Estimating heterogeneity of treatment effects in clinical trials

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Methodological Issue Being Addressed We present a method to estimate heterogeneity of treatment effect (eHTE) in existing clinical trial datasets. We apply this method to demonstrate instances of heterogeneous drug response in past clinical trials in psychiatry.

Introduction Personalized medicine is heralded as the key to advancing psychiatry. Yet clinical trial results and meta-analyses are reported as mean and standard deviation only. This precludes evaluating information about heterogeneity of treatment effects (HTE) and obfuscates attempts to determine if subgroups are present or if enrichment might be appropriate.
Here, we start with the null hypothesis (H0) that an effective drug has equal benefit on all participants (HTE = 0). We present a method to test H0 and demonstrate situations in which Ho can be rejected: H1) a small subgroup of patients show large response to active drug (while the rest do not separate from placebo), and H2) a subgroup of patients in both arms show large response and a second subgroup shows a smaller response that favors active drug.

Methods We develop a measure 'estimated heterogeneity of treatment effect' or eHTE which estimates variability in individual treatment effect. Response curves are compared between treatment arms, and the difference (e.g. drug minus placebo) in cumulative response across percentiles is calculated. eHTE is the standard deviation of response difference across percentiles and approximates HTE. Simulated normal distributions are used to assign a p-value to eHTE. Using simulated cases, we demonstrate that eHTE can inform the choice of enrichment strategy. We then calculate this measure in real clinical trial datasets.

Results Testing this method on real clinical trial data reveals reproducible instances of heterogeneity. For example, in a trial comparing venlafaxine for MDD, we find significant treatment heterogeneity (PeHTE = 0.01). This heterogeneity can be accounted for by a COMT gene polymorphism. In a trial of Dasotraline for treatment of binge eating disorder (BED) we observe heterogeneity (PeHTE = 0.003), with responder and non-responder subgroups that are shifted by treatment. Impressively, this heterogeneity is replicated in both arms of a subsequent clinical trial of Dasotraline for BED (PeHTE (4mg) = 0.009, PeHTE (6mg) = 0.002). We describe other real-world examples where heterogeneity is or is not detected with this approach and discuss the implications of these results to clinical guidelines for individualized treatment.

Conclusion eHTE, as an analytical index, describes the range of treatment responses and not just mean change. This measure of treatment heterogeneity is useful in clinical development and may

provide valuable information to clinicians and patients about the range of treatment responses. This study was supported by funding from Sumitomo Pharma America, Inc

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