ECKER ECKER

Poster Download

Oldeland J., Beuermann J., Ecker C.

Digital twins and PROCOVA – a compromise for HTA?

Background

The benefit assessment for orphan drugs is a highly discussed topic. HTA agencies often criticize the body of evidence for orphan drugs due to lack of RCT data [1]. Nevertheless, single-arm studies are often the only option for health technology developers when no therapeutic alternatives are available. Furthermore, conducting a properly powered RCT might be impossible due to the rareness of the orphan disease. A recently developed method [2] could help to overcome the problem of underpowered RCTs and simultaneously make use of real-world data or single arm trials to generate a digital twin of the randomized subjects, allowing for better powered RCT designs for orphan drugs.

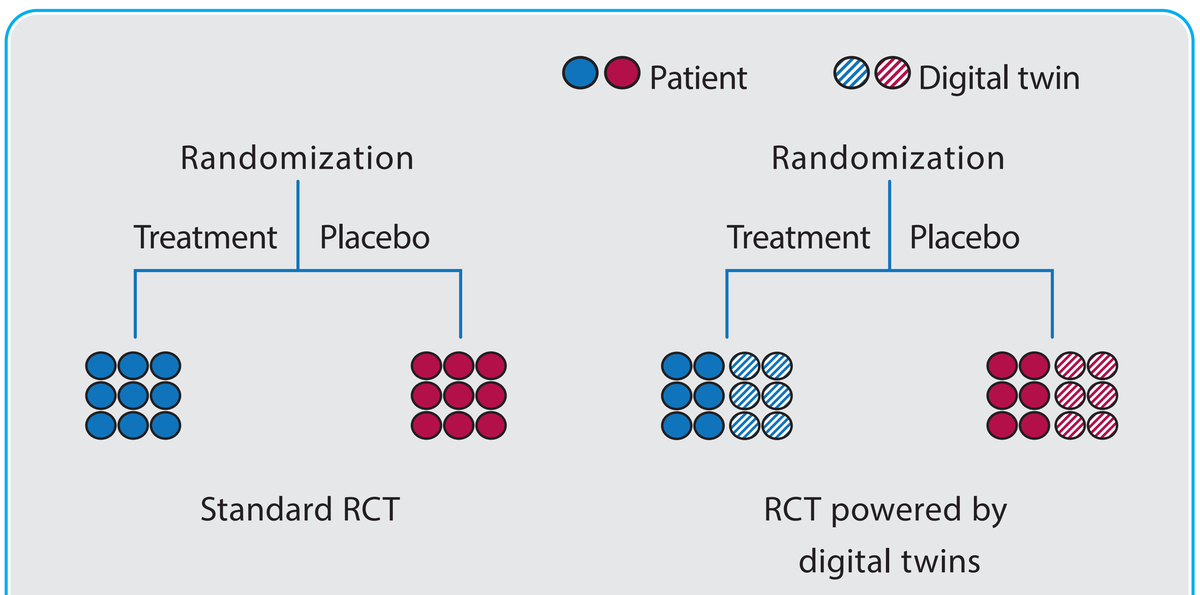

Fig 1.) Example application of digital twins. Digital twins are created using the PROCOVA model and are then used to multiply the actually recruited patients.

PROCOVA

Prognostic Covariate Adjustment (PROCOVA) is a new statistical method [2] using machine learning algorithms, based on the idea of digital twins. PROCOVA is intended to improve the efficiency of Phase 2 and 3 clinical trials, by using trial subjects' predicted outcomes on placebo (prognostic scores generated by machine learning algorithms) in linear covariate adjustment. If correctly applied, it can reduce the sample size (Fig. 1) noticeably without any additional assumptions needed in comparison to standard ANCOVA. The application of PROCOVA requires multiple steps [2]. A hypothetical example is displayed in Figure 2. The digital twin is created using a prognostic score, which is integrated into analysis of the RCT. Instead of creating subjects, the prognostic score leads to a better estimation of the treatment effect. First extensions to CMH [4] and MMRM [5] have been published recently for different indications. Hence, PROCOVA can be applied to longitudinal and binary endpoints. Potentially, this method could also be extended to time-to-event data.

