Establishing An Optimal Individualized Treatment Rule for Pediatric Anxiety with Longitudinal Modeling for Evaluation

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Background

An **Individualized Treatment Rule (ITR)** is a special case of dynamic treatment regimen when there is a single decision rule. This rule inputs information about a patient and recommends a treatment based on this information.
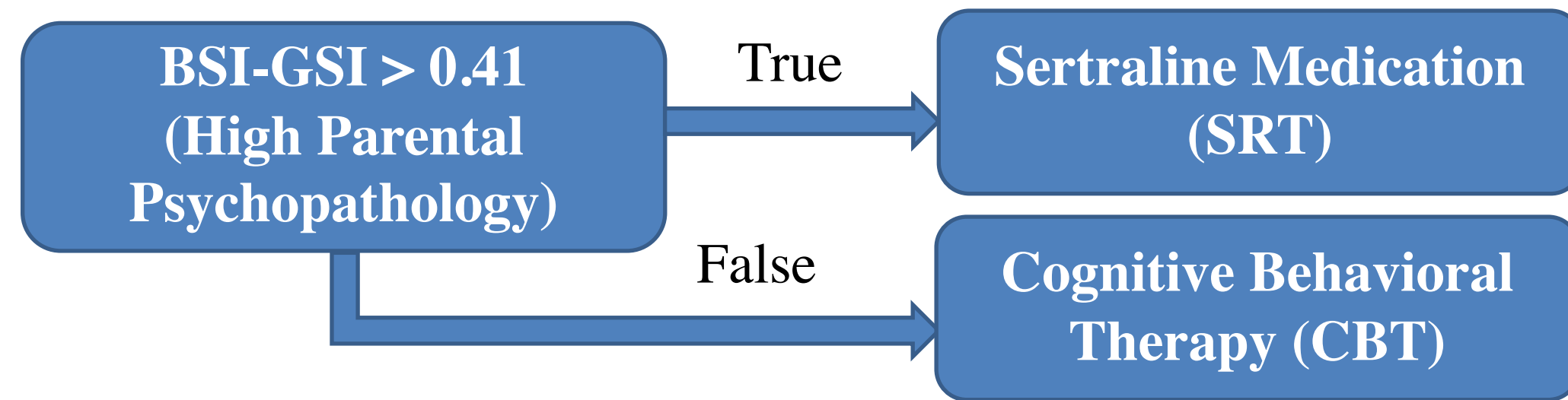
Figure 1. An example Individualized Treatment Rule for Child Anxiety

Figure 1 shows an example of ITR to guide the decision between medication (SRT) vs therapy (CBT). BSI-GSI measures the psychopathology of the child's parent; it is collected shortly after the child's anxiety diagnosis. High values of BSI-GSI means the parent reports having greater psychological problems. This ITR recommends treating the child with SRT if BSI-GSI>0.41 (high parent psychopathology); otherwise, it recommends CBT.

Child/Adolescent Anxiety Multimodal Study (CAMS) is a completed federally-funded, multi-site, randomized placebo-controlled trial that examined the efficacy of Sertraline Medication (SRT), Cognitive Behavior Therapy (CBT), and their combination (COMB) against pill placebo (PBO) for the treatment of separation anxiety disorder (SAD), generalized anxiety disorder (GAD) and social phobia (SOP) in children and adolescents.

- Randomized N = 488 youth with anxiety disorder, ages 7-17
- 4-arm trial: CBT(139), SRT(133), COMB (140), PBO (76)
- Well-characterized sample, with over 67 baseline covariates
- The primary outcome is the Pediatric Anxiety Rating Scale (PARS), a continuous measure of anxiety symptoms, at the end of 12 weeks
- Conclusion: COMB is the most effective treatment compared with SRT and CBT

Research Objective

Since patients vary in baseline features and COMB is expensive in real-world clinical trials, we aim to construct and evaluate an interpretable, parsimonious, and cost-saving Individualized Treatment Rule. Our ITR guides clinicians on deciding personalized treatment plans between SRT versus CBT for patients with pediatric anxiety disorders. The optimal ITR maximizes the difference in magnitude between PARS at week 12 and PARS at week 0, on average.

