

DISCLOSURES

This study was funded by Sarepta Therapeutics. IA and KG are employees of Sarepta.

BR, SMS, and TB are employees of Broadstreet HEOR, which received funds from Sarepta to conduct this study.

DF received consulting fees related to this work and has a proprietary interest in Health Utilities Incorporated, Dundas, Ontario, Canada.

HUInc. distributes copyrighted Health Utilities Index (HUI) materials and provides methodological advice on the use of HUI.



May 17-20, 2021
Session: Mixed Diseases and Condition Studies

SAREPTA

THERAPEUTICS

THE DRIVERS OF HEALTH STATE UTILITIES IN DUCHENNE MUSCULAR DYSTROPHY (DMD): A STUDY USING THE HEALTH UTILITIES INDEX MARK 3 (HUI3)

Basia Rogula,¹ Ivana Audhya,² Shelagh M. Szabo,¹ David Feeny,³ Talshyn Bolatova,¹ Katherine L. Gooch²

¹Broadstreet HEOR, 201 – 343 Railway St, Vancouver BC Canada

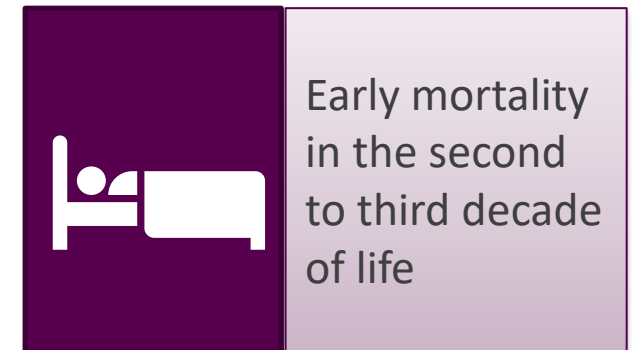
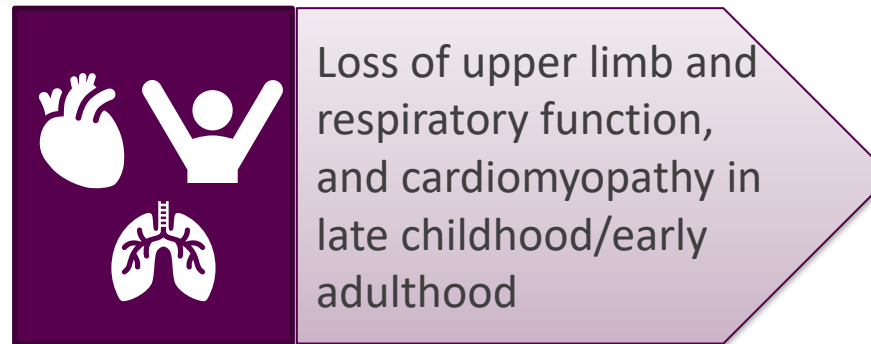
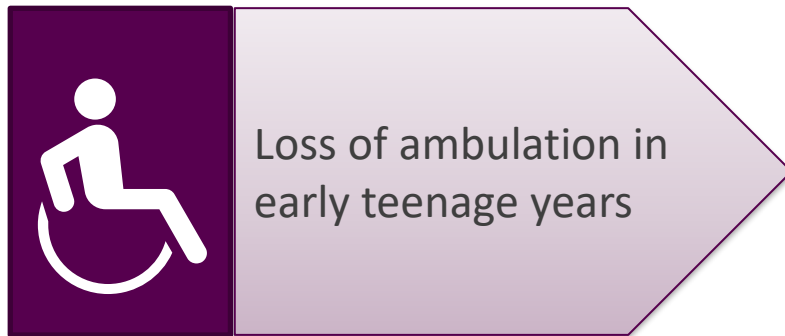
²Sarepta Therapeutics, 215 First St, Cambridge MA 02142 USA

³McMaster University and Health Utilities Inc, Hamilton, ON Canada

BACKGROUND

DUCHENNE MUSCULAR DYSTROPHY

- DMD: A rare, progressive neuromuscular disorder caused by mutations in the gene for dystrophin^{1,2}
- While individual disease courses are heterogeneous, on average, progression in DMD leads to:^{3,4}



- The relentless, progressive functional loss in DMD dramatically affects health-related quality-of-life (HRQoL).

1. Wein N, Alfano L, Flanigan KM. Genetics and emerging treatments for Duchenne and Becker muscular dystrophy. *Pediatric clinics of North America*. 2015;62(3):723-742.

2. Crisafulli S, Sultana J, Fontana A, Salvo F, Messina S, Trifiro G. Global epidemiology of Duchenne muscular dystrophy: an updated systematic review and meta-analysis. *Orphanet J Rare Dis*. 2020;15(1):141.

