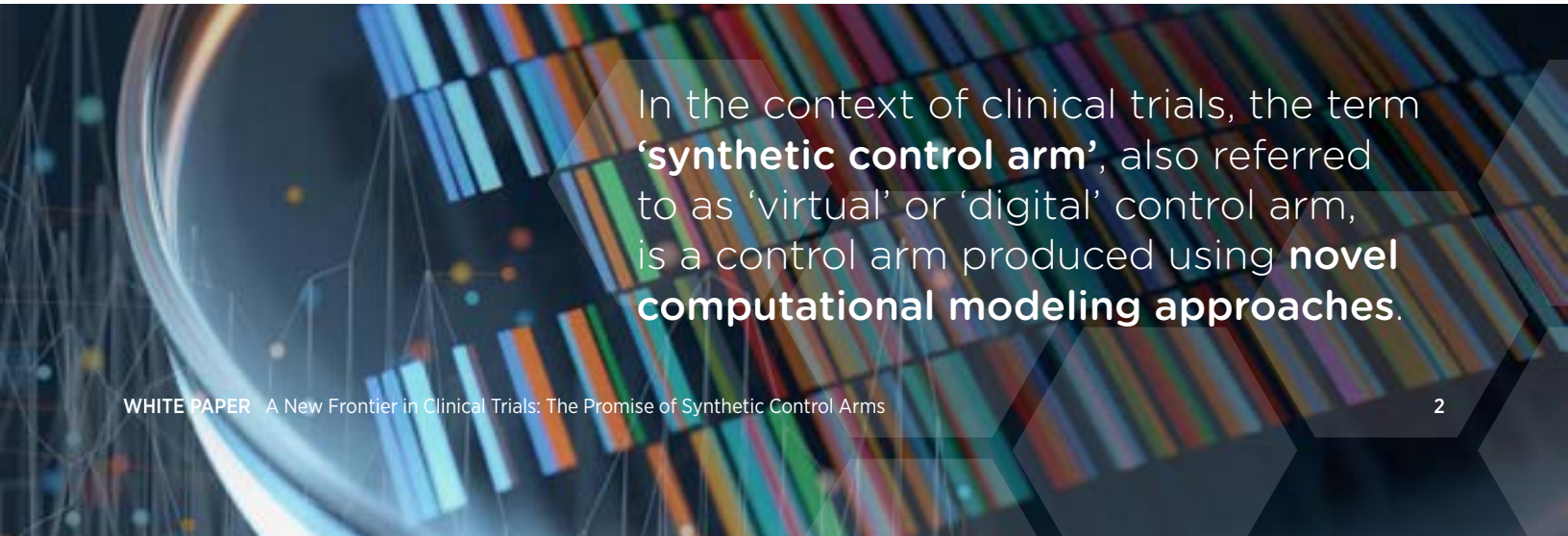
Clinical trials are a critical component of the drug development process, providing the scientific evidence needed to determine the safety and efficacy of new treatments. With both the United States and European regulatory agencies, the gold standard for clinical trials is the randomized controlled trial (RCT), where patients are randomly assigned to either an investigational treatment arm or a placebo or standard-of-care (SOC) comparator arm. By convention, the last two are termed the control arm in a clinical trial. The design and execution of clinical trials can be challenging, particularly when selecting an appropriate control arm. For some diseases, there may not be an existing SOC. Particularly with rare diseases, it may be unethical or impractical to assign patients to placebo, leaving investigators with few options for comparing outcomes between treatment groups.

In situations where a traditional control arm is not feasible or ethical and there is no available SOC treatment, synthetic control arms (SCAs) have emerged as a potential solution. In the context of clinical trials, the term 'synthetic control arm,' also referred to as 'virtual' or 'digital' control arm, is a control arm produced using novel computational modeling approaches. These modeling approaches rely on actual patient data, which may include real-world clinical data, genetic, or multiomic data. Such data empower mechanistic modeling, artificial intelligence (AI) algorithms, and/or statistical modeling to construct a digital control group that closely mimics the characteristics of the treatment group in a clinical trial.

