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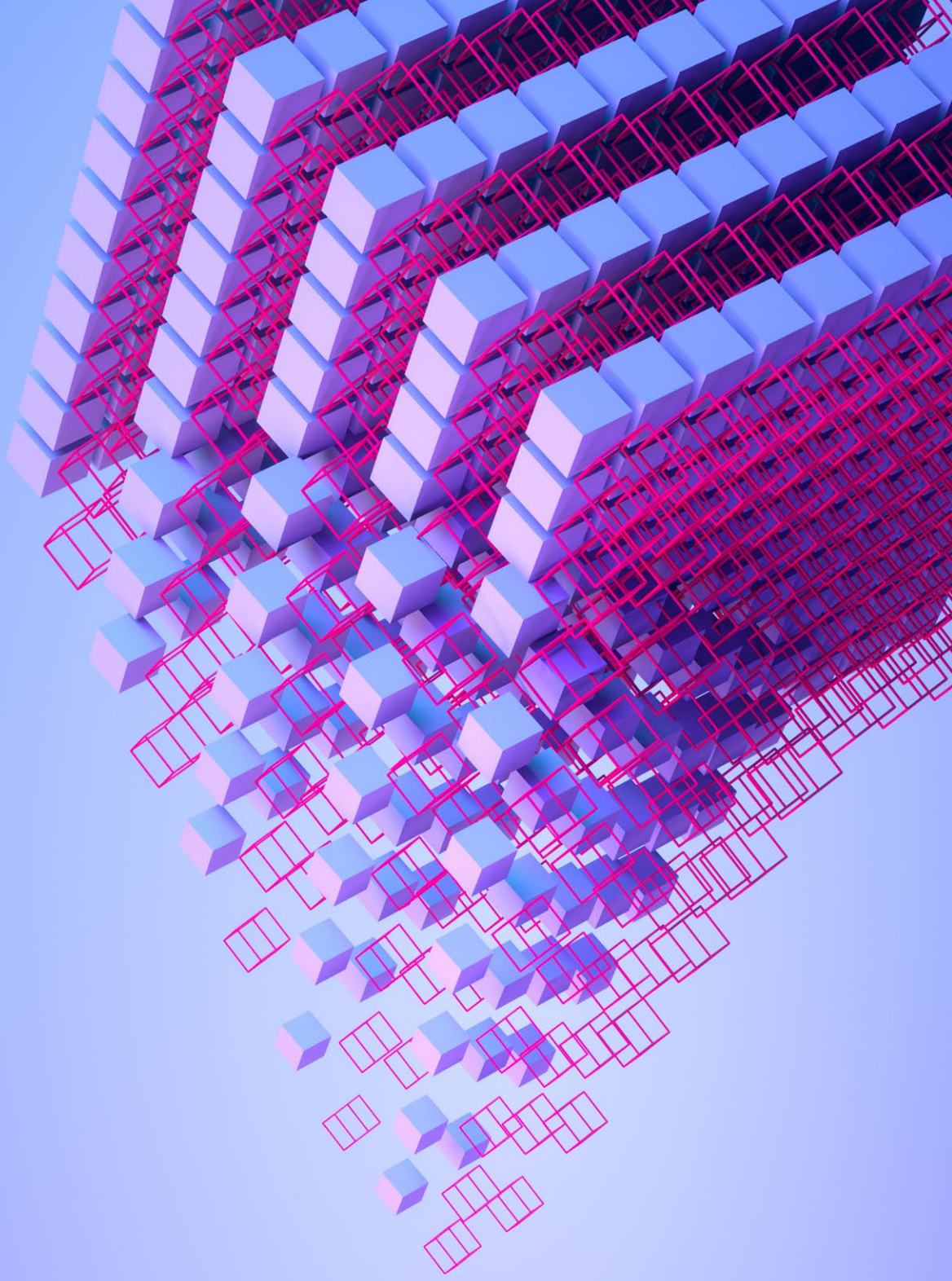
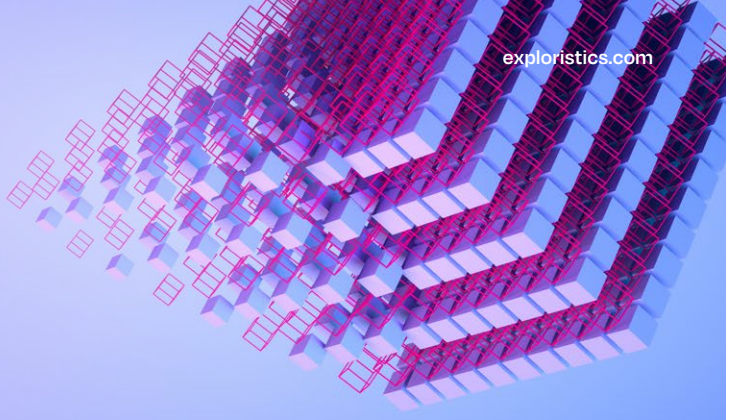
INNOVATIVE ANALYTICS SOLUTIONS