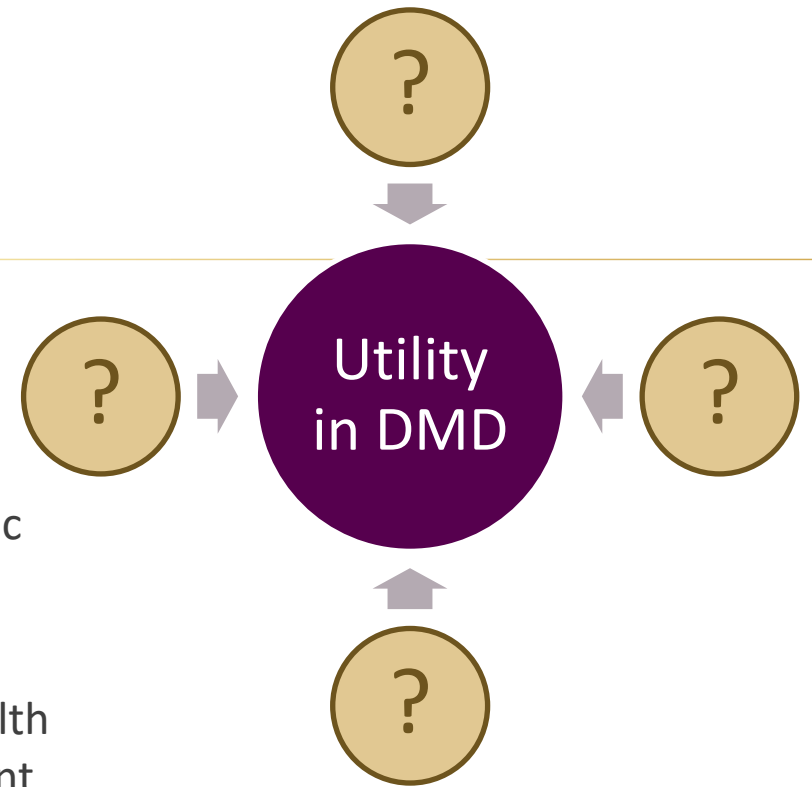
3. Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. *The Lancet. Neurology*. 2018;17(3):251-267.

4. Yiu EM, Kornberg AJ. Duchenne muscular dystrophy. *Journal of paediatrics and child health*. 2015;51(8):759-764.

BACKGROUND

UTILITY IN DUCHENNE MUSCULAR DYSTROPHY

- Utility scores
 - Values anchored between 0 (dead) and 1 (full health),
 - Reflect individuals' preferences for the HRQoL implications of specific health states
 - Required inputs in cost-effectiveness evaluations of new therapies
 - Generic multi-attribute utility instruments such as the EQ-5D or Health Utilities Index (HUI) are commonly used for the indirect measurement of utilities
- Limited data on health state utilities in DMD exist¹
- The drivers of utility in DMD are not well understood



1. Szabo et al., Quality of Life Research 2019.

OBJECTIVE

To investigate drivers of health state utility among patients with DMD, by determining the association between attribute levels and utility scores.

METHODS

DATA AND MEASURES

- Included in the analysis are placebo-treated ambulant boys with DMD with exon 51 skip amenable mutations, recruited under NCT01254019 (provided by BioMarin Pharmaceuticals Inc).
- Family members (proxy respondents) completed the 15-item HUI questionnaire, at baseline, 24 weeks, and 48 weeks (or early withdrawal).
 - For the attributes considered with the HUI questionnaire, higher levels equate to worse levels of function.
 - The overall HUI utility score ranges from 0-1.0 with higher scores equating to better utility.
- Analyses were performed on baseline values, and data available through weeks 48.

HUI3 attributes

- Impairment levels range from 1 to 5 or 6
- 1: none, 2: mild, 3: mild or moderate, 4: moderate or severe, 5+: severe

Vision	Hearing	Speech	Ambulation
			
Dexterity	Emotion	Cognition	Pain
			

HUI2 attributes

- Impairment levels range from 1 to 4 or 5
- 1: none, 2: mild, 3: moderate, 4+: severe

Sensation	Mobility	Emotion	Fertility
			
Cognition	Self-care	Pain	Fertility
			

METHODS

ANALYSIS

Summarized baseline characteristics

Tabulated levels of impairment on each HUI attribute

Calculated proportion of patients with moderate-severe impairments* in each attribute

Computed mean (standard deviation [SD]) HUI attribute levels and utility scores

Estimated the percent of variability in HUI scores across patients explained by each attribute with the R^2 measure from linear regression analyses

In statistics, R^2 is the proportion of variance in an outcome variable that's explained by predictor variable(s).

