SAFE TO ASSUME?
UNPACKING REGRESSION ASSUMPTIONS FOR UTILITY DATA

Brittany Humphries[1], Andre Verhoek[2], Angeliki Kaproulia[2], Gabriel Tremblay[1], Bart Heeg[2]
[1]Cytel, Toronto, Canada; [2]Cytel, Rotterdam, Netherlands

MSR139

INTRODUCTION

- Health-related quality-of-life, often reported as utility scores, is an important endpoint in the evaluation of healthcare interventions.
- Yet the analysis of utility data is complicated by its distributional properties (**Table 1**), which raise statistical challenges.[1]
- A review of utility values submitted for NICE cancer medicine appraisals found that, in cases where a submission was rejected because of EQ-5D utility data, the reason was generally related to inappropriate data adjustment, not data reliability.[2]

OBJECTIVE

- As there is no consensus on the most appropriate regression for analyzing utility data, our objective was to develop a framework to evaluate common regression methods.

METHODS

- We reviewed electronic databases (e.g., PubMed) and websites of HTA agencies to identify the most used regression approaches for analyzing utility data.[1,3-11]
- A conceptual framework was then created to illustrate the ability of each regression model to handle the unique distributional features of utility data (i.e., skewed, multimodal, bounded, heteroscedastic, time dependent, with individual or group effects).
- Using this framework, we examined the strengths and limitations of each approach.

RESULTS

- Conventional methods, such as ordinary least squares regression, are widely used to analyze utility data despite violation of key assumptions surrounding normality and independence (**Figure 1**).
- Some regression assumptions are more robust to violation (e.g., normality of observations) while others are managed at the study design-level (e.g., independence of observations).
- While there are advantages in using more complex models, such as mixed effects models, this comes at the cost of untestable assumptions.
- When selecting a regression approach, ensuring a balance between feasibility, interpretability and statistical correctness is critical.

IMPLICATIONS

- Health technology assessment is a process of making statistical inference from clinical, health-related quality of life, and economic data so that decision-makers can assess the value of new technologies.
- Inappropriate statistical analysis can result in unreliable estimates of cost-effectiveness that fail to provide accurate and robust information to inform resource allocation decisions.
- This framework provides an overview of the ability of common regression models to analyze utility data, with the aim of supporting evidence-based decision-making.

For more information, please contact

Gabriel Tremblay at gabriel.tremblay@cytel.com

Disclosures

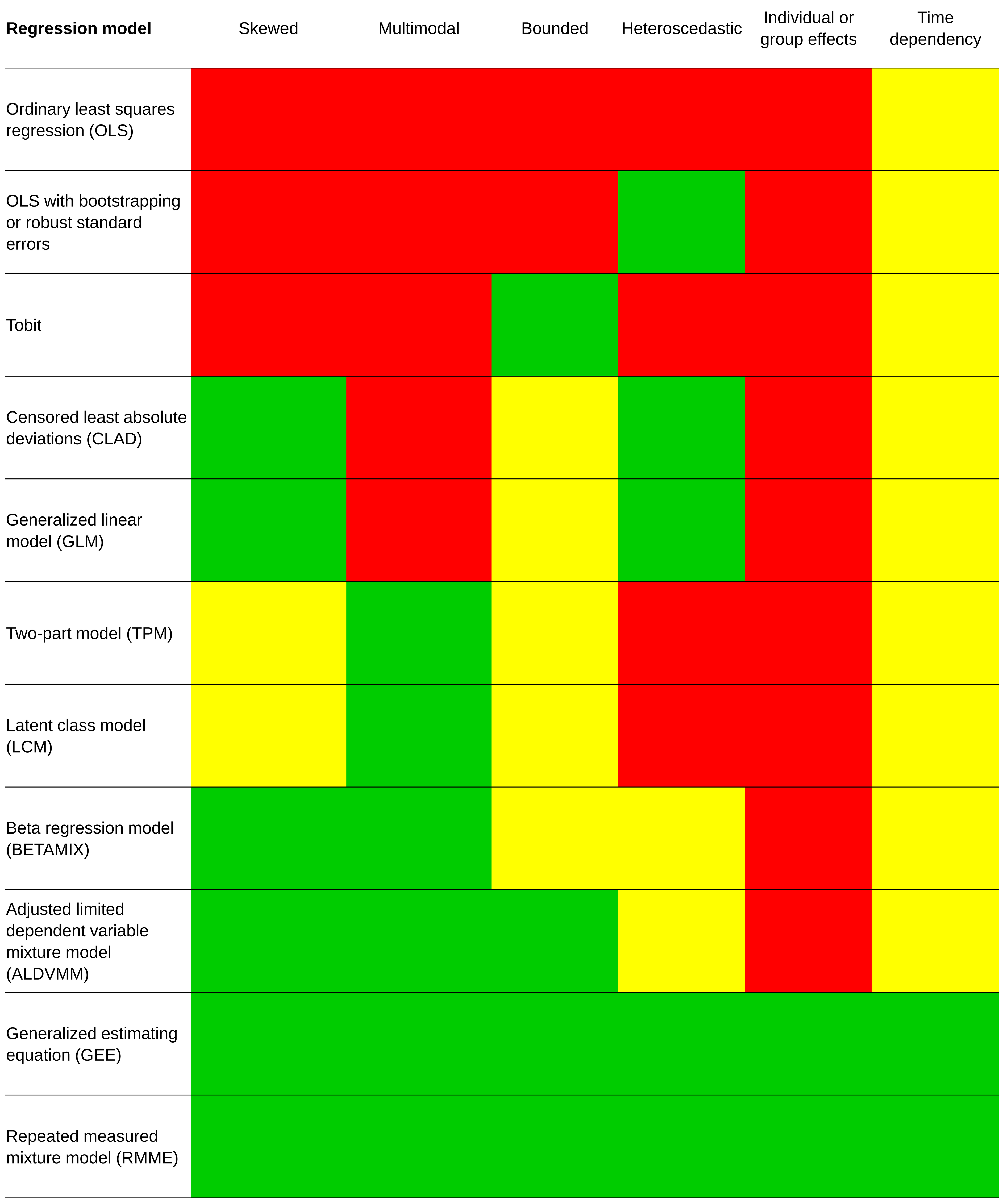
This study was investigator-initiated and received no funding.