Whitepaper

Are synthetic control arms the future standard in clinical trials?



Synthetic Control Arms

Are synthetic control arms the future standard in clinical trials?

The role of non-randomized evidence in clinical studies, drug development, and healthcare decision-making is rapidly expanding. Here we give an overview of how synthetic controls can add value to clinical studies, and the emerging methodologies used in constructing and analysing synthetic controls.

What is a synthetic control arm?

A synthetic control arm (SCA), also known as external controls, is a group constructed from individuals who are not part of the same study as a group receiving a treatment but are nevertheless compared to that treatment group with the aim of evaluating the effect of the treatment. A SCA can serve as the sole comparator in a single-arm trial setting, or supplement data within a randomized clinical trial (RCT) which already has a control group.

Why use an SCA in clinical trials?

Randomization is considered to be an essential tool for evaluating treatment efficacy, as it eliminates selection bias, balances groups with respect to confounding variables, and forms the basis for statistical tests with the assumption that groups under investigation are alike in all important aspects except for the intervention that they receive [1] . The RCT is considered to be the gold standard in drug development, however is highly time consuming, costly and has a high failure rate [2]. Reasons for this could be due to factors such as failing to recruit enough patients, or overestimating treatment effects from previous uncontrolled trials.

The use of SCAs to design and analyse clinical studies has the potential to accelerate the drug development process, reduce time and costs, and alleviate patient burden. Certain indications and rare diseases make it difficult to recruit enough patients for an RCT. Often, sick patients do not want to be enrolled in a trial where they may be randomized to a placebo group with no chance of improving their condition. And in some cases, such as in severe or highly contagious diseases, it would be highly unethical to withhold potential treatments or randomize to placebo. SCAs may increase the propensity of patients to enrol in an RCT by lessening, or entirely removing, the chance of them being randomized to a placebo group.

Aside from regulatory submission, SCAs have also been used for go/no-go trial decisions and extensively in post-marketing or post-authorization safety studies (PASS). SCAs provide actionable information by describing patterns of response and adverse events associated with the drug's use in the general population.

What is the view of regulators in the use of SCAs?

There is clear precedent in the use of SCAs in regulatory decision making. For example, the FDA approved Merck's Bavencio (avelumab) for the treatment of metastatic Merkel cell carcinoma, based on a single-arm trial and a synthetic comparator arm which used historical control of matched patients. Roche used synthetic control data to expand access to Alecensa (alectinib), a treatment for non-small-cell lung cancer, in 20 European markets. The FDA discusses ways in which SCAs could be beneficial in the following clinical settings [3, 4] :

- A **by reducing the risk** of early stopping of Phase III trials facing long patient enrolment or follow-up periods, or that have secondary endpoints containing low prevalence subgroups,
- B **by increasing reliability** in single arm Phase II trials using progression free or overall survival, which traditionally is known to have high false positive rates,
- C **by increasing the power** of randomized Phase II trials which are often underpowered for binary endpoints,
- D **to demonstrate safety and efficacy** in orphan drugs without standard of care.