Calculated mean changes in each attribute level among patients with large declines in utility (≥ 0.2) over 48 weeks, to understand drivers of large changes in utility

At baseline and over time

RESULTS

COHORT CHARACTERISTICS

- Sixty-one ambulant boys with DMD were included.

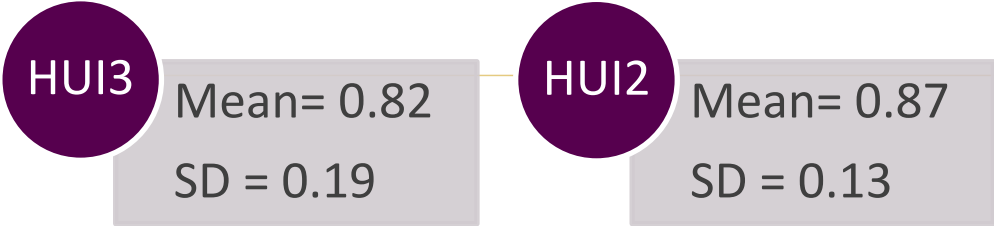


Table 1 Baseline characteristics, ambulant boys with exon 51 skip amenable DMD (n=61)

	Mean (SD)
Age, years	8.0 (2.4)
NSAA total score	21.0 (8.1)
6MWD (m)	348 (92)
Timed 10m walk test (s)*	7.5 (3.6)
Timed RFF (s)*	13.4 (15.9)
Unable to RFF independently, n (%)	19 (31)
Unable to RFF even with use of a chair, n (%)	6 (10)

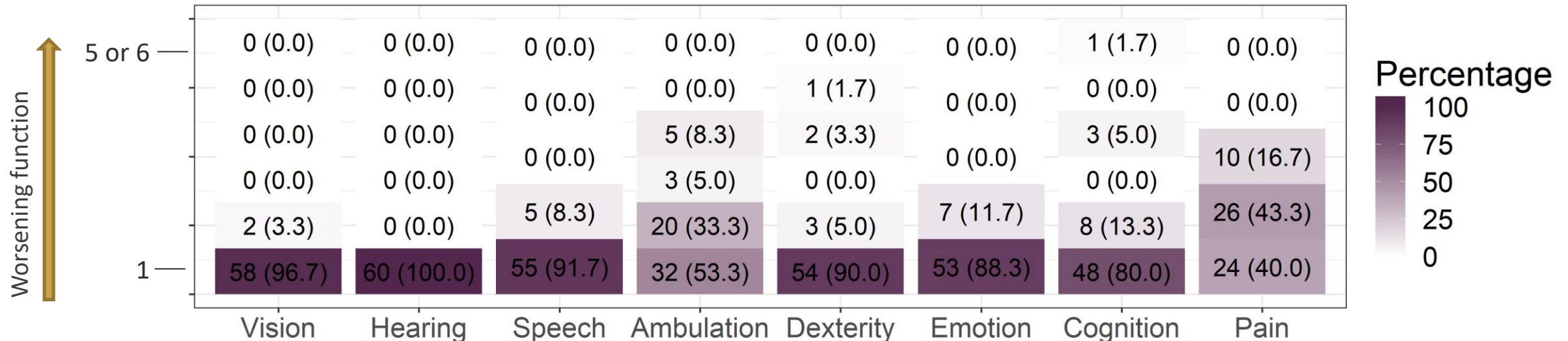
6MWD = six-minute walk distance; NSAA = North Star Ambulatory Assessment; RFF = rise from floor; SD = standard deviation. The NSAA is a 17-item instrument with potential scores ranging from 0-34; lower scores indicate a higher degree of functional impairment.

*n=55

RESULTS

HUI3 ATTRIBUTE LEVELS AT BASELINE

Heatmap: n (%) patients with each level of impairment in each HUI3 attribute at baseline*



