Multi-stage adaptive enrichment trial design with subgroup estimation Neha Joshi, Merck & Co. Inc., Kenilworth, NJ and Anastasia Ivanova, Department of Biostatistics, UNC Chapel Hill, Chapel Hill, NC

MOTIVATION

- Increase statistical power to detect treatment effect if new therapy only works in a subgroup.
- Reduce number of subjects who have no apparent benefit from being exposed to side-effects.

INTRODUCTION

Y: continuous outcome $X = (X_1, \dots, X_m)$: continuous (some predictive) S: subgroup defined based on X

Define Utility: $U(S,\gamma) = P(X \subset S)^{\gamma} [E(Y|1,X) - E(Y|0,X)]$

 $U_1 = U(S, 0.5), U_2 = U(S, 0.75)$

SUBGROUP ESTIMATION

- 1. Estimate treatment effect for i^{th} subject: Δ_{i}
- Methods: LM, OGLASSO, SVM, CART, and RF
- LM and OGLASSO include quadratic terms and interactions
- 2. Define $S(\Delta) = \{x_i : \Delta > \Delta_i\}$, *i* candidate subgroups
- 3. Determine $\Delta^* = argmax U(S(\Delta))$
- 4. 'Best' Subgroup, $S^* \equiv S(\Delta^*) = \{x: \Delta > \Delta^*\}$



SIMULATION STUDY (contd.)

- 0-100% with 100% being the best.

- Type I error rate was preserved.

Neha Joshi, Jason Fine, Rong Chu & Anastasia Ivanova (2019) Estimating the subgroup and testing for treatment effect in a post-hoc analysis of a clinical trial with a biomarker, Journal of Biopharmaceutical Statistics, 29:4, 685-695.

Joshi, N., Nguyen, C., Ivanova, A. (2020). Multi-stage adaptive enrichment trial design with subgroup estimation. Journal of Biopharmaceutical Statistics in press.

Ivanova, A., Israel E., LaVange, L.M et al (2020). The Precision Interventions for Severe and/ or Exacerbation-Prone Asthma (PrecISE) adaptive platform trial: statistical considerations. Journal of Biopharmaceutical Statistics in press.

• Y is generated from a step-wise function using X_1, X_2 .

• Estimation methods are built using $X_1 - X_4$.

• % U: Ratio of utility for the estimated subgroup and the best possible utility (utility for true theoretical subgroup),

• Boxplots show comparison of estimation methds w.r.t % U, OGLASSO performs the best (n = 400).

• Total sample size for enrichment design, n = 360.

• The power in partially enriched population was higher by 5%-13%, compared to a non-enriched trial.

• Cannot achieve perfect subgroup estimation with assumed sample size for design (%U = 70-90%).