

## Key Methodological Advancements

- **Current Best Practice**
  - Simultaneously model observed scores and drop-out mechanism
  - Referred to as Joint Process Model
  - Virtually no methods development for survival analysis in item response theory (IRT) framework
- **What is New**
  - Developed IRT framework for evaluating patient reported outcomes (PRO)-based scores in survival analysis context
  - Created a longitudinal IRT model that incorporates the drop-out mechanism
  - Proposed approach models the IRT scores and the drop-out mechanism simultaneously
- **Why it Matters**
  - Improved estimates of Quality of Life (QoL) in survival analysis context
  - Better recovery of treatment arm separation
  - Drop-out no longer obscures differences in QoL

## Objective

- Outcome-dependent missingness threatens the validity of inferences made from statistical analysis
- Valid modeling requires the use of statistical approaches that adjust for this type of missing data
- Many sophisticated approaches suited to this data require custom coding

## Background

- Missing QoL score can arise from several processes
- The type of missingness has implications for how data should be modeled
- Missing Completely at Random (MCAR):
  - All statistics appropriate, no assumption ever violated
  - Descriptive statistics often preferred
  - However, important to confirm data is MCAR before using descriptive statistics
- Missing at Random (MAR):
  - Descriptive statistics not appropriate
  - Use likelihood-based approaches OR multiple imputation
- Missing Not at Random (MNAR):
  - In the context of survival designs, the missingness may be outcome-dependent
  - The PRO scores will produce biased treatment efficacy estimates
  - This bias can lead to the incorrect inferences regarding efficacy across treatment arms

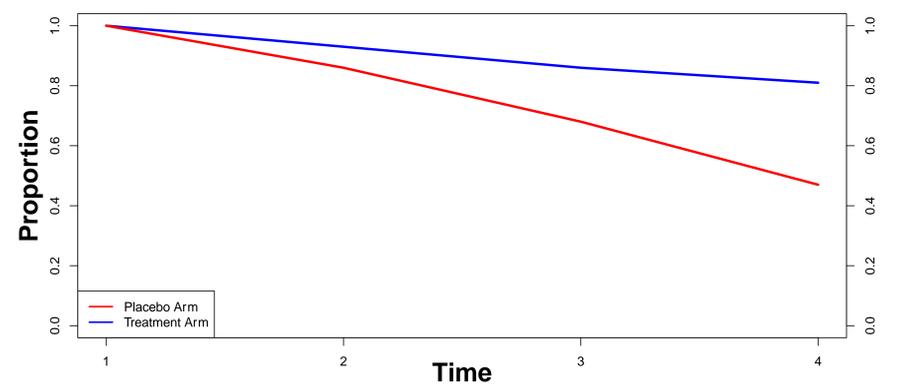
## Methods

- Re-code items to create discrete hazard function
  - Discrete hazard function models probability of subject drop-out
  - Survival item indicates, at timepoint  $t$ , whether the subject dropped out, had already dropped out, or was still in the study
- A two-parameter model (2PL) model can be used to relate QoL to probability of drop-out
- $$\int_{\theta} \prod_{t=1}^T \prod_{j=1}^J \prod_{c=1}^C P(X_{itjc} | \theta_{it}, D_{it}) P(D_{it} = 1 | \theta_{it})^{D_{it}} [1 - P(D_{it} = 1 | \theta_{it})]^{1-D_{it}} d\theta.$$
- If subject remained in the study at timepoint  $t$ :  $D_{it} = 0$ , and  $X_{itj} = c$ 
  - Both the discrete hazard function and the item response function contribute to the likelihood
- If subject dropped-out at timepoint  $t$ :  $D_{it} = 1$ , and  $X_{itj}$  is NA
  - The discrete hazard function contributes to the likelihood, but not the item response function
- If subject dropped-out at earlier timepoint: both  $D_{it}$  and  $X_{itj}$  are NA
  - Neither the discrete hazard function nor the item response function contribute to the likelihood

## Simulation Study with MNAR data

- A simulation study based on empirical PRO data is employed here to illustrate the advantages of such an approach (**Figure 1**)
- MNAR drop-out via discrete hazard function
- 5 items, 4 timepoints
- Implemented in commercially available IRT software (i.e., FlexMIRT)

Figure 1. Survival Rate Among Patients in MNAR Simulation



## Results – Simulation Study

- The results of the simulation study illustrate the utility of the proposed method
- In **Figure 2**, a longitudinal IRT model that ignores drop-out fails to detect separation
- In **Figure 3**, the proposed IRT model to jointly model QoL scores and drop-out allows for the accurate estimation of separation of the treatment arms

Figure 2. Unadjusted Model of Change in Quality of Life Over Time

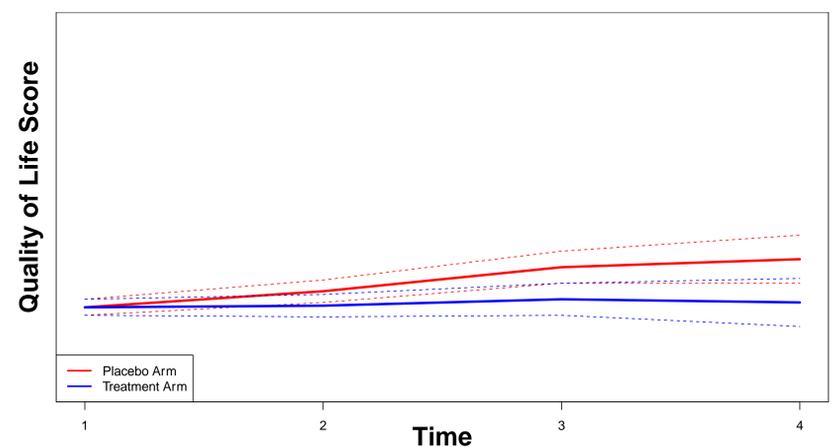
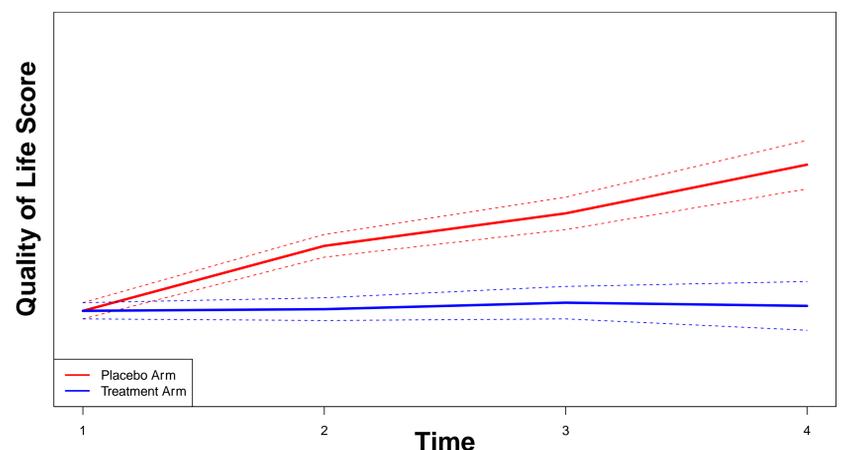


Figure 3. Proposed Model of Change in Quality of Life Over Time



## Additional Simulation Study with MCAR Data

- Simulation study was repeated with MCAR data
- Estimated parameters of discrete hazard function are  $\approx 0$
- Proposed approach identifies MCAR data

## Conclusions

- An IRT-based method has been developed that can better estimate the treatment effect in a survival analysis context
- Method can also identify MCAR data
- This approach can be implemented in standard commercial IRT software