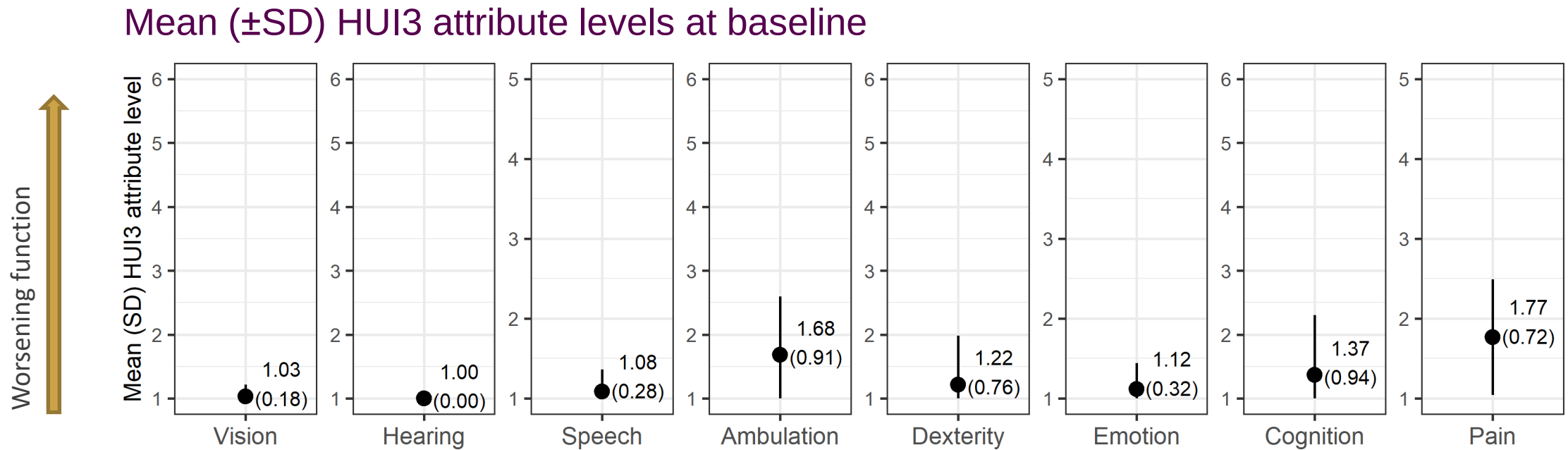
* 1 patient was missing HUI3 information at baseline.

Of the HUI3 attributes, moderate or severe impairments at baseline were most often reported for pain (17%), ambulation (13%), cognition (7%), and dexterity (5%).

At baseline, 23% of patients had at least some impairment in ≥ 3 attributes; 57% had at least some impairment in 1 or 2 attributes; and 20% had normal function across all attributes.

RESULTS

HUI3 ATTRIBUTE LEVELS AT BASELINE

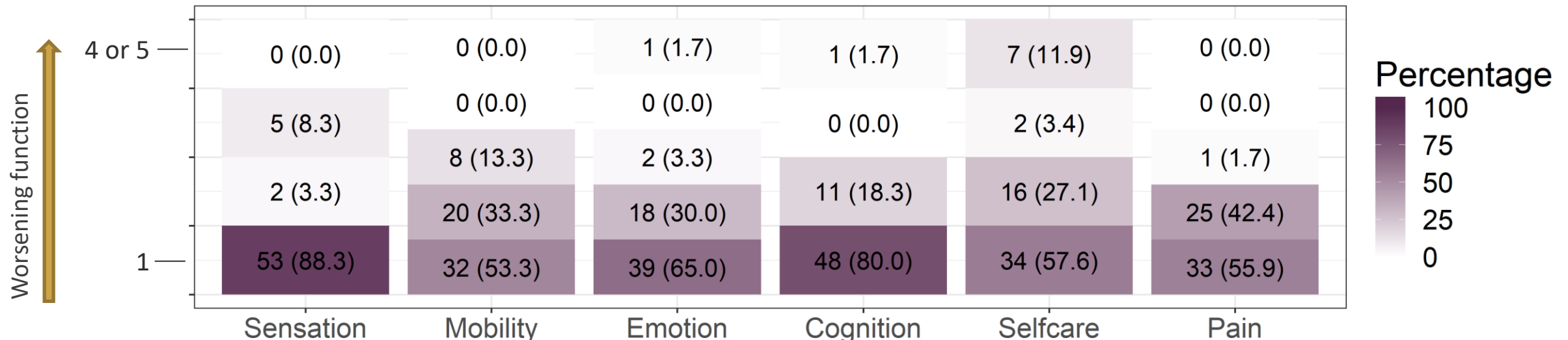


At baseline, the greatest level of impairments were noted for pain (1.8), ambulation (1.7), cognition (1.4), and dexterity (1.2).

RESULTS

HUI2 ATTRIBUTE LEVELS AT BASELINE

Heatmap: n (%) patients with each level of impairment in each HUI2 attribute at baseline*



