PROCOVA™: A 3-Step Procedure to Apply Historical Data and Deep Learning to Reduce Sample Sizes in RCTs Aligned with Regulatory Guidance

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TwinRCTs™ Blend New Advances in Technology with the Most Trusted and Reliable Forms of Evidence Generation

Historical Control Data

The availability of historical data has dramatically improved in the last decade with greater openness to sharing de-identified data.

Deep Learning

Recently, there have been major advances in methods for developing strongly predictive AI models, particularly in the area of deep learning.

Novel RCT Designs

Leveraging rich data and advanced AI to add power without bias requires randomization. The traditional RCT is a core building block of the TwinRCT.

A TwinRCT includes a robust technique to improve the statistical efficiency of randomized clinical trials. First, historical control arm data is used to train a machine learning model of disease progression. The model will be applied to the baseline measurements of each subject in a future trial to create a prognostic digital twin: a longitudinal clinical prediction of their outcomes, in the hypothetical scenario where the subject receives placebo. Prognostic digital twins are incorporated into the trial analysis as a covariate.

Digital Twin Disambiguation

The term digital twin has gained traction as a description of several very different healthcare technologies. The TwinRCT relies on prognostic digital twins.

Electronic Health Records **are not** prognostic digital twins. EHR describes the present and the past, not the future.

Digital Biomarkers **are not** prognostic digital twins. They can provide supplemental health information about the present state.

Prognostic digital twins **are** a comprehensive probabilistic prediction of a trial patient's study outcomes based on their individual baseline data.

3 Steps to More Efficient Clinical Trials with PROCOVA

1. Train and evaluate a prognostic model to predict outcomes on control (i.e., create prognostic digital twins).
2. Account for the prognostic model while estimating the sample size required for a prospective study.
3. Estimate the treatment effect from the study using a linear model to adjust for participants' predicted control outcomes.

Quotes from Draft EMA Qualification Opinion

"The proposed procedures as described in a handbook for trial statisticians could enable increases in power or precision of treatment effect estimates in phase 2 and 3 clinical trials."

"The proposed prognostic covariate procedure is an acceptable statistical approach for primary analysis of clinical trials."

"Type I error control, unbiased effect estimation and confidence interval coverage are not dependent on the choice or performance of the prognostic model."

"It is agreed that taking into account explained variation due to covariates, such as the prognostic score in PROCOVA, results in reduced residual variance and hence will result in smaller sample size than assuming an unadjusted analysis."

How Much Can the Sample Size Be Reduced?

The minimum sample size for an RCT can be calculated prospectively by leveraging formulae for the variance. The expected variance of the treatment effect using an unadjusted ANOVA model is shown in Equation 1 below, where σ^2 represents variance and n represents sample size. The subscripts $_0$ and $_1$ indicate control and treatment arms, respectively.

Equation 1

$$\sigma_0^2/\, n_0 + \sigma_1^2/\, n_1$$

In contrast, the expected variance of the treatment effect using PROCOVA is shown in Equation 2 below. In PROCOVA, two additional parameters are added. The correlation coefficient, ρ, represents the correlation between the prognostic digital twins and the observed outcomes in an out-of-sample dataset (i.e., data that was not used to train the model). The deflation parameter, λ, is incorporated to obtain a conservative estimate. These parameters, together known as the expected correlation, are assigned in Step 1 and Step 2 of the PROCOVA procedure, respectively.

Equation 2

$$\sigma_0^2(1-(\rho_0\lambda_0)^2)\,/\,n_0 + \sigma_1^2(1-(\rho_1\lambda_1)^2\,/\,n_1$$

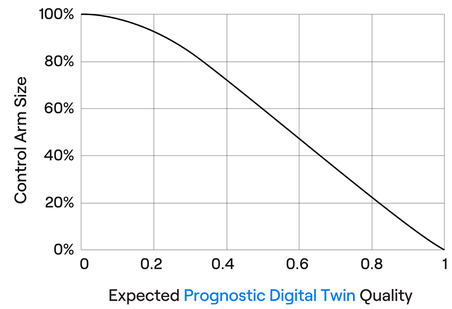
When the original design is a 1:1 randomization and a common variance ($\sigma_0^2 = \sigma_1^2$), common correlation, and a common deflation parameter are assumed across study arms, the sample size reduction achievable in the control group can be described by Equation 3 below.

Equation 3

$$2(\rho\lambda)^2/(1+(\rho\lambda)^2)$$

The Art of PROCOVA Step 2

Equation 3 shows that the sample size reduction is a function of the product of ρ, which is calculated in Step 1, and λ, which is assigned in Step 2. If we refer to this product as the expected prognostic digital twin quality, we can plot the attainable sample size reduction as shown below.



The quantities ρ and λ are thus very important for evaluating the potential of the PROCOVA procedure. ρ provides an estimate of prognostic digital twin performance, and λ serves as a deflation factor to protect against overly optimistic estimates of ρ. Using the best available out-of-sample data, and applying the future trial inclusion criteria, the Step 1 estimate of ρ is an objective calculation. The assignment of λ in Step 2, in contrast, is a collection of rules of thumb that is integral to a full understanding of the PROCOVA procedure prior to its use for trial sample size reduction.

Suggested λ Values

Value	Scenario
.95	Model performance has been evaluated with >1 out-of-sample dataset that is close to in-sample estimates
.9	Model performance has been evaluated with 1 out-of-sample dataset that is close to in-sample estimates
Subtract .05 for each of these conditions	- Significant differences in standard of care (SOC) between the out-of-sample data used in Step 1 and the SOC applicable to the control arm in the planned trial - Significant differences in data completeness in the out-of-sample data used in Step 1 and the expected data completeness in the planned trial - If the model includes known predictive biomarkers (as opposed to prognostic biomarkers)

Evaluating these and other scenarios that may lead to more conservative assignments of λ will generally require a collaborative discussion with model developers, the trial statistician, and clinical experts.

Conclusions

As demonstrated by the EMA draft qualification opinion, PROCOVA offers an innovative approach that leverages historical data and machine learning to reduce the control arms in clinical trials. Successfully applying the procedure without unwittingly lowering study power requires special attention to the deflation parameter λ that is assigned in Step 2. With the appropriate considerations, the PROCOVA procedure provides a solution for prospective sample size reduction that is safe, unbiased, and achievable.