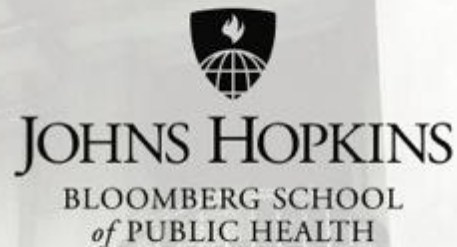


# **Choosing outcomes that are appropriate across a population: Quantitative approaches**

John F P Bridges PhD  
Associate Professor  
Department of Health Policy and Management



# Transparency

- **Patient-Centered Outcomes Research Institute (PCORI)** Methods Program Award (ME-1303-5946)
- Johns Hopkins-FDA **Center for Regulatory Science and Innovation** (CERSI)
- **Parent Project Muscular Dystrophy (PPMD)**  
(supported by Santhera).
- **Center for Medicine in the Public Interest (CMPI)**  
(supported by InterMune)
- **LUNGeivity**  
(supported by Celgene)



# Overview

- Demonstrate **why stated-preferences methods matter** measuring health and clinical outcomes
- Demonstrate how **stated-preference methods differ from traditional measurement** techniques
- Illustrate how stated-preference methods can be used to **prioritize outcomes**





Why do stated-preferences  
methods matter?

# Becoming patient-centered

*“A patient reported outcome (PRO) is a measurement of any aspect of a patient’s health status that comes directly from the patient (i.e., without the interpretation of the patient’s responses by a physician or anyone else)”*

## **FDA Guidance for Industry**

*“When assessing potential beneficial and harmful effects, patient-relevant endpoints (PRE) and not their surrogates (i.e. disease-relevant aspects) should primarily be taken into consideration”*

## **IQWiG Methods**



# Why patient-relevance matters

Reed Johnson and colleagues sought to examine the QLQ-30 and to assess the **assumption** regarding the **underlying valuation** of the scale.

*“We have **no grounds** to believe that the EORTC QLQ items are **sufficiently non-linear** to warrant any correction before using them in summated scales. ... At the present time **we recommend** using scales based on **unweighted** summed scores.” (EORTC QLQ-C30 Scoring Manual, 1999, p. 13)*

Johnson FR, Hauber AB, Osoba D, Hsu M, Coombs J, Copley-Merriman C. Are chemotherapy patients' HRQoL importance weights consistent with linear scoring rules? A stated-choice approach. Qual Life Res 2006;15:285-98.