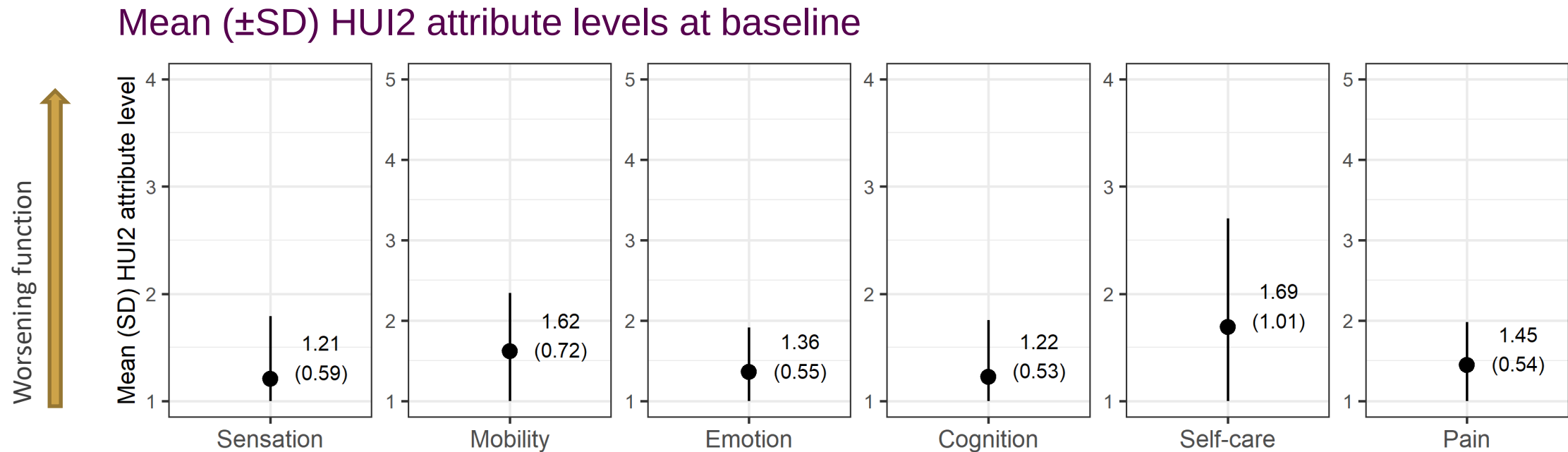
* The sensation, mobility, and emotion attributes each had 1 patient was missing a value, while self-care and pain each had 2 patients missing a value.c

Of the HUI2 attributes, moderate or severe impairments at baseline were most often reported for self-care (15%), mobility (13%), and sensation (8%).

At baseline, 32% of patients had at least some impairment in ≥ 3 attributes; 47% had at least some impairment in 1 or 2 attributes; and 21% had normal function across all attributes.

RESULTS

HUI2 ATTRIBUTE LEVELS AT BASELINE

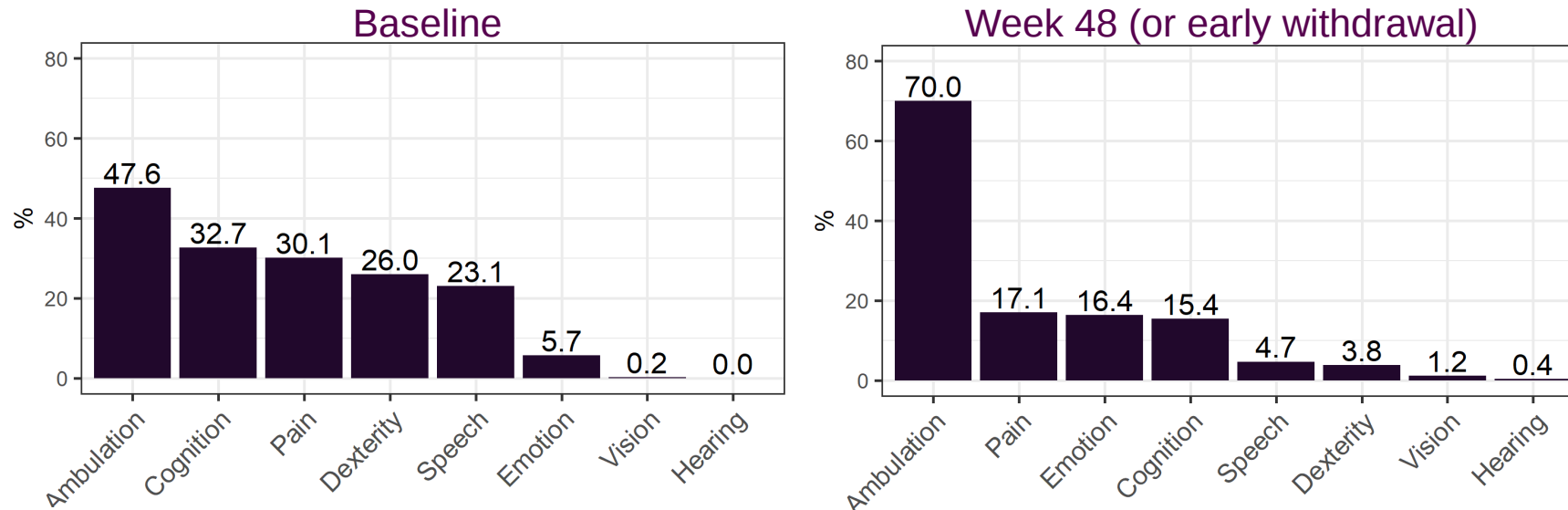


At baseline, the greatest level of impairments were noted for self-care (1.7), mobility (1.6), pain (1.5), and emotion (1.4).

