Patient-reported outcomes in multiple sclerosis clinical trials: Measurement lessons from the EXPAND study

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Topic: 13: Patient reported outcomes

Abstract text: **Introduction:** The phase 3 EXPAND trial (n=1651) demonstrated that siponimod delayed progression in people with secondary progressive multiple sclerosis (MS). Patient-reported outcomes (PROs) quantified subjective experiences. PROs have unique properties and performance requirements influencing results

Aim: To examine EXPAND PRO properties, and their implications for clinical trial results, using modern (Rasch model) and classical test theory methods

Method: For MSWS-12, we studied the impact on change scores of the somewhat skewed baseline (BL) score distribution (mean 1.39 logits; floor effect 5.1%) in the context of the PROs restricted measurement range

For MSWS-12 and MSIS-29 physical, we investigated the presence, magnitude and effect on change scores of response dependence; the extent to which post-BL PRO item responses depend on BL PRO item responses. For EQ-5D, we assessed performance characteristics for evaluating cost-effectiveness.

Results: For MSWS-12**,** the mean change in all placebo participants at 18 months (n=250) was 0.6 logits. However, the mean change (1.048 logits; n=55) in less disabled participants (MSWS-12 BL score range=1-21) was 13 times the mean change (0.081 logits; n=101) in more disabled participants (MSWS-12 BL score range=32-42) where the measurement range is more constrained

For MSWS-12 and MSIS-29 physical, response dependence was identified and quantified. When accounted for, response dependence had underestimated change measurement by up to 25%

For EQ-5D, only 29% of 243 possible EQ-5D health profiles were observed. Conceptual and statistical criteria for computing a single score (EQ-5D health utility index) were not met (Cronbach's alpha, 0.61; first principal component explained 40%; person separation index, 0.56). EQ-5D item-scored health status correlated only 0.40 with EQ-5D thermometer-scored health status (16% shared variance). EQ-5D item scores remained unchanged in up to 93.5% of patients, when there was change in other related PROs. Results question EQ-5D's validity and responsiveness

Conclusions: All measurement issues demonstrated cause Type II error. These can underestimate treatment effects, differences between groups and cost-effectiveness. Lessons for future trials include: carefully match PRO scale range and BL sample score distribution to enhance change measurement; use methods that identify, quantify and account for response dependence; the EQ-5D is a suboptimal health utility measure for this population

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