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Constructing an SCA using real world data versus historical trials – the pros and cons

Curating the synthetic control population from external sources and justifying their inclusion into the current study is one of the key challenges in efficacy studies. SCAs must be carefully and thoroughly considered as any matching on selection criteria or adjustments made to account for population differences should be specified prior to selection of the control and performance of the study to minimise bias.

SCAs can be generated from real world data (RWD) extracted from hospital and GP health records, medical claims, and mobile apps. The key advantage of using RWD for SCAs is that they often reflect the typical use of treatments in the clinical setting and tend to encompass patients with widely varying characteristics and co-morbidities. While there may be a large pool of patients to select for use in an SCA, it can often be difficult to align outcome measurements and eligibility criteria as the data is not collected specifically for trial purposes. For example, the definition of relapsed/refractory status in oncology differs between RWD and clinical trials. This could result in the inclusion of unfit patients into SCAs and introduce a source of error. Another one is the choice of index date (baseline), which would affect progression and other time to event studies.

In contrast, using historical trials to generate SCAs results in groups that are more tightly aligned in their baseline characteristics, and data more suited for assessing efficacy and compliance. However, untreated historical control groups tend to have worse outcomes than an apparently similarly chosen control group in a randomized study [1], possibly reflecting publication bias or bias in the selection of these trials for SCAs. The process of applying and receiving access to patient data from multiple historical trials adds another layer of complexity and costs, however it could be outweighed by the savings in patient enrolment.

Methodologies to match SCAs to the treatment group

There are many statistical techniques available to match the external data to the intervention group and to balance patient characteristics between groups, all of which have varying degrees of statistical efficiency [5].

- The simplest approach uses multivariable regression techniques to adjust the observed treatment effect against imbalanced patient demographics and disease characteristics. However, due to small sample sizes this often results in sparse data and loss of precision.
- Adjustments for observed confounders using inverse probability weights or propensity scores **(Figure 1)** were adopted early into SCAs due to being easy to implement and their potential to summarize many variables into a single weight or score for each patient. Clinical studies with SCAs often employ these approaches.

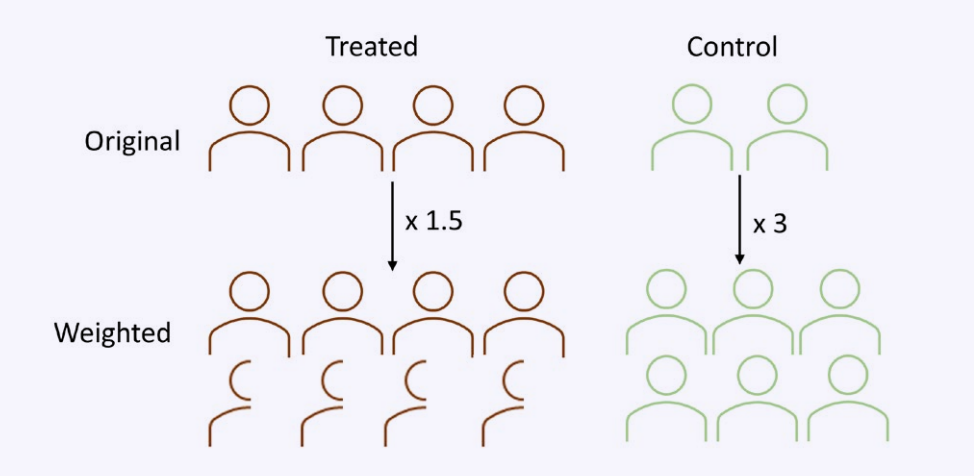

Figure 1. A schematic representation of inverse probability weighting, where individuals are assigned weights based on their likelihood of belonging to the treatment group, calculated from a set of covariates. The weights result in each patient (observation) having equal influence in the estimates of the final model.