Methods

We proposed a four-step analytic strategy:

Step 1. Split the data for training (70%) and evaluation (30%)
- Ensure the two datasets are balanced by treatment assignment (CBT vs SRT) and baseline severity level (baseline PARS)

Step 2. Prune the 67 baseline covariates based on their potential for a qualitative interaction with treatment (score U_j), using a specialized variable screening algorithm for subset analysis with the training dataset (Gunter, et al. 2011)
- Let $A = \{0, 1\}$ denote treatment; let R denote the outcome (PARS); let $a^* = argmax_a \hat{E}[R|A = a]$ be the best treatment on average
- For each covariate X_j calculate the score U_j:

$$D_j = (\max_{0 \leq i \leq n}(\hat{E}[R|X_j = x_{ij}, A = a^*] - \hat{E}[R|X_j = x_{ij}, A \neq a^*]))$$

$$- (\min_{0 \leq i \leq n}(\hat{E}[R|X_j = x_{ij}, A = a^*] - \hat{E}[R|X_j = x_{ij}, A \neq a^*]))$$

$$P_j = \frac{1}{n}\sum_{i=1}^{n} 1\{\arg\max_a \hat{E}[R \mid X_j = x_{ij}, A = a^*] \neq a^*\}$$

$$U_j = (\frac{D_j - \min_{1 \leq k \leq p} D_k}{\max_{1 \leq k \leq p} D_k - \min_{1 \leq k \leq p} D_k})(\frac{P_j - \min_{1 \leq k \leq p} P_k}{\max_{1 \leq k \leq p} P - \min_{1 \leq k \leq p} P_k})$$

- Create a scree plot of U_j scores; select cut-off at inflection point

Step 3. Generate the optimal ITR with the screened covariates, using a data-driven approach known as "Decision List" with the training dataset (Zhang, et al. 2015)
- Used the covariates left to the green line (high potential for a qualitative interaction with treatment) in Figure 2
- Simple class of ITR based on "if-then-else" statements
- Visualizations (Figure 4) of patients' proportions recommended to CBT group versus SRT group based on ITR facilitates meaningful exchange between data scientists and clinical scientists

Step 4. Evaluate the optimal ITR vs. only providing PBO, only providing SRT, only providing CBT, and providing COMB , using longitudinal analysis with the evaluation dataset
- Estimate mean PARS (higher PARS means the child/adolescent has higher severity level in anxiety disorders) through week 0 (start of the treatment) to week 12 (end of the treatment)
- Compare the longitudinal trajectories of ITR vs. SRT, CBT, COMB