In this white paper, we explore the concept of SCAs and their potential to transform the clinical trial landscape. We begin by providing an overview of the emergence of SCAs before delving into the workflow of constructing an SCA. We discuss the methodology used in constructing virtual patients and examine the benefits of SCAs, including their potential to accelerate timelines, reduce risks, increase efficiency, and reduce patient enrollment, thus resulting in cheaper and faster trials. We discuss the challenges of SCAs, including issues related to model validation, regulatory approval, statistical, and virtual patient methodology. We offer insights into regulatory considerations[1] surrounding SCA use and briefly highlight a global initiative to establish best practice guidelines for *in silico* modeling and simulation in clinical trials, which includes input from the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA).

In addition, we discuss some of the key considerations for researchers and sponsors when planning and executing a clinical trial with an SCA. We conclude by pointing out the value of strategic partnerships and collaborations for ensuring seamless implementation of the trial process flow, from trial design and construction of the virtual control to trial execution, as well as the regulatory considerations for achieving regulatory approval under this paradigm.

This white paper is aimed at a broad audience, including those in the pharmaceutical/biotechnology development space, healthcare providers, and anyone interested in the future of drug development. We hope it will provide a useful introduction to the concept of SCAs and stimulate further discussion and research in this exciting and rapidly evolving field.



Emergence of Synthetic Control Arms: Brief Overview

The emergence of SCAs in clinical research has unfolded progressively over the last decade, triggered by several pivotal moments in technology and regulation. Around the early 2010s as big data analytics began gaining traction, the potential for using existing external data to form control groups in clinical trials became a subject of academic and industry discussion, even though RCTs with human control arms remained the universal standard to clinical trial research.

By 2015, advancements in AI and machine learning (ML) had improved data-matching capabilities, providing more credibility to the concept of SCAs. Concurrently, regulatory bodies such as the FDA and EMA began recognizing the value of real-world evidence, thereby increasing interest in SCAs as viable alternatives to conventional RCTs.

