

Incorporation of Treatment Preferences to Endpoint Selection

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Case Study: Fragile X Syndrome

- Fragile X syndrome (FXS) is the most common inherited form of intellectual disability, occurring in approximately
 - 1 of every 4000 males (moderate to severe disability)
 - 1 of every 8000 females (milder) ¹
- Clinical presentation includes diverse cognitive, physical, communication, behavioral and motor manifestations in a very heterogeneous population
- Results from cytosine-guanine-guanine repeat expansions in the FMR1 gene² on the X chromosome and the subsequent disruption in FMRP expression
 - regulates the synthesis of many synaptic proteins; absence leads to abnormalities in brain development and function

Clinical Development Status

- Target identification has led to increased clinical trial execution in this population but there has been limited success; FXS remains a high unmet medical need due to few positive studies
- Methodologic issues including inadequate outcomes measures has contributed to clinical failure
 - 20 trials between 2002-2017 evaluated 7 primary endpoints using 10 different tools³
- NIH Meeting results in Working Group tasked with identifying FXS outcome measures in the domains of cognition, behavior and emotion
 - 2013 recommendations included collaborations to identify core measures, creation of a new behavior rating scale, **inclusion of input from patients or their proxies, and caregivers**⁴
 - 2017 evaluation of instruments indicated moderate quality, limited info on reliability, validity, and sensitivity to treatment; recommendation for continued development of objective measures that **reflect meaningful improvements in quality of life**⁵

Opportunity and Method to Elicit Feedback

- Caregivers of individuals with FXS provide a unique and important perspective on desired outcomes; could contribute to establishing consensus on relevant endpoints
- **CONJOINT ANALYSIS** is survey-based method for determining the relative importance (i.e., preferences) that individuals place on a defined set of disease or treatment outcomes
 - present respondents with a structured set of trade-off questions in which improvements in different disease outcomes vary systematically between treatment options. Statistical analysis of the resulting pattern of choices reveals the implicit preference weights respondents^{6,7}
 - Study to estimate the relative importance that caregivers of males with FXS place on potential outcomes
 - Examined Relative Value and Effect Size of Improvement