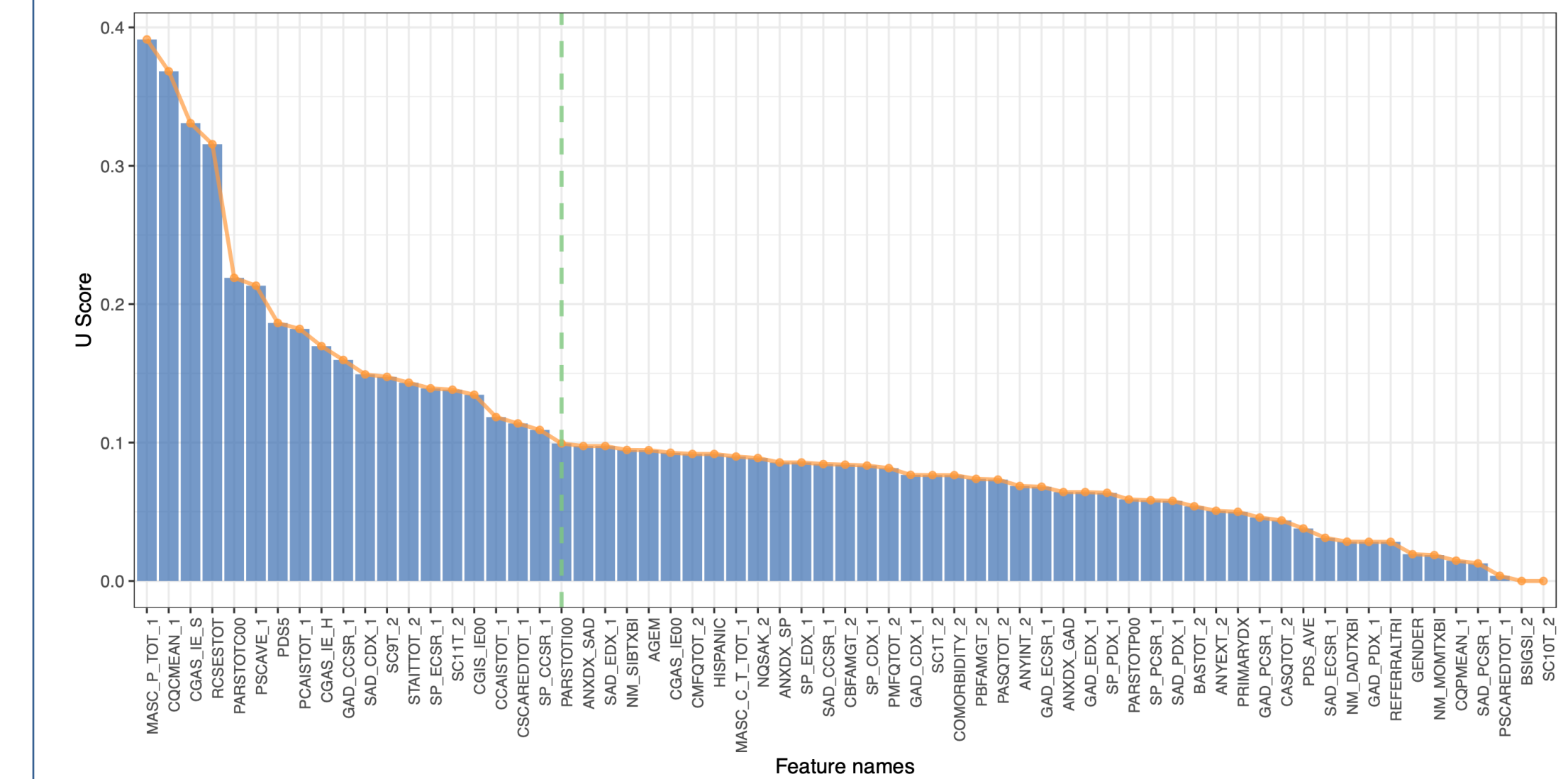## Results

Step 2. Variable screening based on score U_j

Figure 2. The scree plot for baseline covariates using U_j scores
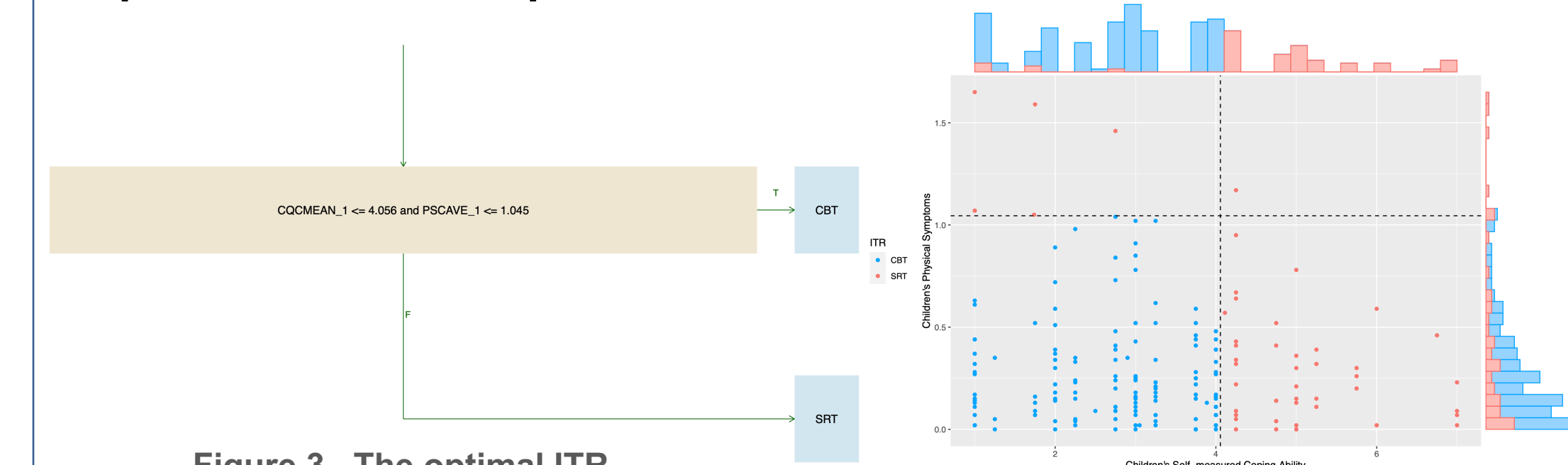
Step 3. Generate the optimal ITR