RESULTS

DRIVERS OF OBSERVED VARIATION AROUND MEAN HUI3 UTILITY IN THE STUDY SAMPLE

Variability in HUI3 utility, across patients, explained by each attribute*



* Percentages across attributes add up to over 100% due to correlation between attributes.

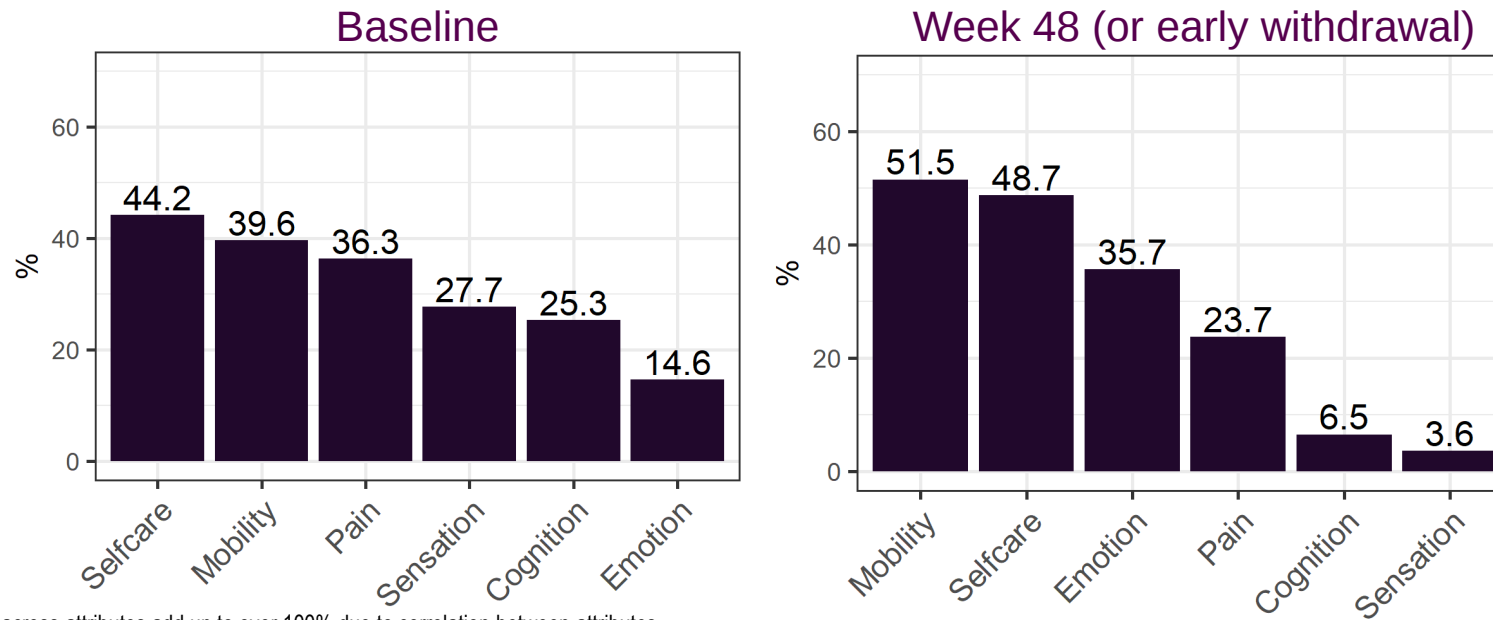
At baseline: Together, ambulation, cognition, pain, and dexterity explained 96% of observed variability in utility, across the entire study sample.†

At week 48, ambulation accounted for a higher proportion of variability in HUI utility than at baseline (70% vs 48%).

RESULTS

DRIVERS OF OBSERVED VARIATION AROUND MEAN HUI2 UTILITY IN THE STUDY SAMPLE

Percent of variability in HUI2 utility, across patients, explained by each attribute*



* Percentages across attributes add up to over 100% due to correlation between attributes.

At baseline: Self-care (44.2%) and mobility (39.6%) together explained 57% of observed variability in utility, across the entire study sample.†

At week 48, mobility accounted for a higher proportion of variability in HUI utility than at baseline (52% vs 40%).

