White paper

New methods for improving External Control Arms



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Summary

External Control Arms (ECA) address some of the practical, ethical and cost challenges of recruiting in-trial randomized control arms. Yet ECAs have their own limitations. Mechanistic modeling, such as that developed at Novadiscovery (NOVA), can create more robust ECAs that overcome these limitations and provide deeper insights into treatment effects at both the population and individual patient level.

Introduction

The randomized controlled trial (RCT) has long been considered the methodological gold standard for evaluating new drug efficacy and safety. It aims to provide objective evidence of the efficacy of a new treatment by randomly allocating patients to either an experimental treatment arm or a "control arm", which can be an existing standard of care, an alternative treatment, or a placebo.

The randomization process aims to balance out any unknown variables among patients across the two (or more) arms, ensuring that any differences in outcome that do emerge can reliably be attributed to the treatment, and not to any other factor.

The problem

In some cases, building a robust control arm can be difficult:

➔ When there are few subjects available, for example in rare diseases or certain cancer subtypes

➔ When giving placebo is ethically unacceptable, for instance in cases of severe disease with no alternative treatments

When assessing combination therapies, such as in oncology, there may be too many combinations to investigate through a regular RCT. The trial design may limit the focus to just a few combinations among all the possible ones.

Further, random allocation to treatment or control arms, even if correctly done, guarantees only "average" similarity across the arms. The patients in each arm may be similar *as a group*, but the individuals in each arm may vary considerably. That means bias can creep in: if group A has several patients that respond above-average, and several below-average responders, this may generate a group level result that hides important differences. Checking group comparability is of little help: it deals only with mean values.

The current approach : RWD-driven external control arms

Increasingly, real world data and evidence (RWD/RWE) are used to supplement RCT data, providing additional information on safety, effectiveness in the real-world setting, and/or on particular patient subgroups.

RWD is also gaining traction as a tool for building external control arms. Instead of recruiting patients into a control arm as part of a trial, data is collected from sources such as medical records, other (similar) clinical trials, including historical trials, databases or the literature. This data then stands in as control arm data.

External control arms should ideally include data from individuals that match, as far as possible, the subjects in the active arm of the real trial.

In some cases, it makes sense to select more than one historical/matched control subject for each real subject. Statistical techniques exist to help adjust the ECA data to match as closely as possible that of the experimental group.

However, using RWD to build an ECA has several drawbacks. Most relate to inconsistencies in patient and/or trial design characteristics between the real and external arms. These inconsistencies can lead to erroneous trial conclusions.

Differences in selection criteria:

Selection criteria for patients in the real world data cohort are unlikely to precisely match those used for the active trial. Patients' baseline characteristics - such as age and health status - may also be inconsistent.

Inconsistent index date:

This is particularly important when the study measures time-to-event: the time taken for patients to reach a predefined clinical outcome. If the index date - the baseline from which that time-to-event is measured

- is inconsistent across the cohorts, it could bias the result. There is also the problem of immortal time bias, caused, for instance, by delays between the start of a follow-up period, and when patients in the treatment arm actually receive their medicine. This can bias results in favor of the treatment, since patients that experience an event before starting treatment may be re-categorised into the no-treatment arm.

Hidden characteristics:
Hidden characteristics are between-patient differences that are not observable, but which can affect the outcome of a trial. They present a challenge to external control arms (and indeed most multi-arm trials). A patient from the RWD cohort may closely match one from the actual trial on all measured characteristics, but differ on certain hidden characteristics, for instance at the cellular level, which impact the treatment effect.

NOVA's solution

NOVA's knowledge-based models capture disease- and treatment-relevant biological entities and their functional relationships using mathematical equations. They are calibrated using RWD or actual trial data. Using these models, NOVA can build "virtual" patient populations with exactly the same measured characteristics as real patients in a real experimental arm.

Our approach also addresses the hidden characteristics problem by digitally cloning each real patient as often as needed, to account for the plausible distributions of these un-observed characteristics. The plausible distributions can be inferred, to a reasonably accurate degree, from the literature-derived physiological and biological dynamics included in NOVA's disease models.

A knowledge-based modeling approach can aggregate multiple trial datasets in order to increase the likelihood of including all relevant patient characteristics required for a meaningful ECA.

At NOVA, we refer to these virtual populations as 'Synthetic Control Arms'.

NOVA's virtual populations provide highly realistic cohorts - for example, with plausible weight-height correlation and distributions - which take into account multiple relevant patient characteristics, from the cellular and molecular level, to tissues, organs and whole-body.

➔ These populations are unlimited in size and scope, and allow developers to select a sample to use as a synthetic control arm.

➔ Unlike RWD-generated external control arms, NOVA's SCAs are fully contemporaneous cohorts, to which any reference treatment can be applied - including no treatment at all (for a natural history control).

➔ NOVA's SCAs also enable individually-matched cohorts in which each physical patient in the actual trial is matched with one or more virtual patients in a control arm. The strength of this 'digital twins' approach is that trial patients may be digitally reproduced as many times as necessary to capture as wide a range of potential variables as possible. This also allows researchers to capture critical sources of intra-patient variability - for instance, a range of hidden characteristics which may all be associated with the same or similar observed variables.

SCAs thereby offer powerful alternatives to RWD-generated controls, using a unique combination of knowledge and data. They overcome the weaknesses of conventional ECA and help address regulators' and health technology assessment bodies' questions.

Beyond Synthetic Control Arms : intra-patient controls

The advantages of NOVA's modeling approach extend beyond synthetic control arms. Creating multiple digital twins for a given physical subject enables intra-patient comparisons - meaning each patient can be compared to him or herself, during parallel time periods, under a range of different treatment conditions. This unique feature would of course be impossible in real life.

Creating Intra-patient controls allows researchers to carry out a wide range of further experiments to elucidate treatment effects and how different patient characteristics - including previously unknown or hidden ones - may impact them. It becomes possible to identify best-responders to a given treatment, and to tease out commonalities among them.

Treatment benefit can also be measured at the individual level, opening up new and better ways to assess treatment efficacy and effectiveness. For instance, a given trial may be deemed successful if 90% of subjects in the target population show an individual benefit greater than X. Further, by compiling these individual clinical benefits, the impact of a treatment on very small patient subgroups can also be measured.

Metrics based on the clinical benefit for individuals and groups of individuals are likely to be highly relevant to regulators and patients, and take us a further step toward personalized medicine.