Meaningful Within-Patient Change for Patient-Reported Outcome Measures: Model-Based Approach Versus Cumulative Distribution Functions

Jinma Ren, Andrew Bushmakin, Paul Cislo, Joseph C. Cappelleri

Statistical Research & Data Science Center, Pfizer Inc.

Introduction

- From a regulatory standpoint, FDA is more interested in what constitute a meaningful within-patient change (MWPC) in scores from the patient perspective, which has been updated in the recent FDA Patient-Reported Outcome (PRO) Guidance in 2018.[1]
- The FDA recommends the use of anchor-based methods supplemented by empirical cumulative distribution function (eCDF) curves to establish a MWPC for PRO measures.
- In practice, the estimates obtained from anchor-regression and anchor-eCDF approaches may not closely align.
- This phenomenon has appeared in our real-life data with repeated PRO measures and another study in the literature.[2][3]
- To help interpret their results, we investigated and compared these approaches.

Methods

- ***Study design & data source***
  - Both repeated measure linear regression model (RMM, the anchor-regression method) and anchor-eCDF approaches were used to estimate a MWPC on a target PRO measure.
  - An empirical dataset and a simulated dataset were used including 500 patients with up to 6 visits per patient, target PRO (range 0 to 10), and an anchor measure on patient global impression of change (PGIC) from 1 (much better) to 5 (much worse).
  - The simulated dataset was same with empirical dataset expect for the target PRO measures generated by multivariate normal distribution for each level of anchor change.
- ***Anchor-regression methods***
  - In the RMM model, the change of PRO scores from baseline was treated as the dependent variable (outcome), the change of anchor PGIC scores from baseline was set as the independent variable (predictor), and an unstructured covariance matrix was used to cope with the repeated measures.
  - The change of PGIC was set as both categorical and continuous variables in the model, separately.
- ***Anchor-eCDF methods***
  - eCDF-derived medians by each visit and the median of them (eCDF_median_visit) were calculated.
  - We also calculated the mean of eCDF-derived means by each visit (eCDF_mean_visit) for the purpose of sensitivity analysis.
- ***Bootstrapping***
  - We applied bootstrapping (1000 iterations) to estimate the mean and 95% confidence interval of MWPC for both anchor-regression and anchor-eCDF methods in both datasets.

Results

- **The distribution of the PRO score changes affected the degree of concordance between anchor-regression and anchor-eCDF estimates.**
  - The estimates of MWPC in the empirical dataset were obviously different between RMM and anchor-eCDF approaches. ***[Figure 1A, Figure 2A & 2B]***
  - The estimates of MWPC in the simulated dataset tended to be concordant between RMM and anchor-eCDF approaches. ***[Figure 1B, Figure 2C & 2D]***
  - This phenomenon was confirmed in the bootstrapping samples. ***[Figure 3A & 3B]***
- **Anchor-regression estimates were more robust than anchor-eCDF estimates.** ***[Figure 3A & 3B]***
  - The confidence intervals of anchor-eCDF estimates were much wider than those of RMM estimates.
  - The anchor-eCDF estimates varied noticeably across visits.

Figure 1. **Estimates of within-patient change in target PRO by anchor-regression and anchor-eCDF approaches**