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- More advanced techniques such as Bayesian dynamic borrowing **(Figure 2)** are becoming increasingly popular as it leverages information from multiple external studies to use as priors in the current study. A key advantage is that it can utilize all available information across both internal and external data and weigh the contributions of multiple sources of data adequately, therefore maximizing the ability to draw clinically relevant conclusions [6, 7]. This technique uses a meta analytic approach, with the weights attached to the SCA depending on how well it matches the in-study control. Therefore, the cons would be that it uses summary data rather than individual patient level data and the study would require some internal controls.

- Microsimulation **(Figure 3)** has been used extensively in health economics and large-scale population studies but has been gaining traction for use as a synthetic control method. Microsimulations use external patient data to inform patient trajectories for the outcomes of interest, then simulated trial cohorts are constructed using this information [9]. Microsimulation has the advantage of giving a high-resolution view of rare patient subgroups, minimizing the risk of patient attribute disclosure, and enables researchers to model long-term outcomes that might not be feasible in a randomized study [8, 9]. However, it requires reliable data to inform simulations and may not have all the features that using real data would have.

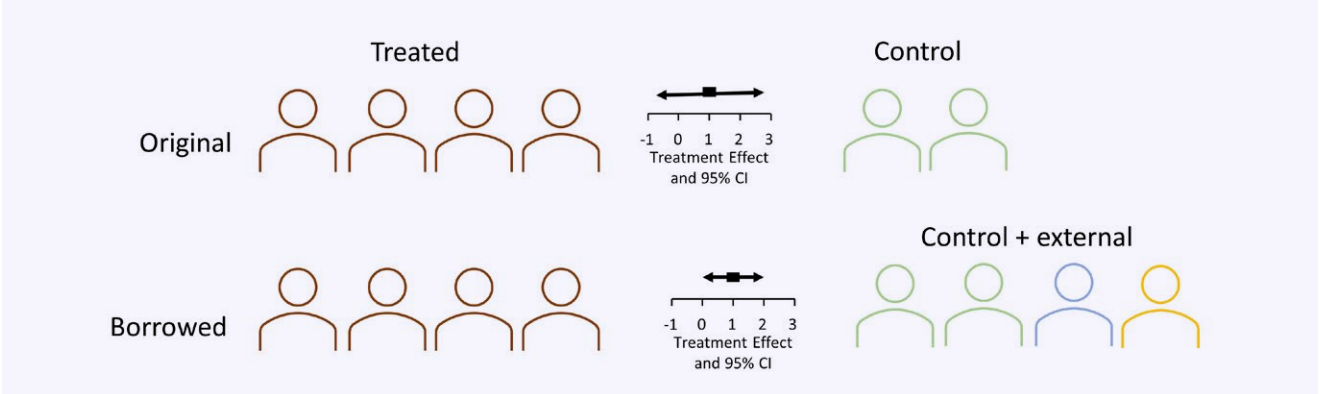

Figure 2. Diagram showing how dynamic borrowing from external controls to supplement internal control data can increase the precision of treatment effects. The potential for introducing bias using this technique can be minimized by examining the compatibility between the internal vs external controls.