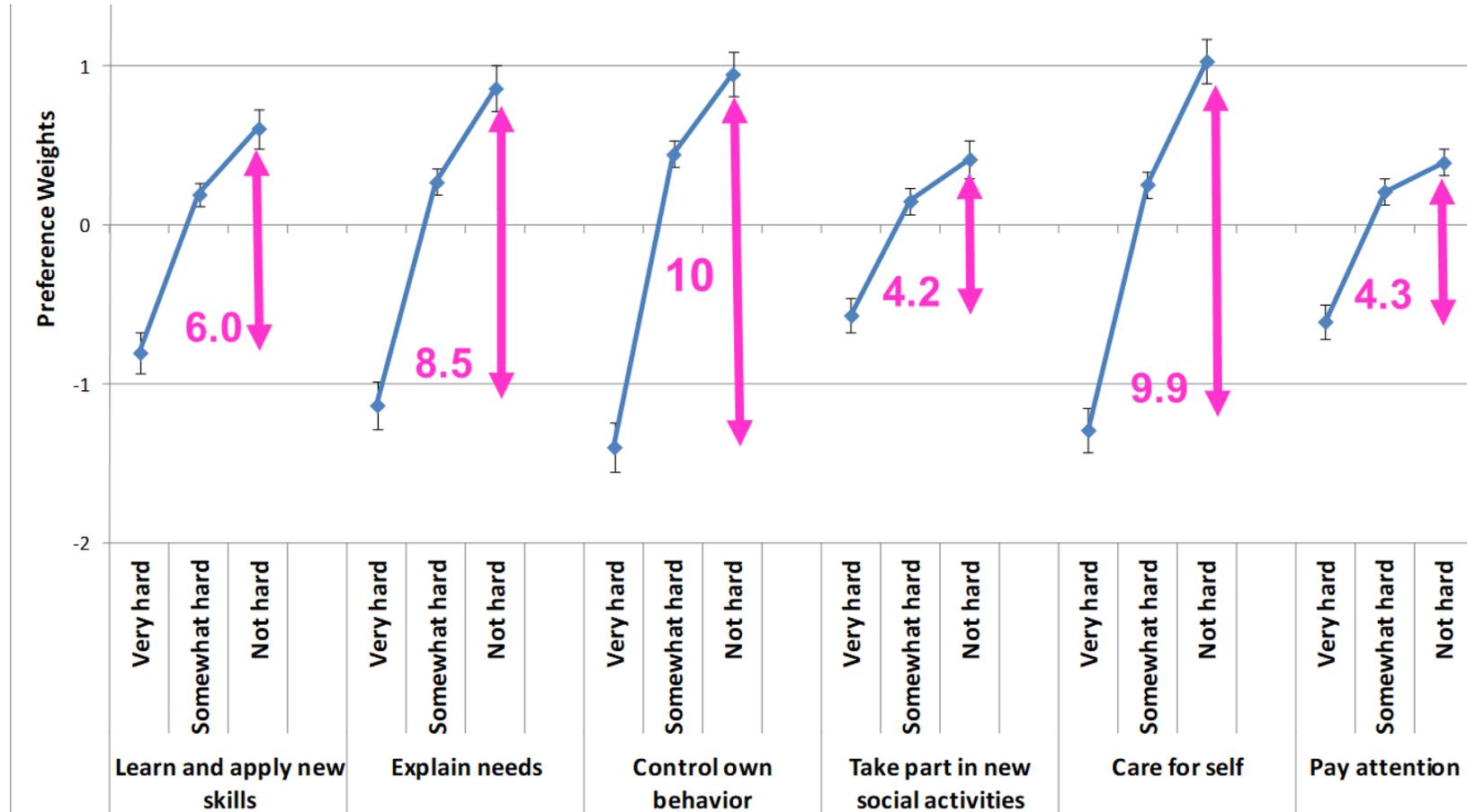
Methodology

- SURVEY CREATION, VALIDATION AND ADMINISTRATION
 - list of potential outcomes that included disease features for the discrete choice experiment was developed based on a literature review
 - importance of the top 22 potential outcomes was rated by 5 FXS experts
 - field test version of the survey was created and pretested with 15 families who had a son with FXS.
 - final version of the survey was created with 6 attributes accompanied by a short definition (LEARN, EXPLAIN, CONTROL, SOCIAL, CARE, and ATTENTION) and 3 levels of each (very hard, somewhat hard, and not hard)
 - fractional factorial experimental design with 54 trade-off questions was constructed, divided into 6 versions that were randomly assigned
 - Internal validity testing included transitivity, test-retest, and logic tests