RESULTS

CHANGE IN UTILITY FROM BASELINE TO WEEK 48

HUI3 attribute	Mean (SD) change	HUI2 attribute	Mean (SD) change
Ambulation	0.39 (1.29)	Mobility	0.23 (0.80)
Emotion	0.18 (0.56)	Self-care	0.15 (0.80)
Vision	0.04 (0.34)	Emotion	0.14 (0.71)
Cognition	0.03 (0.83)	Pain	0.08 (0.57)
Hearing	0.01 (0.11)	Sensation	0.05 (0.56)
Pain	0.01 (0.76)	Cognition	-0.01 (0.45)
Speech	0.04 (0.34)		
Dexterity	-0.03 (0.67)		

HUI3

Mean (SD) week 48 utility = 0.75 (0.22)
Mean (SD) utility change from baseline = -0.06 (0.19)

HUI2

Mean (SD) week 48 utility = 0.81 (0.18)
Mean (SD) utility change from baseline = -0.05 (0.14)

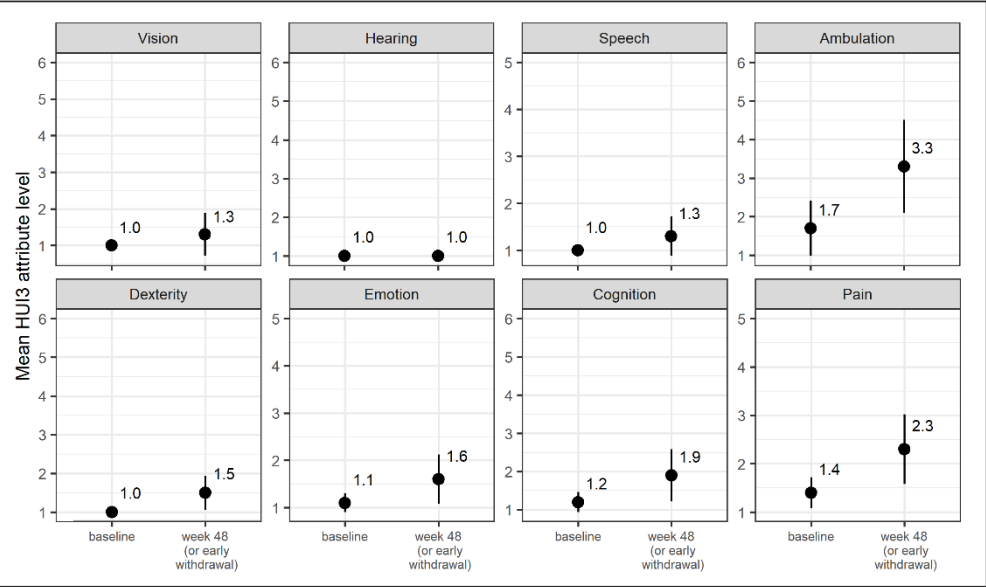
The largest mean changes* in attribute levels over time were seen in ambulation (+0.4) and emotion (+0.2) for the HUI3; and mobility (+0.2), self-care (+0.2), and emotion (+0.1) for the HUI2.

RESULTS

DRIVERS OF LARGE DECLINES IN UTILITY

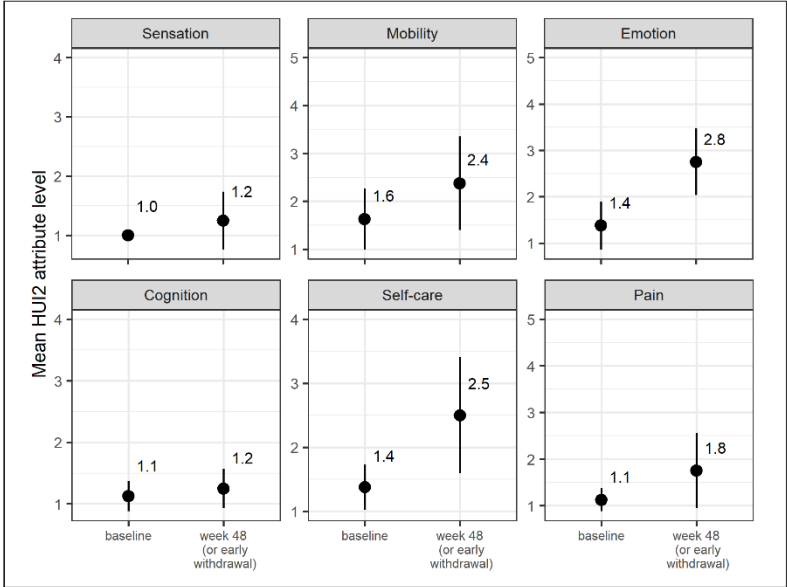
- We looked at mean changes in HUI attributes among patients with large drops (≥ 0.2) in utility to better understand which attributes were driving declines in utility.