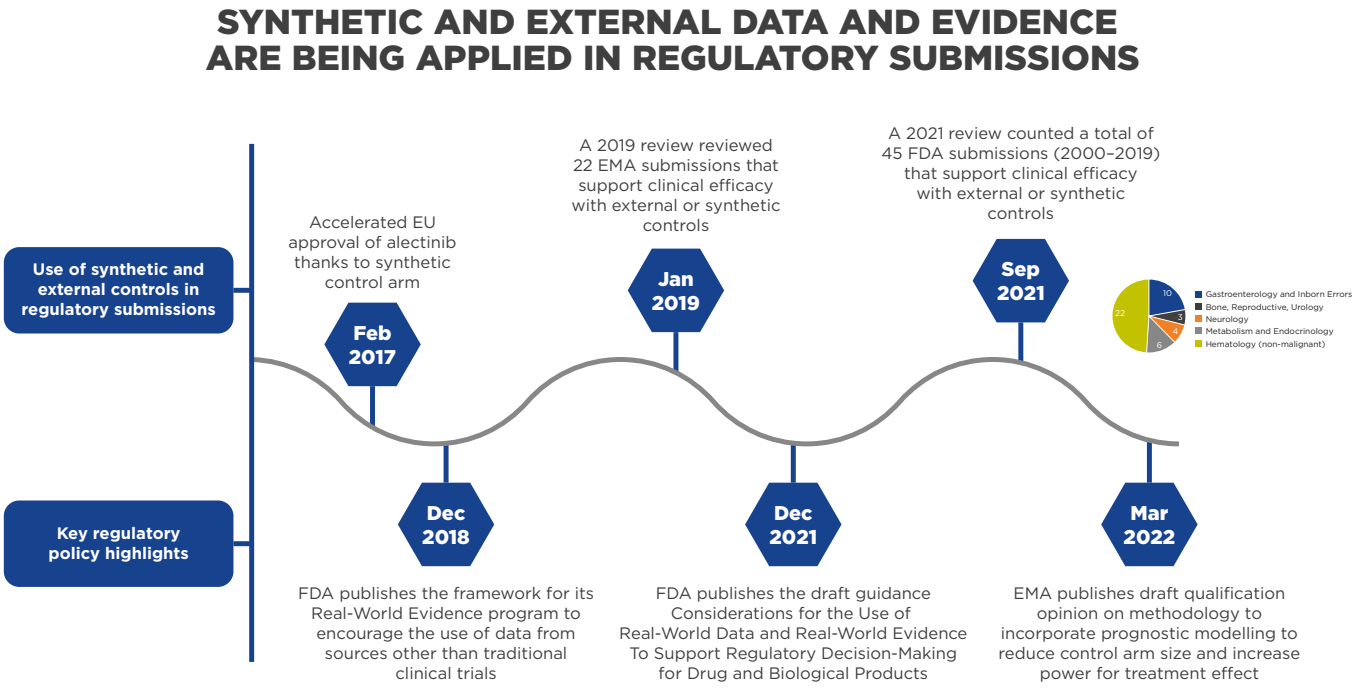


Figure 1: Key regulatory highlights regarding SCAs: Anderson et al. Journal of Clinical Epidemiology (2018), Jahanshahi, et al. Ther Innov Regul Sci 55, 1019–1035 (2021).

Clarifying Concepts

External control arm – consists of actual patient data collected outside of the clinical trial to form a control arm (e.g., real-world data or the control group from a previous clinical trial).

Synthetic control arm (SCA) – consists of virtual (or digital) patient data generated with the aid of computational methods, including mechanistic modeling and statistical methods, to form a control arm. SCAs are more versatile than external control arms, since virtual patients can be generated with full customization of the population composition, trial duration, and trial design parameters.

Building a Synthetic Control Arm – Unveiling the Process

Before delving into the benefits of SCAs, we need first to understand the technical and scientific workflow for creating virtual patients used collectively to form an SCA. The most important task in creating virtual patients involves leveraging historical data from patients who have the disease, in order to generate synthetic data that adequately represents the disease characteristics of a true patient. This requires a combination of detailed knowledge of disease pathophysiology and access to sufficient amounts of relevant historical patient clinical data. Depending on how well both the pathophysiology and the complexity of disease progression are understood, as well as the degree of availability of clinical data, one of several methodologies can be applied to generate virtual patients.

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In the case of a predictable and homogenous disease course, supported by sufficient historical external data, virtual patients may be constructed using a mathematical or statistical model that describes the disease only from its symptomatic and pathological standpoint. However, in most cases, diseases present a complex and heterogeneous disease course. To capture the complex underlying dynamics, virtual patients can be created by leveraging advanced ML and AI methodologies. Such methods can capture complex interrelationships in the data and generate diverse and more reliable virtual patient data.

On the other hand, if disease pathophysiology is well understood, a strong mechanistic model-based simulator of disease progression can be generated. This approach can capture the symptomatic progression of the underlying disease via a mechanistic disease model, such as a quantitative systems pharmacology (QSP) model. The QSP approach provides major advantages over mathematical, ML and AI methods, including possibilities of incorporating multi-scale personalization of the model by involving biomarkers in the simulation, or incorporating a virtual treatment schedule for a SOC treatment.

Virtual patients can therefore be generated using different underlying methodologies depending on the level of understanding of the disease pathophysiology and extent of availability of clinical data. It is important to note that the process of generating virtual patients will thus vary depending on the therapeutic area and data availability. To illustrate the process further, we describe below the development of a virtual patient model which, in this case, consists of a QSP model of the underlying disease.

The process of building a QSP model can be captured in three systematic steps broadly outlined as (i) defining the clinical disease model, (ii) constructing disease mechanistic models, and (iii) producing virtual patients using simulations based on the disease mechanistic models. Each step involves a complex array of key inputs and considerations that reflect the underlying biological mechanisms of the disease, as well as the characteristics of actual patients with the disease.

The key elements involved in each step are broadly described as follows:

Step 1: Defining the clinical disease model

The first principle is to map out the pathophysiology of the disease being studied and construct the conceptual clinical model that describes it. This is achieved by identifying key elements (or parameters) of the immune system that trigger the disease manifestation, such as specific genetic markers, biomarkers, etc. This physiological pathway, outlined in the context of well-defined immune system parameters, defines the clinical disease model. For some diseases, it is possible that the full physiological pathway is described by a constellation of disease sub-models, each explained by several immune system parameters. In such cases, the interplay of these clinical disease sub-models provides the complete clinical outline of the actual disease model.

Step 2: Constructing disease mechanistic models

This step requires the mathematical construction of disease mechanistic models, using actual immune system data from patients with the disease to characterize the clinical disease model from Step 1. The patient data parameters needed for this step can be extracted from a variety of historical external data sources including, for instance, existing bio-databanks containing genetic, multiomic, or biomarker data on patients with the disease, or perhaps from existing real-world data sources or possibly external data from previously completed clinical trials. There are multiple avenues for accessing relevant external data on patients with the disease that could be leveraged for the purpose of constructing mathematical disease mechanistic models. However, for some diseases it can be challenging to secure the necessary data.

