Value-Based Assessment of Clinical Trial Outcomes: A Hypothetical Example Using the Childhood Autism Rating Scale in Autism Spectrum Disorder

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INTRODUCTION

- In childhood autism spectrum disorder (ASD), the Childhood Autism Rating Scale—2nd edition (CARS2) instrument is used to assess severity and change.[1]
- We previously conducted a discrete choice experiment (DCE) with 563 caregivers from 5 European countries using the standard version of the CARS2, i.e., the CARS2-ST.[2,3]
  - Caregivers were asked to proxy-report preferences for CARS2 health state profiles on behalf of children and adolescents with ASD.
  - For the purpose of the DCE, 2 items were removed from the CARS2-ST system* (Level & Consistency of Intellectual Response and General Impressions). The first was considered to be non-modifiable and the second would lead to double counting.
- This study enabled an assessment of latent utility for CARS2-ST profiles. We use latent utility scores directly from a multinomial logit model, which were not re-scaled on the 0 = dead, 1 = perfect health scale. Hereafter, we refer to latent utility as "utility."

OBJECTIVES

- This research explores the application of proxy patient preferences, as estimated by a DCE, to hypothetical clinical trial results in childhood ASD as measured by (between-group) changes from baseline.
- We sought to understand the variation in benefit, i.e., in added utility, that can arise as a result of different sources of CARS2-ST score improvements.

METHODS

Analysis 1: Hypothetical Individual with ASD

- We first explored the impact of a 3-point improvement in CARS2-ST score for 2 hypothetical individuals, one with "mild to moderate" and the other with "severe" ASD.
  - Schopler et al. 2010 produced a diagnostic categorization system where total scores of 30 or above indicate that an individual is "autistic." This is subdivided into "mild to moderate autism" (30 to 36.5) or "severe autism" (37 to 60).[1]
  - Since our DCE excluded 2 of the 15 CARS2 items, the category thresholds were rescaled accordingly. Using the mid points of the categories, the rescaled scores for "mild to moderate" and "severe" were 29 and 42, respectively.
- Two scenarios were considered in this analysis:
  1. A 3-point CARS2 score improvement is derived from the 6 CARS2 items associated with the greatest preference weights as estimated by the DCE.
  2. A 3-point CARS2 score improvement is derived from the 6 CARS2 items associated with the lowest preference weights as estimated by the DCE.
- Each scenario was then compared in terms of the change in utility values.

Analysis 2: Hypothetical Clinical Trial Population with ASD

- To mimic a clinical trial context, we expanded the analysis from simulating individuals to simulating a sample of 100 children and adolescents with ASD.
- The simulations were performed using R software to generate scenarios for a population with an average CARS2 baseline score of approximately 42, i.e., the "severe" autism group:
  - A 3-point CARS2 score improvement is derived randomly across all the 13 CARS2 items.
  - A 3-point CARS2 score improvement is derived from 6 CARS2 items.
  - Variation around the 3-point improvement was permitted, allowing simulated patients to improve to greater and lesser degrees. We also assumed it was possible to experience an increased CARS2 score, i.e., worsening.
- Using the simulated data, we created 3 scenarios:
  1. The population has a randomly distributed improvement across all 13 items.
  2. The population has improvement in the 6 attributes with the greatest preference weights as estimated by the DCE.
  3. The population has improvement in the 6 attributes with the lowest preference weights as estimated by the DCE.
- Each of the 3 scenarios was compared in terms of the change in utility values with a linear regression fitted to the simulated data. The intercept was anchored at zero since no change in CARS2 scores is not expected to impact utility.

RESULTS

Analysis 1

- Table 1 shows that a substantially greater percentage increase in utility is achieved when the source of CARS2 improvement is derived from the 6 attributes with the greatest preference weights compared with those with the lowest 6 attributes.
- For the individual with mild to moderate ASD, the difference was 16.41 percentage points across the 2 scenarios. The magnitude was similar but slightly higher for the individual with severe ASD at 17.75 percentage points.

