Upstrapping To Determine Futility: Predicting Future Outcomes Nonparametrically From Past Data

Jess Wild MS, Alexander Kaizer PhD (University of Colorado Anschutz Medical Campus)

Background: Clinical trials often involve some form of interim monitoring to determine futility before planned trial completion. While many commonly used parametric options for interim monitoring exist, nonparametric based interim monitoring methods are also needed to account for more complex trial designs and analyses. The upstrap is one recently proposed nonparametric method that may be applied for interim monitoring.

Methods: Upstrapping involves repeatedly resampling existing interim data with replacement and determining the likelihood of trial success based on comparison to preselected p-value and proportion threshold criteria. To evaluate the potential for upstrapping as a form of interim monitoring, we conducted a simulation study considering different sample sizes with several different proposed calibration strategies for the upstrap. We first compared trial rejection rates across a selection of threshold combinations to validate the upstrapping method. Then we applied upstrapping methods to simulated clinical trial data, directly comparing their performance with more traditional alpha-spending interim monitoring methods.

Results: The method validation results showed that upstrapping can produce reasonable results across a variety of simulations settings. Although there are many potential approaches to calibration, our three proposed approaches had different strengths depending on the stopping rules used. For interim futility monitoring, upstrapping performed similarly well across performance metrics compared to alpha-spending methods, without large disadvantages in type I error rate or power.

Conclusions: Upstrapping is a promising tool for performing interim futility monitoring. When properly calibrated, upstrapping may be comparable to alpha-spending methods in predicting trial futility but with a smaller expected sample size.