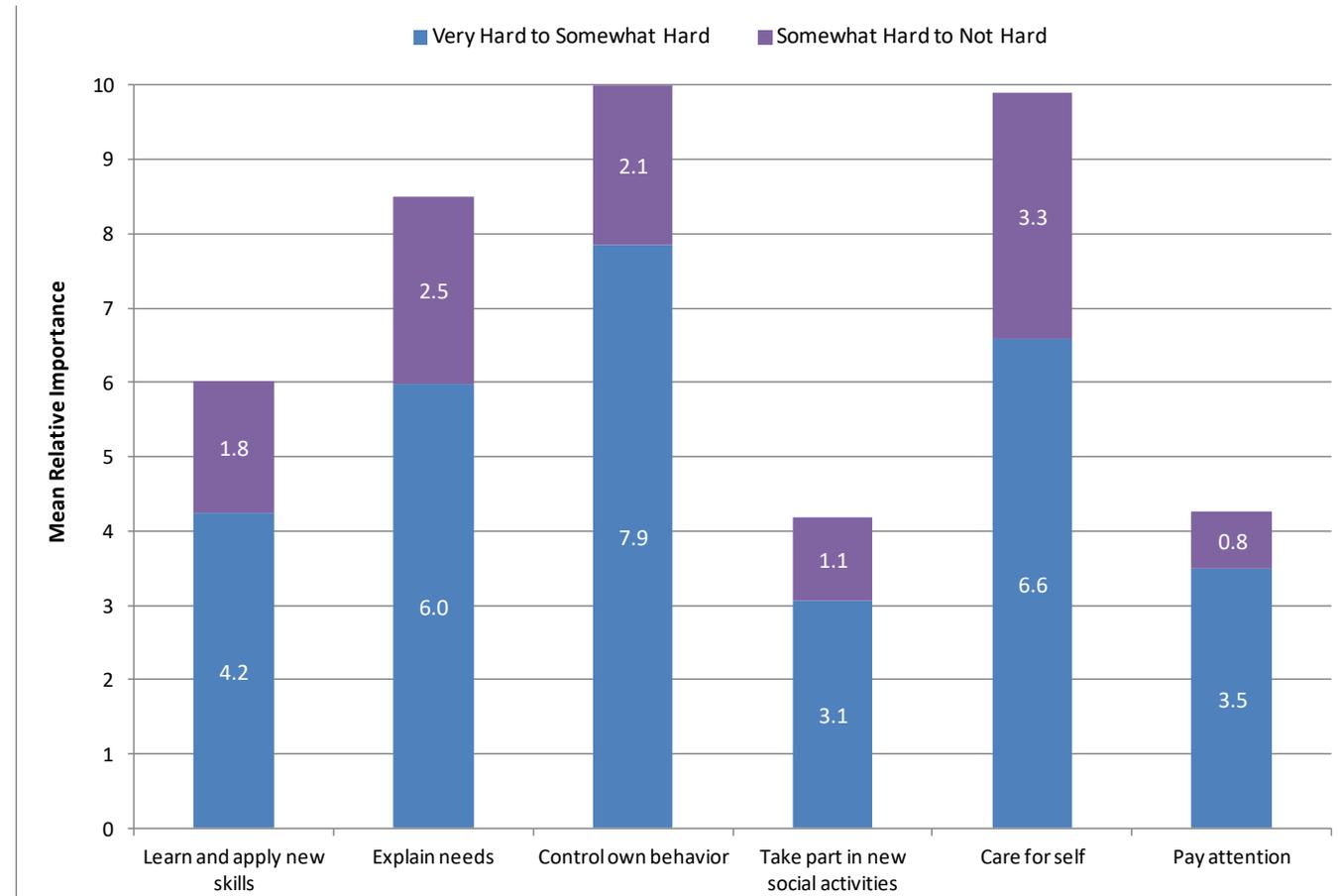
Sample Conjoint Survey Question

Thinking about Quality of Life for a Person with Fragile X		
Now we would like you to compare Medicine A and Medicine B that affect all six abilities we have described.		
1. In your opinion, which medicine would result in a better overall quality of life for a person with fragile X?		
Ability	Medicine A	Medicine B
Learn and apply new skills	Somewhat hard	
Explain needs	Very hard	Not hard
Control own behavior	Somewhat hard	Very hard
Take part in new social activities	Somewhat hard	
Care for self	Somewhat hard	Not hard
Pay attention	Somewhat hard	Very hard
Which medicine do you think would result in the better quality of life?	<input type="checkbox"/>	<input type="checkbox"/>