Mean change in HUI3 utility attributes (n = 10)



The largest declines in attribute levels were seen in ambulation (+1.6), pain (+0.9), cognition (+0.7), dexterity (+0.5), and emotion (+0.5).

Mean change in HUI2 utility attributes (n = 8)



The largest declines in attribute levels were seen in emotion (+1.4), self-care (+1.1), and mobility (+0.8).

DISCUSSION

- In this sample of ambulatory boys with DMD, the largest impairments across HUI attributes that describe patient HRQoL were observed in:
 - Ambulation, pain, cognition and dexterity; for the HUI3
 - Self-care and mobility for the HUI2
 - These findings have clinical face validity given the neuromuscular impairments experienced by boys with DMD
- These attributes explained the majority of observed variability in utility scores, and changes in utility over time
 - Overall, and among those with large declines in utility (among whom the changes were more pronounced)
- Limitations include that as all boys included in this study were skip 51 amenable, findings may not be generalizable to boys of all genotypes
- Assessing how utility is related to other functional assessments in DMD represents an important future direction
- Findings from this study highlight the importance of the following domains as drivers of health state utility in ambulatory DMD:
 - HUI3: Physical function (ambulation & dexterity), pain, and cognition.
 - HUI2: Physical function (mobility), and ability to perform self-care.
- These findings are also valuable in augmenting scarce data on health state utilities for ambulatory boys with DMD.

THANK YOU

For any questions please contact:

Basia Rogula

brogula@broadstreetheor.com

SUPPLEMENTAL SLIDES



RESULTS

HUI3 ATTRIBUTE LEVELS

HUI3 attribute levels at baseline*

HUI3 attributes								
Levels	Vision	Hearing	Speech	Ambulation	Dexterity	Emotion	Cognition	Pain
	N = 60*	N = 60*	N = 60*	N = 60*	N = 60*	N = 60*	N = 60*	N = 60*
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
1 (normal)	58 (96.7)	60 (100.0)	55 (91.7)	32 (53.3)	54 (90.0)	53 (88.3)	48 (80.0)	24 (40.0)
2	2 (3.3)	0 (0.0)	5 (8.3)	20 (33.3)	3 (5.0)	7 (11.7)	8 (13.3)	26 (43.3)
3	0 (0.0)	0 (0.0)	0 (0.0)	3 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	10 (16.7)
4	0 (0.0)	0 (0.0)	0 (0.0)	5 (8.3)	2 (3.3)	0 (0.0)	3 (5.0)	0 (0.0)
5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)
6	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-	1 (1.7)	-
Mean level (SD)	1.03 (0.18)	1.00 (0.00)	1.08 (0.28)	1.68 (0.91)	1.22 (0.76)	1.12 (0.32)	1.37 (0.94)	1.77 (0.72)
Impairment level								
None or mild	60 (100.0)	60 (100.0)	60 (100.0)	52 (86.7)	57 (95.0)	60 (100.0)	56 (93.3)	50 (83.3)
Moderate or severe	0 (0.0)	0 (0.0)	0 (0.0)	8 (13.3)	3 (5.0)	0 (0.0)	4 (6.7)	10 (16.7)

* 1 patient was missing HUI3 information at baseline.

RESULTS

HUI2 ATTRIBUTE LEVELS

HUI2 attribute levels at baseline*

HUI2 attributes						
Levels	Sensation	Mobility	Emotion	Cognition	Self-care	Pain
	N = 60*	N = 60*	N = 60*	N = 60*	N = 59*	N = 59*
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
1 (normal)	53 (88.3)	32 (53.3)	39 (65.0)	48 (80.0)	34 (57.6)	33 (55.9)
2	2 (3.3)	20 (33.3)	18 (30.0)	11 (18.3)	16 (27.1)	25 (42.4)
3	5 (8.3)	8 (13.3)	2 (3.3)	0 (0.0)	2 (3.4)	1 (1.7)
4	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	7 (11.9)	0 (0.0)
5	-	0 (0.0)	1 (1.7)	-	-	0 (0.0)
Mean (SD) level	1.21 (0.59)	1.62 (0.72)	1.36 (0.55)	1.22 (0.53)	1.69 (1.01)	1.45 (0.54)
Impairment level						
None or mild	55 (91.7)	52 (86.7)	57 (95.0)	59 (98.3)	50 (84.7)	58 (98.3)
Moderate or severe	5 (8.3)	8 (13.3)	3 (5.0)	1 (1.7)	9 (15.3)	1 (1.7)

* The sensation, mobility, and emotion attributes each had 1 patient was missing a value, while self-care and pain each had 2 patients missing a value.