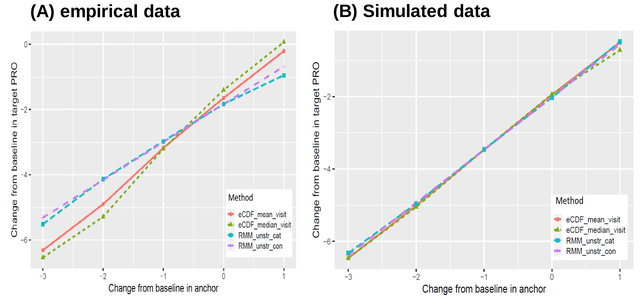


Figure 2. eCDF/ePDF curves of target PRO change from baseline by anchor change

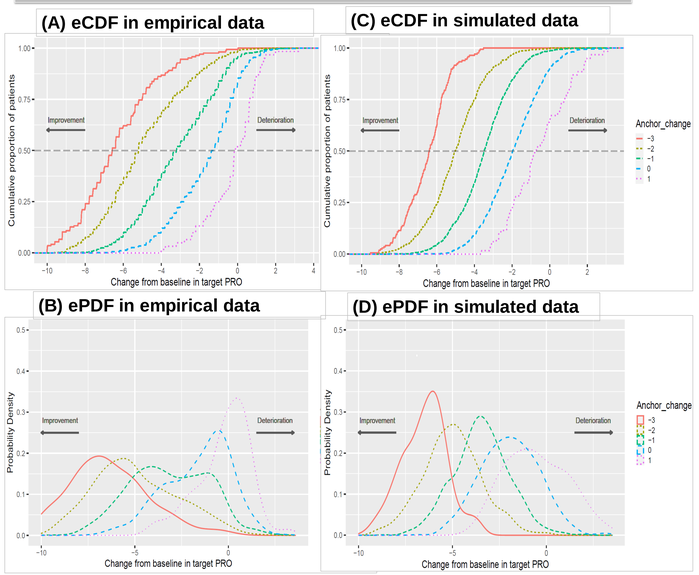
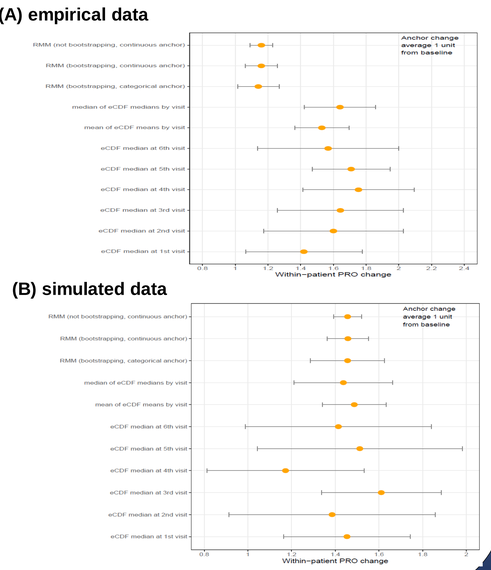


Figure 3. WMPC **in target PRO given one-level anchor change (bootstrapping and parametric model results)**



Conclusions

- **The estimates of MWPC between anchor-regression and anchor-eCDF methods may not necessarily align in practice.**
- **The difference between anchor-regression and anchor-eCDF estimates for MWPC could be explained by the fact that, unlike the eCDF-derived median, the RMM-derived mean considers all available measurements across time.**
- **The anchor-regression methods demonstrated more robust (narrower confidence interval) despite the skewness of distribution of PRO data compared to the anchor-eCDF methods.**
- **We recommend that the anchor-regression approach be given preference over the anchor-eCDF approach.**

Limitations

- This study did not explore other scenarios, such as small sample sizes and varying number of visits, which can be explored in future research.
- We only generated normally distributed PRO scores in the simulated dataset.
- Future studies might investigate other circumstances when the within-patient PRO change is not normally distributed (e.g. gamma). Based upon what we have learned from this study, the PRO change with a skewed distribution can lead to a noticeably different estimate of MWPC between anchor-regression and anchor-eCDF (especially eCDF-derived median) methods.
- More iterations will certainly help to improve the precision of sampling distribution and narrow the width of confidence interval of WMPC estimates.

Reference

1. FDA, Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims, in Guidance for Industry. 2009, US. Food & Drug Administration.
2. Meaningful within-patient change in WOMAC domains in patients with moderate-to-severe osteoarthritis. Conaghan PG, Dworkin RH, Schnitzer TJ, Berenbaum F, Bushmakin AG, Cappelleri JC, Viktrup L, Abraham L. Poster presentation at the American College of Rheumatology Convergence 2020: The ACR's All-Virtual Annual Scientific Meeting, November 5-9, 2021.
3. Speck, R.M., et al., Psychometric validation and meaningful within-patient change of the Migraine-Specific Quality of Life questionnaire version 2.1 electronic patient-reported outcome in patients with episodic and chronic migraine. Headache, 2021. 61(3): p. 511-526.

The American Statistical Association (ASA) Biopharmaceutical Section Regulatory-Industry Statistics Virtual Workshop (September 21-23, 2021)