Figure 3. The optimal ITR

Figure 4. Proportion of CBT group vs. SRT group in ITR
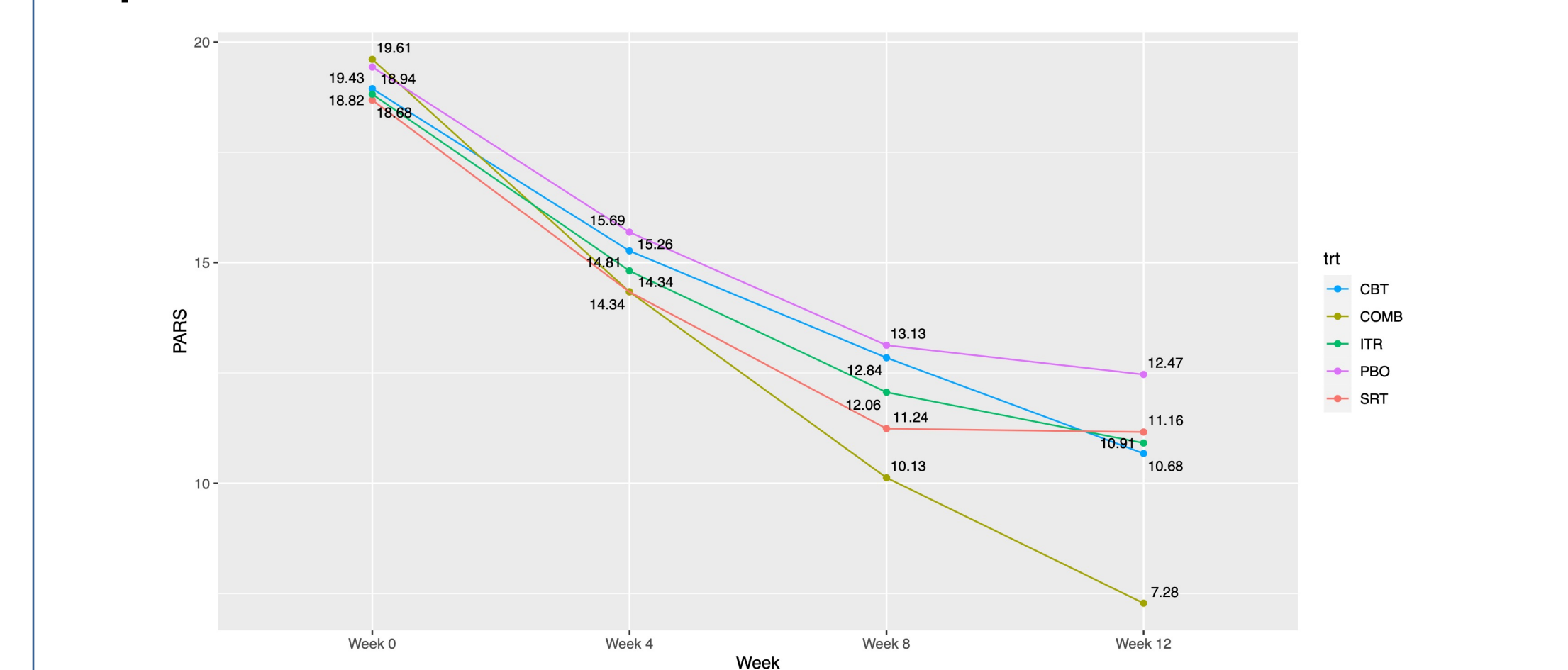
Step 4. Evaluation

Figure 5. Longitudinal trajectories of ITR vs. SRT, CBT, COMB, PBO

Discussion

The optimal ITR (Figure 3) suggests only 2 covariates are significant for customized treatment plans: 1) children's physical symptoms caused by anxiety disorder (PSCAVE_1); 2) children's self-measured coping ability for their anxiety (CQCMEAN_1). The longitudinal trajectories indicates ITR has non-inferiority pattern compared with SRT, CBT, COMB.

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References

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