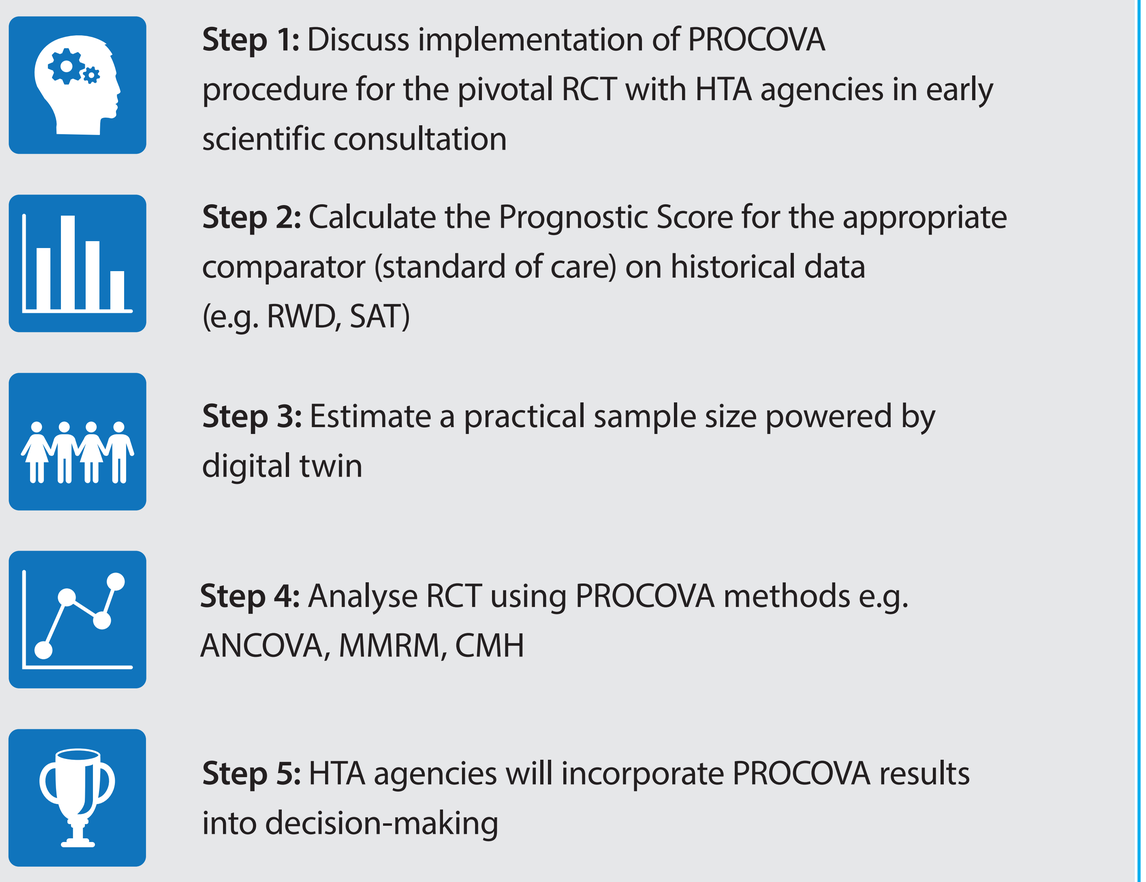

Fig 2.) Five steps to prepare PROCOVA for HTA, RWD = real-world data, SAT = single-arm trial, RCT = randomized controlled trial, HTA = health technology assessment, MMRM = mixed models for repeated measures, CMH = Cochran-Mantel-Haenszel test

Conclusion

- PROCOVA is a promising method to generate better evidence for orphan drugs in particular, and cases where low sample sizes can be expected.
- To lower the risk for the health technology developer when integrating this method into their study design, there must be clear communication by the HTA bodies under which circumstances results of a PROCOVA would be acceptable like EMA did in 2022 for drug authorization [5].
- HTA bodies should give an opinion on the method and consider including PROCOVA in guideline updates.
- Health technology developers should verify whether PROCOVA could be applied in planned and ongoing studies.

References

[1] Kranz et al. "Reforming EU and national orphan drug regulations to improve outcomes for patients with rare diseases." BMJ 381 (2023).

[2] Unlearn.AI, Inc PROCOVA™ Handbook for the Target Trial Statistician, Version 1.0, (2021).

[3] Vanderbeek et al. "Prognostic Covariate Adjustment for Binary Outcomes Using Stratification." arXiv preprint arXiv:2212.09903 (2022).

[4] Ross JL et al. Enhancing Longitudinal Clinical Trial Efficiency with Digital Twins and Prognostic Covariate-Adjusted Mixed Models for Repeated Measures (PROCOVA-MMRM), (2024).

[5] EMA Qualification opinion for Prognostic Covariate Adjustment (PROCOVA™), (2022).

Ecker + Ecker GmbH · Warburgstr. 50 · 20354 Hamburg · Germany
+49 (40) 41 330 81-0 · info@ecker-ecker.de · www.ecker-ecker.de