Step 3: Generating virtual (or synthetic) patients

This final step involves executing a series of complex computational simulations based on the mathematical predictive models constructed in Step 2. The goal of the simulations is to generate digital estimates of the array of immune system parameters. Each constellation of estimated immune system and patient demographic parameters collectively defines an individual virtual patient having the disease of interest. By necessity and in compliance with good computational practices and other regulatory guidances such as FDA's Complex Innovative Design (CID) guidance or reference to FDA's Model-Informed Drug Development (MIDD) pilot program, this final step also involves the calibration, validation, and verification of the mathematical models that generate the digital patient.

Virtual patients generated using such mechanistic modeling approaches are versatile and represent robust sources of synthetic data, especially since they are built on both knowledge of the disease mechanism and actual patient data. It is evident from the approaches described above that generation of reliable and accurate virtual patient data is a multifaceted problem that requires effective collaboration between multidisciplinary experts, as well as appropriate computing infrastructure and computing power.

Benefits of Synthetic Control Arms

SCAs have emerged as a promising approach to improve the efficiency and effectiveness of clinical trials. Based on the use of computational models to construct a virtual control group that closely mimics the characteristics of the treatment group in a clinical trial, SCAs are an important element of the AI revolution in the pharmaceutical industry.[2, 3] In the following section, we highlight the benefits and opportunities that SCAs bring to the clinical trials space, while shedding light on some of the key considerations to their adoption.

Reduce number of patients needed:

Traditional clinical trials require large numbers of patients to participate, which can be time-consuming and costly. SCAs provide a unique avenue for significantly decreasing the number of patients needed in a trial, thus greatly minimizing the patient enrollment load. The net advantage is to eliminate the burden of requiring patients with debilitating diseases to stay on an inactive placebo treatment for the duration of a trial.

Reduce cost of clinical trials:

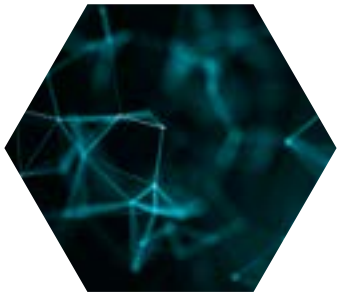
Compared to traditional RCTs, the use of SCAs can potentially bring about substantial cost savings in clinical trials. By eliminating the need for placebo groups, the number of patients required for enrollment decreases, thereby reducing the cost of patient recruitment, screening, and follow-up. Industry experts and academic discourse increasingly acknowledge the financial efficiency of SCAs, particularly noting that they can reduce the required patient pool, compared to traditional Randomized Controlled Trials (RCTs).

Accelerate timelines and increase efficiency:

SCAs offer significant advantages in terms of accelerating clinical trial timelines and increasing overall efficiency. Traditional trials often face delays due to challenges such as site management and patient enrollment, resulting in lengthy timelines. However, the use of SCAs yields substantial efficiency by significantly reducing the time and resources required for patient recruitment, trial monitoring, and overall clinical trial conduct. This accelerated timeline allows for faster drug development and delivery of new treatments to patients. In line with industry consensus, the incorporation of SCAs is increasingly being recognized as a time-saving strategy.

Decrease risks:

In addition to reducing the total number of patients to be enrolled, SCAs also help to reduce the risks associated with experimental treatments by reducing the risk of bias in estimating treatment effect, which may arise in unblinded placebo-controlled trials. By using augmented control arms, SCA approaches can rescue a clinical trial when patient enrollment is insufficient, or the study has not met its targets. A study published in the *Journal of the National Cancer Institute* found that using external control arms improved the accuracy and reliability of clinical trial results, compared to traditional RCTs.[4]



SCAs are an important element of the **AI revolution** in the pharmaceutical industry

Key Considerations with Synthetic Control Arms

Quality and reliability of virtual patient data:

When generating SCAs it is important to ensure that the external data used to construct virtual patients, as well as the resulting virtual patients, are valid and sufficiently representative of the conditions of the planned clinical trial. This is critical because inaccurate or inadequate data may not be representative of the general condition one seeks to mimic in a virtual patient and can lead to biased results and inaccurate conclusions about the efficacy and safety of new treatments. Researchers must carefully consider the process for collecting the required data needed for generating representative virtual patients.