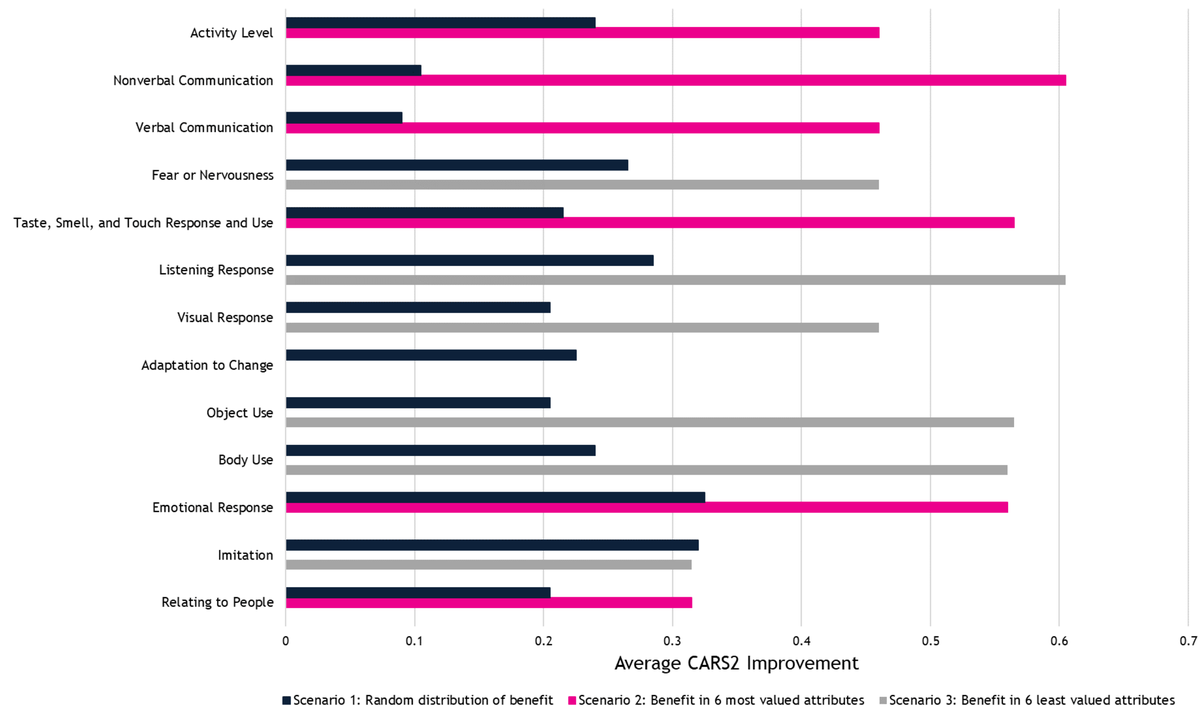
Table 1. Analysis 1: Hypothetical Individual Improvement in Utility Scores

	Baseline Utility	Follow-up Utility	Percentage Change in Utility
Individual with mild to moderate ASD			
CARS2 utility derived from 6 items with greatest preference weights	-2.234	-1.598	28.46%
CARS2 utility derived from 6 items with lowest preference weights	-2.234	-1.965	12.05%
Individual with severe ASD			
CARS2 utility derived from 6 items with greatest preference weights	-4.317	-3.218	25.44%
CARS2 utility derived from 6 items with lowest preference weights	-4.317	-3.985	7.69%