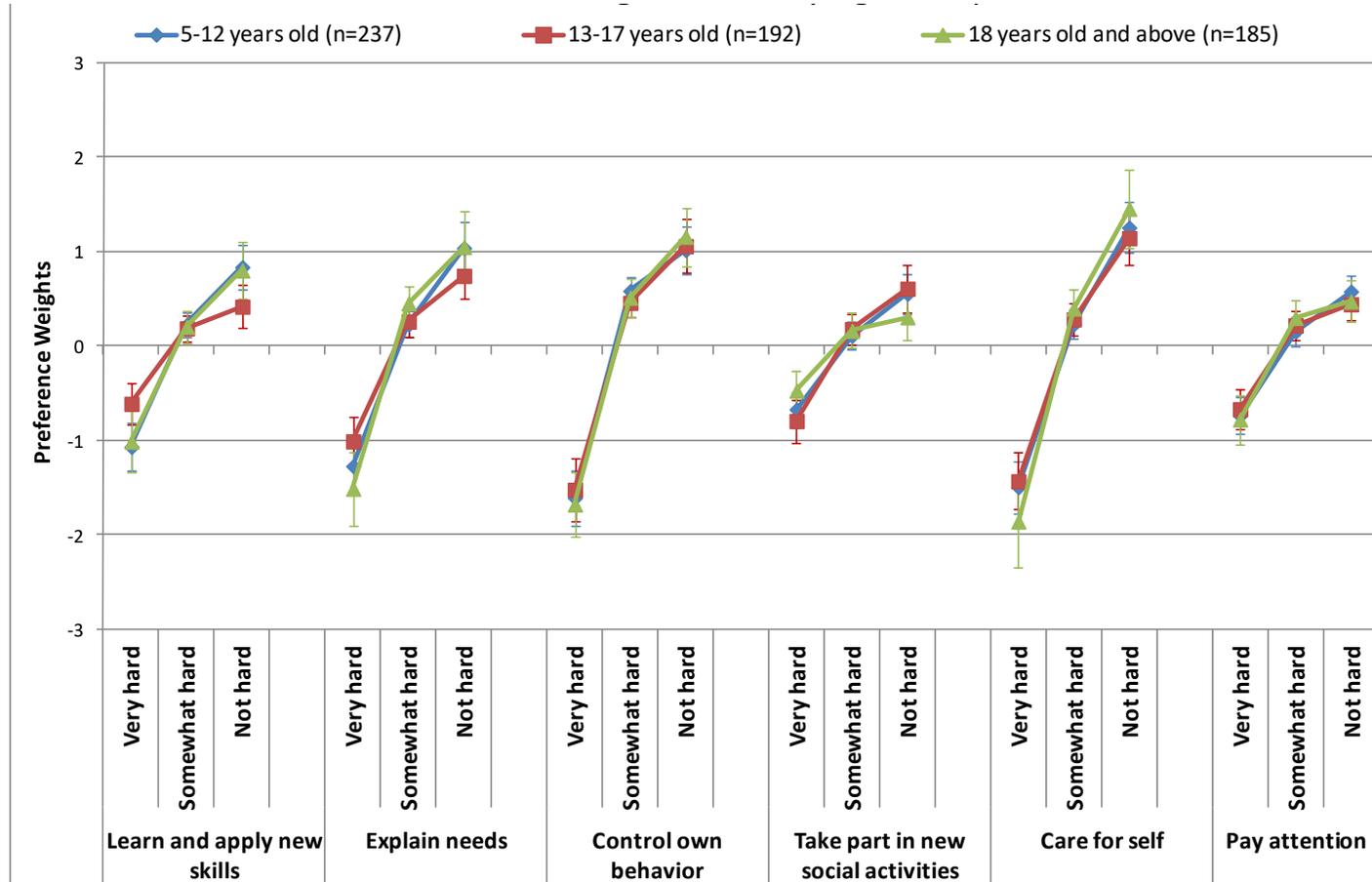
Results: Relative Value of Outcomes



Improvements in more severe outcome levels contributed most to overall importance



Age Did Not Influence Relative Importance



Patient Demographics

Statistic or category	Immediate & extended family members (n=614)	National fragile X survey (n=976) ⁸
Attention problems	92.8%	84%
Hyperactivity	60.6%	66%
Aggressiveness towards others	36.0%	38%
Self-injury (such as hitting head or biting hand)	38.8%	41%
Autism	50.0%	46%
Seizures	10.7%	18%
Anxiety	81.8%	70%
Depression	12.4%	12%
General development delay or mental retardation	92.9%	96%

- National Fragile X Foundation announced of the survey on its home and Facebook pages: 1261 responses to participate, 741 were eligible and 642 respondents completed the survey
- First study to quantify the relative importance that caregivers place on improving different disabilities associated with FXS

Conclusions, Strengths and Limitations⁹

- Large sample size, an experienced and educated sample of respondents, and low response error provided good statistical precision
- Established that significant differences exist in how different outcomes are valued
- Improving the ability of individuals with FXS to control their own behavior mattered most to caregivers
 - this may represent a concern of the caregiver for his/her own well-being caused by potential injury
 - relative importance of self-care and self-control could indicate better coping ability on the part of caregivers for certain features seen such as inattention or decreased sociability
 - preferences may be skewed by homogeneity of respondents (members of advocacy group, relatively high education and income levels)
- **Partial improvement of some outcomes were valued more than a full resolution of other symptoms**
 - findings should guide further exploration of those endpoints and effect sizes that matter most to caregivers
 - outcomes important to families should be considered by health care workers when designing and implementing treatment plans

⁹ Caregiver Preferences for the Treatment of Males with Fragile X Syndrome

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