This process involves alignment with important aspects of the trial, such as study design, sample size, and inclusion/exclusion criteria among others, as well as comparing the populations of any leveraged external data to ensure they are similar in terms of demographics, disease severity, comorbidities, and other relevant factors.[5] Additionally, the generated virtual patient data must undergo a stringent validation and verification process that considers the limitations of both the external data and the virtual patient model and that complies with both regulatory guidelines and good simulation practices (GSPs).

Model validation:

To ensure scientific credibility of results of trials that implement SCAs, it is required by regulatory bodies to demonstrate objective evidence of the validity and reliability of the computational models that generate the virtual patient data. It is also important to demonstrate the adequacy of the matching process used to show that the generated virtual patients reasonably match the actual patients in the active treatment arm of the trial. The current FDA guidance on Complex Innovative Designs (CID) offers general recommendations in using simulation for model validation with innovative study designs. However, while the CID guidance does not prescribe a specific framework for the validation process, FDA does require evidence of model validation and leaves that to the discretion of the sponsor.

As mentioned earlier, approaches for generating SCAs may include flexible modeling methods that leverage more complex ML techniques. In this regard, there remains a need to establish a broadly consistent framework for model validation, in the context of *in silico* trial methodologies, that is based on standardized requirements for good simulation practices.

Good Simulation Practice:

The evolving use of modeling and simulation in pharmaceutical drug development and other related fields, triggers the need for a set of guidelines and principles that ensure the validity, reliability, and accuracy of simulation results. An international consortium of over 144 experts around the world (academia, industry, and regulators), including the **Avicenna Alliance**, **VPH Institute** and the EU-funded project **InSilicoWorld**, are collaborating to build consensus around good practices for the use of computer modeling and simulation in a regulated environment. The consortium has produced a guidance document that establishes common guidelines for modeling and simulation. The document is entitled *"Toward Good Simulation Practice: Best Practices for the Use of Computational Modeling & Simulation in the Regulatory Process of Biomedical Products"* and will be published as an open-access book by Nature Springer at the beginning of next year. The designated editors for the Good Simulation Practice book are Professor Marco Viceconti, chair of industrial bioengineering at the Alma Mater Studiorum, University of Bologna, and Luca Emili, CEO of InSilicoTrials.

Statistical methods:

An important consideration with SCAs is selecting appropriate statistical methods for adequately matching the virtual patients in the control arm to the intervention group. This process involves creating a synthetic control group that closely matches the characteristics of the intervention group, such as age, gender, disease severity, and other relevant factors. SCA technology comes with different statistical challenges compared to traditional clinical trials, and to ensure accuracy and reliability in the results, fit-for-purpose statistical and computational techniques need to be developed. The choice of statistical method is highly important as it can influence the outcomes and introduce biases or confounding factors if not carefully designed and validated.

Evidence-assessment/evaluation:

An important aspect associated with the use of SCAs is the need for rigorous evaluation of historical evidence (or external data) that underlie the generation of a virtual patient. The reliance on external data sources for constructing virtual patients could introduce bias that may impact the reliability of the generated data representing the virtual patient. However, with careful evaluation of the appropriateness of relevant external data, as well as astute implementation of robust statistical methods, the SCA can be used to reliably build evidence.

As a general consideration, it is worth highlighting prevailing regulatory perspectives that recognize the value of *in silico* methods in non-clinical and clinical research. These perspectives underscore the growing acceptance and adoption of *in silico* technologies across different regulatory agencies.

USA: **The FDA Modernization Act 2.0** aims to modernize and streamline drug development regulations: the act represents a radical shift in how new drugs and treatments are created. This recognition opens the door for the use of computer models and in silico technology to support drug development.

FDA's Model-Informed Product Development (MIPD) initiative aims to advance the use of modeling and simulation in product development. Its goal is to integrate information from diverse data sources to help decrease uncertainty and lower failure rates, and to develop information that cannot or would not be generated in clinical trials. MIPD encompasses model-informed drug development (MIDD), a computational modeling approach that involves developing and applying exposure-based biological and statistical models derived from preclinical and clinical data sources to inform drug development or regulatory decision-making.

