Paper outline

1 Abstract (200 words)

- Objective
- Study Design and Setting
- Results
- Conclusion

2 Introduction

- Generalizing overall treatment effects estimated in RCTs to individuals often is problematic (Rothwell, 1995; Kravitz, 2004; Rothwell, 2005;)
- Subgroup analyses (SGAs) play central role for the assessment of HTE, despite well-known issues (references).
- Several guidelines have been proposed to outline the appropriate settings of SGAs (references).
- Earlier work has provided framework separating predictive HTE approaches from descriptive ones in an attempt to complement previous categorizations of exploratory-confirmatory SGAs (Varadhan, 2013)
- More recent work (PATH, EnE) focuses on predictive HTE based on risk prediction modeling and differentiates it from causal inference approaches
  - Risk is a mathematical determinant of risk (explain that!!), so focusing on risk-based approaches provides a viable option.
  - There are earlier implementations, mainly assuming constant relative treatment effect (Califf, 1997; Dorresteijn, 2011)
- In parallel, methods for the evaluation of predictive HTE have been transported from the prediction modeling field (c for benefit, else?)
- Even though stratifying on risk is an improvement, as it is less prone to overfitting compared to effect modeling approaches (van Klaveren, 2019), it still may not be appropriate for individualizing benefit predictions. Jumps at cut-offs are not realistic.
- This results in need for smoother types of analyses for HTE...

3 Methods

- Describe different approaches to individualize
- Describe base-case scenario
- Describe deviations from base-case scenario
- Evaluation methods
  - Evaluation is performed on validation dataset
  - Metrics description

4 Results

4.1 Simulation results

4.2 GUSTO trial results

5 Discussion

6 Figures and Tables

- 6 in total (both figures **and** tables)