Table 1. Key features of utility data

Skewed	Often left skewed if population is very healthy because most patients will have a utility score near 1. Can also be right skewed if population being studied is very sick
Multimodal	Data can be multimodal if there are sick patients or other types of latent subgroups that influence utility. For example, if group 1 has a low pain threshold and group 2 has a high threshold, this would create multi-modality through different scoring on the pain domain of the EQ-5D
Bounded	Scores range from −0.59 (worse than death) to 1.00 (perfect health)*
Heteroscedastic	Error terms are unlikely to be identically distributed because individuals with higher utility scores also tend to have scores that are less variable
Individual or group effect	If data is clustered (e.g., neighborhood or practitioner is the unit of randomization in a trial) observations will not be independent
Time dependency	If the data is longitudinal (i.e., utility is measured at baseline and follow-up) observations will not be independent

** Lower bound depends on method of valuation*

Figure 1. Ability of regression models to handle key features of utility data



Legend: Red = regression model cannot handle feature; Yellow = regression model can partially handle feature; Green = regression model can handle feature

References

1. Pullenayegum EM, Tarride JE, Xie F, Goeree R, Gerstein HC, O'Reilly D. Analysis of health utility data when some subjects attain the upper bound of 1: are Tobit and CLAD models appropriate? Value Health. 2010 Jun-Jul;13(4):487-94. doi: 10.1111/j.1524-4733.2010.00695.x.
2. Takada S, Narukawa M. Acceptability of Manufacturer-Proposed Utility Values for NICE Cancer Medicine Appraisals: Analysis of Manufacturers' Information Sources. Int J Technol Assess Health Care. 2022 Mar 17;38(1):e25. doi: 10.1017/S0266462322000149. PMID: 35297362.
3. Wolowacz SE, Briggs A, Belozeroff V, Clarke P, Doward L, Goeree R, Lloyd A, Norman R. Estimating Health-State Utility for Economic Models in Clinical Studies: An ISPOR Good Research Practices Task Force Report. Value Health. 2016 Sep-Oct;19(6):704-719. doi: 10.1016/j.jval.2016.06.001.
4. Hernández Alava M, Wailoo A, Pudney S, et al. Mapping clinical outcomes to generic preference-based outcome measures: development and comparison of methods. Southampton (UK): NIHR Journals Library; 2020 Jun. (Health Technology Assessment, No. 24.34.)
5. Qian Y, Walters SJ, Jacques R, et al Comprehensive review of statistical methods for analysing patient-reported outcomes (PROs) used as primary outcomes in randomised controlled trials (RCTs) published by the UK's Health Technology Assessment (HTA) journal (1997–2020) BMJ Open 2021;11:e051673. doi: 10.1136/bmjopen-2021-051673
6. Monica Hernandez Alava & Allan Wailoo, 2015. "Fitting adjusted limited dependent variable mixture models to EQ-5D," Stata Journal, StataCorp LP, vol. 15(3), pages 737-750, September.
7. Mark Pletscher. Adjusted Limited Dependent Variable Mixture Models of HealthState Utilities in R. 2021. Available from: https://cran.r-project.org/web/packages/aldvmm/vignettes/aldvmm_vignette.pdf
8. Shen, Chung-Wei, and Yi-Hau Chen. "Model Selection for Generalized Estimating Equations Accommodating Dropout Missingness." Biometrics, vol. 68, no. 4, 2012, pp. 1046–54. JSTOR, http://www.jstor.org/stable/41806023. Accessed 19 Sep. 2022.
9. Zeger, S. L., Liang, K.-Y., & Albert, P. S. (1988). Models for Longitudinal Data: A Generalized Estimating Equation Approach. Biometrics, 44(4), 1049–1060. https://doi.org/10.2307/2531734
10. Clark, D.R., & Thayer, C.A. (2004). A Primer on the Exponential Family of Distributions.
11. Arabmazar, A., & Schmidt, P. (1982). An Investigation of the Robustness of the Tobit Estimator to Non-Normality. Econometrica, 50(4), 1055–1063. https://doi.org/10.2307/1912776