Canada: Health Canada is taking a strong stand in animal welfare with the passing of **Bill C-47, Budget Implementation Act, 2023, No. 1.** The amended Food and Drugs Act (FDA) now prohibits cosmetic animal testing in the country. Health Canada collaborates with the international scientific and regulatory community to develop effective alternatives to animal testing.

India: The Government of India recently passed an amendment to the **New Drugs and Clinical Trial Rules (2023)** with an objective to replace animal testing, particularly in drug research. This amendment empowers researchers to embrace non-animal and human-relevant methods, including advanced computational techniques.

Europe: EMA's head, Emer Cooke, recently emphasized the importance of finding alternatives to animal testing in the regulatory process. EMA encourages medicine developers to adopt non-animal methods while upholding scientific rigor and adhering to the **principles of replacement, reduction, and refinement (3Rs)**. With the establishment of the **3Rs Working Party**, EMA facilitates collaboration among key stakeholders to reduce, replace, and refine medicine testing on animals and supports the use of alternatives.

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More specifically, some regulatory agencies have already recognized the potential of SCAs to improve clinical trials. For example, FDA's MIDD program[6] affords sponsors or applicants the opportunity to meet with Agency staff to discuss modeling and simulation approaches in medical product development. This includes developing mechanistically informed models based on pharmacokinetics that predict the disposition of chemicals, medical products and their metabolites in the body, and could be used for examining their potential for bio-persistence.

In addition, the FDA has issued guidance on the use of real-world evidence (RWE) to support regulatory decision-making for medical devices, which includes the use of SCAs. The guidance notes that SCAs can be used to support device approval when traditional RCTs are not feasible or ethical, and that the validity and reliability of the results depend on appropriate statistical methods, careful model specification, and sensitivity analyses.

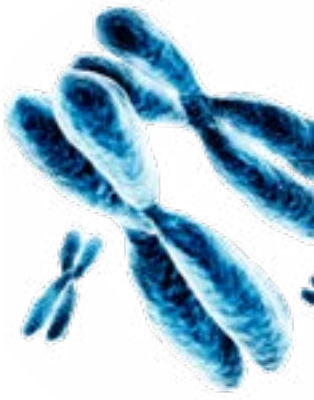
Furthermore, the EMA recognized the potential of SCAs to improve clinical trials. The EMA's Adaptive Pathways program aims to accelerate patient access to innovative treatments by using a more flexible approach to evidence generation, including the use of SCAs. The program emphasizes the need for careful validation and sensitivity analyses to ensure the reliability and validity of the results.[7]

Partnership Between Premier Research and InSilicoTrials in Implementing SCAs for Clinical Trials

In silico trials involving the construction of an SCA provide a unique and scientifically robust pathway for accelerating the approval of new treatments. This is especially true for rare diseases in which administering a placebo in the setting of a RCT may be either unethical or impractical, thereby limiting such trials to a single-arm design. Achieving rapid and successful implementation of such innovative trials requires multi-faceted expertise that addresses the technical modeling aspects, the challenges of trial optimization, and execution that are unique to rare disease trials and the access to credible sources of external data to feed the modeling process. Most importantly, efficient and streamlined collaboration between groups of experts is the key to success with these types of innovative trials.

Figure 2: In silico trials in rare diseases: Recipe for Success

For rare disease trials, a design construct that allows for an *in silico* SCA offers the ability to secure robust inference on treatment efficacy from a single-arm treatment trial. The recipe for the successful implementation of such trials hinges on having a strong collaborative framework that combines proven experience in the trial operations and execution challenges common with rare disease, expertise in modeling and simulation for generating synthetic control patients, and the capability of securing access to suitable external data sources containing the type of data required to characterize the disease. Given the small patient populations common to rare disease trials, achieving efficiency in clinical trial operations and conduct requires access to established networks of experienced clinical sites, proven capabilities in decentralized trial mechanisms, streamlined clinical monitoring strategies, and many other considerations that rely on vetted experience in conducting rare disease trials. In addition, sound expertise and depth of experience in the modeling and simulation approaches pertinent to constructing synthetic control patients is critical.