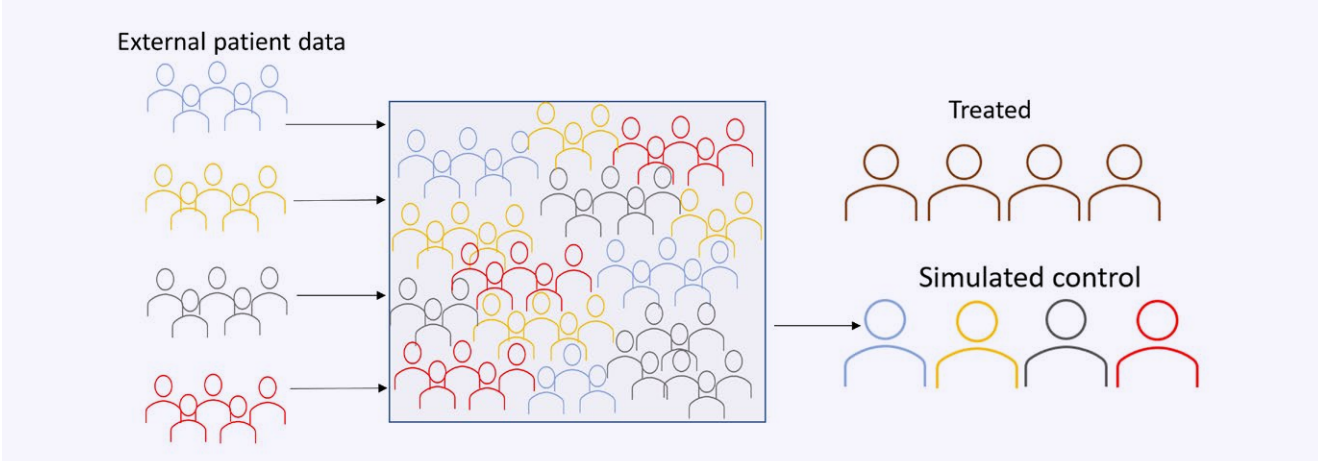

Figure 3. A schematic representation of microsimulation.

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Opportunities for better use of SCAs

With the many benefits offered by SCAs, particularly in relation to studies that are difficult to conduct for ethical and logistical reasons, what challenges remain if they are to contend as a future standard in clinical trials? Going forward, ***transparency*** with regulators is key to building confidence in their value. Regulators are well aware of the difficulties that exist around data standardisation where the data sets for multiple historical trials are combined for use in an SCA. Studies using SCAs can also face challenges in quantifying the impact of potential sources of bias, and in demonstrating the robustness of findings to these bias in a comprehensive and systematic fashion. Failures in regulatory submissions using SCAs are often due to data quality, having a short follow-up, and difficulty aligning measurements. While some of these can be overcome with rigorous and innovative statistical approaches, it is more important to provide a clear auditing path for regulators to assess the decision-making involved in selecting and employing these. ***Engaging with regulators in advance of any analysis*** is strongly recommended, so all analyses, and crucially, sensitivity analyses, are pre-specified.

Judicious use of SCAs is also essential to build confidence in their value with regulators. Some SCAs are used to retrospectively rescue failed studies in circumstances not likely to gain traction with regulators. For regulatory acceptance, it is critical to provide robust evidence in the right context to demonstrate that any conclusions drawn from their use are correct. This requires the use and integration of multiple independent data sources for validation purposes.

Forging a future standard in clinical trials

In conclusion, successful use of SCAs in clinical trials requires time and specialised expertise in their design, to ensure that the right information is extracted from datasets and the correct methodology employed to assess treatment efficacy. Exploristics offer multiple creative solutions supporting the use of SCAs. For example, we can efficiently and comprehensively construct patient populations for a range of disease areas using historical trials and other sources of external data. We also have in-depth knowledge of the concerns regulators might raise when considering trial designs using SCAs. Therefore, while the use of SCAs may not entirely replace RCTs as the gold standard for clinical trials, we believe that developing statistical methodologies as well as close collaboration between regulatory, statistical and clinical partners can boost recognition and acceptance of their value over the next few years.

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About Exploristics

Exploristics is a global provider of state-of-the-art software and biostatistics services to the life sciences sector. We offer key support to organisations involved in the clinical development of new healthcare breakthroughs with our strategic consultancy expertise and flagship simulation software, **KerusCloud**.

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