Analysis 2

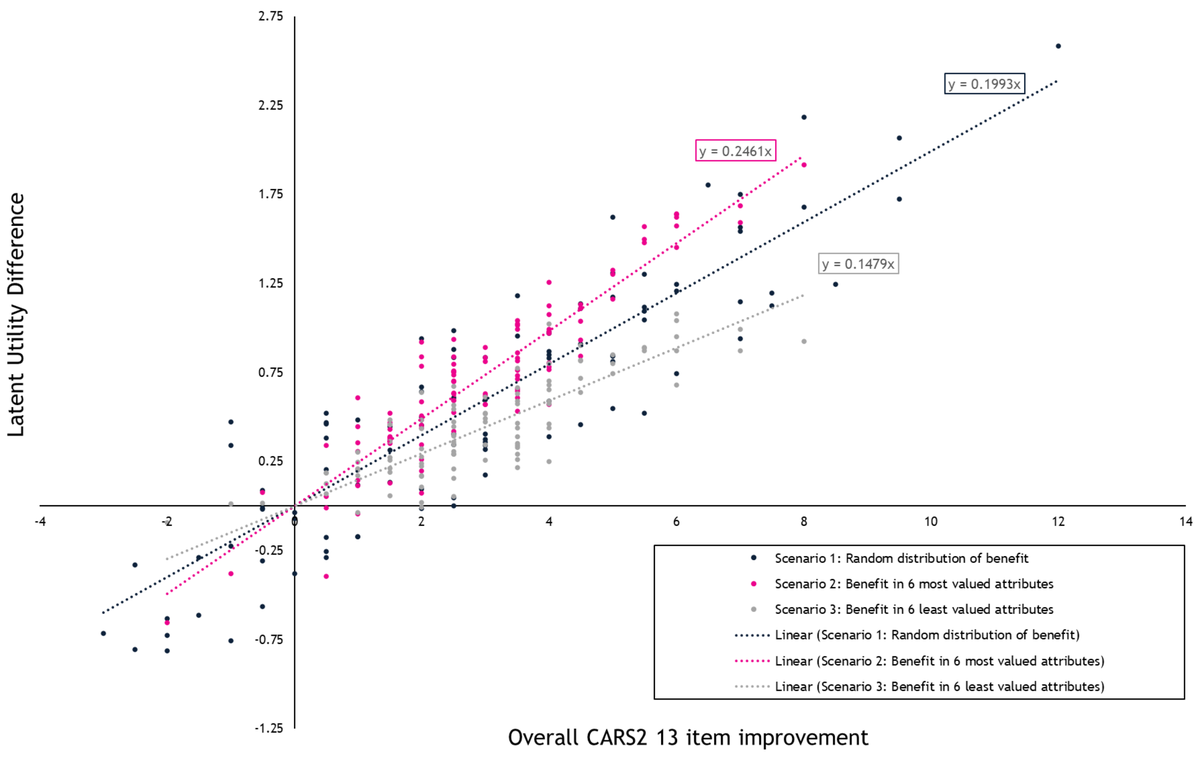
- Figure 1 shows the average CARS2 score improvements in each of the 13 attributes under the 3 scenarios. Under scenarios 2 and 3, changes in CARS2 score were restricted to 6 attributes.

Figure 1. Analysis 2: Average CARS2 Score Improvement by Attribute



- Figure 2 illustrates the variation in utility score improvement when derived from the 3 scenarios. Each scatter point represents a simulated child or adolescent with ASD. The gradient of each line shows the increase in utility from a 1-point increase in the overall CARS2 score.
  - Under the scenario where a 3-point CARS2 score improvement was permitted across all the 13 items, we see a gradient of 0.1993.
  - Under the scenario where a 3-point CARS2 score improvement was restricted to the attributes with the lowest preference weights, we see the lowest gradient of 0.1479.
  - Under the scenario where a 3-point CARS2 score improvement was restricted to the attributes with highest preference weights, we see the highest gradient of 0.2461.
- Within the simulations, a small proportion of children experienced CARS2 worsening. This was more prominent in the sample with random improvement, given that fewer restrictions were imposed.

Figure 2. Analysis 2: Hypothetical Clinical Trial Population with ASD



CONCLUSIONS

- The assessment of clinical trial measures should, where possible, account for the preferences of relevant groups, e.g., patients, caregivers, and clinicians.
- Within this analysis, scenarios varying the source of CARS2 improvement led to substantially different impacts upon the utility of a patient or group of patients.
  - Depending on the initial categorization of ASD—e.g., "mild to moderate" or "severe"—different magnitudes of impact were observed which can be attributed to the specific DCE results.
- Conclusions made from non–preference-based scoring alone can hide meaningful information on how a treatment will affect a patient's health-related quality of life.

REFERENCES

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