To this end, strategic business partners, Premier Research and InSilicoTrials Technologies, have pulled together their established expertise in rare disease trial operations and in complex modeling and simulation, respectively, to bring innovation through collaboration. This partnership aims to maximize the potential for *in silico* methodologies in single-arm clinical trials for rare diseases, thereby enabling evaluation of clinical efficacy despite the otherwise traditional limitations of a single-arm patient trial. The result is to potentially accelerate the pathway to regulatory approval of new treatments for debilitating rare diseases.

Premier Research's Approach

Premier Research is a clinical research organization that is fit-for-purpose for biotech companies and specialty pharma. With over 240 rare disease trials across 88 indications conducted over the past five years alone, including multiple rare cancer indications and cell and gene therapy studies, Premier has deep and extensive experience in all aspects related to the successful study development and operational conduct of rare disease clinical trials, including development of innovative trial designs, driving regulatory and commercial strategies, efficient site identification and study start-up mechanisms, as well as targeted trial management and monitoring strategies.

Highly skilled multidisciplinary experts bring insights and deep analysis to the pre-study period, troubleshoot impediments to trial success and develop optimal trial design and operational strategies aimed at improving study outcomes, all with the goal to bring new treatments to patients faster.

InSilicoTrials' Approach

InSilicoTrials is a pioneering modeling and simulation company that offers an array of *in silico* solutions tailored to enhance the design and analysis of clinical trials. Thanks to our extensive network and profound expertise in modeling, we are well-equipped to offer the optimal methodology for SCAs on a case-by-case basis. This methodology takes into account factors such as demographics, disease severity, and comorbidities. Sensitivity analyses are conducted to affirm the robustness of results, followed by rigorous validation to ensure model accuracy.

Consequently, we create a synthetic control group that mirrors the intervention group with high precision. Beyond this, InSilicoTrials offers invaluable insights into result interpretation and its subsequent implications on clinical trial design and analysis. Our methodologies hold the potential to ease the challenges of clinical trials, especially for rare disease populations, ensuring more efficient and effective outcomes.

Concluding Remarks

There is increasing momentum in drug development towards innovative designs and methodologies that yield efficiencies in clinical trials. The use of data-informed computational modeling and simulation is a critical conduit to achieving breakthrough innovation. This is supported by the major regulatory authorities, who continue to develop and release relevant working practices and guidance documents to enable their adoption and to set expectations for their robustness. The application of computer-generated SCAs in clinical trials is one facet of this innovation, which is driven by computational modeling and simulation techniques and is particularly poignant to rare diseases.

Successful implementation of SCAs in clinical trials requires effective multidisciplinary collaboration between experts in disease mechanistic modeling approaches and experts in trial design, operations, and regulatory strategy, while needing access to the relevant external data that will inform the modeling. The use of synthetic control arms in clinical trials offers the unique benefits of enriching the inference drawn from the trial, reducing the trial costs and most importantly, speeding the time to regulatory approval of new medicines for diseases with unmet need.

[1] *U.S. Food and Drug Administration (2017) Use of real-world evidence to support regulatory decision-making for medical devices: Guidance for industry and Food and Drug Administration staff. https://www.fda.gov/media/99447/download*

[2] *https://pharmanewsintel.com/news/ai-in-the-pharma-industry-current-uses-best-cases-digital-future*

[3] *https://www.globaldata.com/media/pharma/ai-big-data-will-impactful-emerging-technologies-pharma-industry-2023-finds-globaldata-survey/*

[4] *Joshua D Wallach, Oriana Ciani, Alison M Pease, Gregg S Gonsalves, Harlan M Krumholz , Rod S Taylor, Joseph S Ross. (2018) Comparison of treatment effect sizes from pivotal and post approval trials of novel therapeutics approved by the FDA based on surrogate markers of disease: A meta-epidemiological study. Journal of the National Cancer Institute, 112(4), 391-397. https://pubmed.ncbi.nlm.nih.gov/29562926/*

[5] *Kristian Thorlund, Louis Dron, Jay J H Park, and Edward J Mills (2020). Synthetic and external controls in clinical trials: A primer for researchers. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7218288/*

[6] *U.S. Food and Drug Administration (2023) https://www.fda.gov/drugs/development-resources/model-informed-drug-development-paired-meeting-program*

[7] *European Medicines Agency. (2017). Adaptive pathways. Retrieved from https://www.ema.europa.eu/en/human-regulatory/research-development/adaptive-pathways*

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