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CONDITIONAL DISTRIBUTION MODELING AS AN ALTERNATIVE METHOD FOR COVARIATES SIMULATION: COMPARISON WITH JOINT MULTIVARIATE NORMAL AND BOOTSTRAP TECHNIQUES

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ABSTRACT:

Clinical trial simulation (CTS) is a valuable tool in drug development. To obtain realistic scenarios, the subjects included in the CTS must be representative of the target population. Common ways of generating virtual subjects are based upon bootstrap (BS) procedures or multivariate normal distributions (MVND). Here, we investigated the performance of an alternative method based on conditional distributions (CD). Covariates data from a hypertension drug development program were used. The methods were evaluated based on the original dataset (internal evaluation) and on their ability to reproduce an older, unobserved population (extrapolation). Similar results were obtained in the internal evaluation for summary statistics, yet BS was able to preserve the correlation structure of the empirical distribution, which was not adequately reproduced by MVND; CD was in between BS and MVND. BS does not allow extrapolation to an unobserved population. When the

dataset used to inform the extrapolation was well approximated by a MVND, the results from CD and MVND were comparable. However, improved extrapolation performance was observed for CD when deviations from normality assumptions occurred. If CTS is used to simulate within the observed distribution, BS is the preferred method. When extrapolating to new populations, a parametric method like CD/MVND is needed. In case the empirical multivariate distribution is characterized by linearly related covariates and unimodal marginal distributions, MVND can be used because of the simpler statistical framework and well-established use; however, if uncertainty about the MVND assumptions exists, CD will increase the confidence in the simulations compared to MVND.