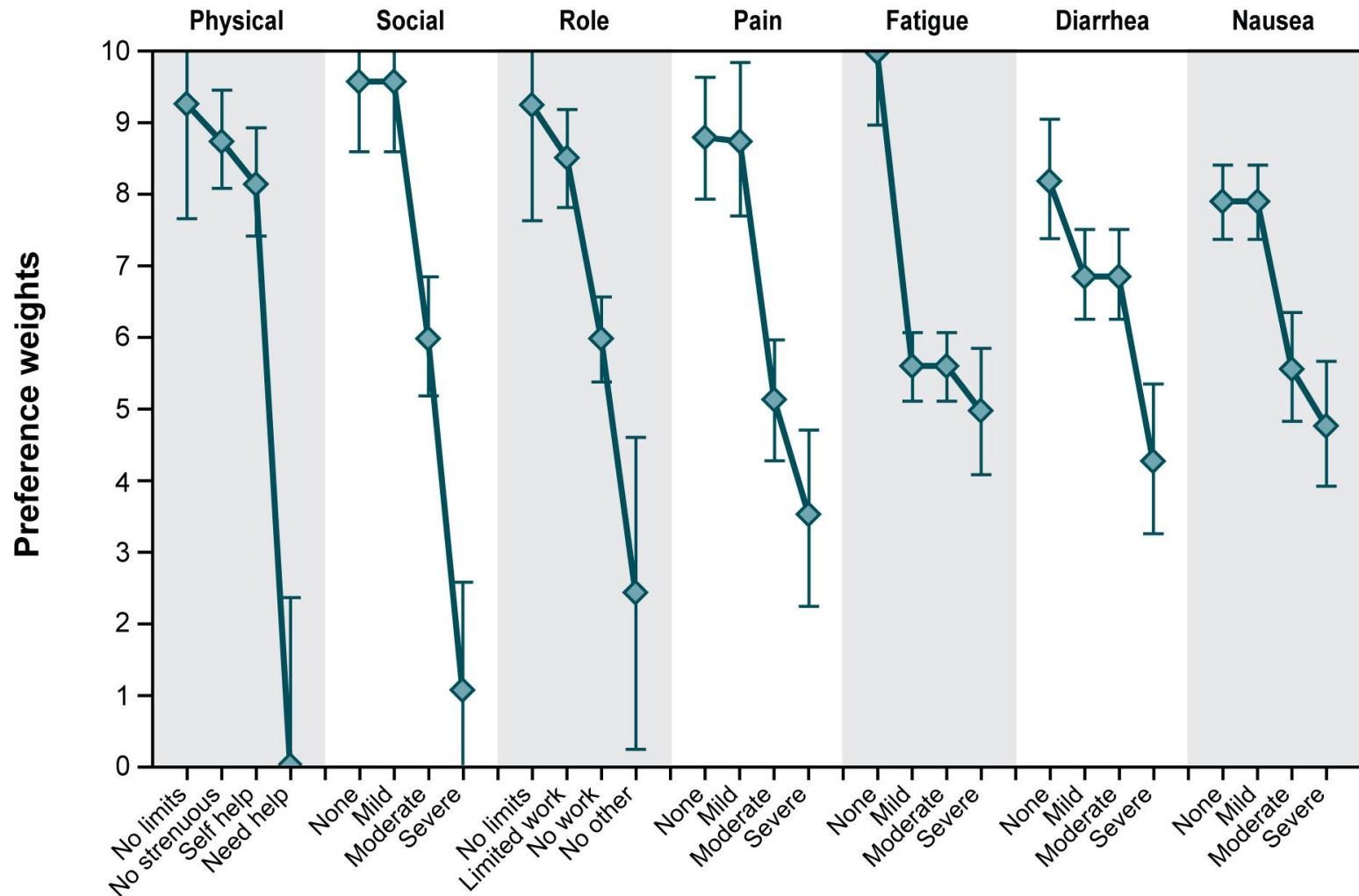
# Conjoint Question

Treatment Impact	Treatment A	Treatment B
Physical Limitations	Unable to do strenuous activities	No physical limitations
Limitations on work and household jobs	Some limitations	Some limitations
Tense, worried, irritable, or depressed	Not at all	Very much
Interference with family or social life	A little	A little
Fatigue	A little (mild)	A little (mild)
Nausea and Vomiting	A little (mild)	A little (mild)
Trouble Sleeping	A little (mild)	A little (mild)
Diarrhea	A little (mild)	A little (mild)

Which treatment would you choose? (Please check one box.)	Choose Treatment A <input type="radio"/>	Choose Treatment B <input type="radio"/>
--	---	---

# Non-linearity results



# Improving the methods

- ISPOR **conjoint analysis working group** (2006-11)
- **Conjoint Analysis & Health Conference** (2007-12)
- **The Patient** journal launched (2008)
- ISPOR **conjoint analysis taskforce** (2008-10)
- ISPOR **experimental design** taskforce (2010-12)
- International Academy of Health Preference Research ([www.IAHPR.org](http://www.IAHPR.org)) (2014)
- **FasterCures** Benefit-Risk Advisory Council (2014)
- ISPOR **Stated-Preference Methods** SIG (2015)
- ISPOR **Patient-focused Benefit-Risk Analysis** working group (2015)



# Why preferences matter



## Patient Preference Information – Submission, Review in PMAs, HDE Applications, and *De Novo* Requests, and Inclusion in Device Labeling

### Draft Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders

#### *DRAFT GUIDANCE*

This guidance document is being distributed for comment purposes only.

You should submit comments and suggestions regarding this draft document within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <http://www.regulations.gov>. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions about this document, contact the Office of the Center Director (CDRH) at 301-796-5900 or Anindita Saha at 301-796-2537 ([Anindita.Saha@fda.hhs.gov](mailto:Anindita.Saha@fda.hhs.gov)) or the Office of Communication, Outreach, and Development (CBER) at 800-835-4709 or 240-402-7800.



U.S. Department of Health and Human Services  
Food and Drug Administration

Center for Devices and Radiological Health

Center for Biologics Evaluation and Research

A large, faint watermark of the University of California seal is visible in the background. It features a shield with a book, a sun, and a star, surrounded by the text 'THE UNIVERSITY OF CALIFORNIA' and '1868'.

Do stated-preference  
methods differ?

# Comparing methods

- As part of a PCORI methods award, we have been **comparing several stated-preference methods** within a broader studies focused on type 2 diabetes
- To compare methods for prioritizing, we focused on methods to prioritize the **barriers and facilitator to self-management**
- We compared two methods in an RCT:
  - Likert scales
  - Best-worst scaling



# Prioritization methods

## Likert Item

- A quantified response to a statement on a symmetric, **balanced scale** according to objective/subjective criteria
- Strengths: simple, intuitive appeal, frequent use
- Limitations: central tendency bias, social desirability bias, acquiescence bias, ceiling/floor effect

## Best Worst Scaling

- A repeated **discrete-choice response** assessing the best/worst statement according to objective/subjective criteria
- Strengths: simple design and analysis
- Limitations: possible floor and ceiling effects
- Limited evidence on strengths and limitations, needs to be further studied



# Barriers and Facilitators

Factor	Description
<b>Access to healthy food</b>	Do you have regular access to healthy food that will support your ability for diabetes self-management?
<b>Healthcare providers</b>	Do your healthcare providers have a positive or negative impact on your ability to self-manage your diabetes?
<b>My own knowledge</b>	Do you feel you know enough about diabetes to self-manage your diabetes?
<b>Staying motivated</b>	Do you usually have the self-control to make the best choices for managing your diabetes?
<b>My ability to pay</b>	Do you have enough money to successfully self-manage your diabetes?
<b>Other health conditions</b>	Do you have other health conditions (mental and physical) that affect how you manage your diabetes?
<b>Family commitments</b>	Does your family have a positive or negative impact on your ability to self-manage your diabetes?
<b>Physical environment</b>	Does the place/location where you live and work provide you with the resources to manage your diabetes?
<b>Local events</b>	Do your local events (e.g. cultural, community, or religious) impact your ability for diabetes self-management?
<b>Work commitments</b>	Does your work (or other responsibilities) affect your ability to self-manage your diabetes?
<b>Support from others</b>	Do you have enough support from friends, co-workers, support groups or others in your community?



# Prioritization via Likert items

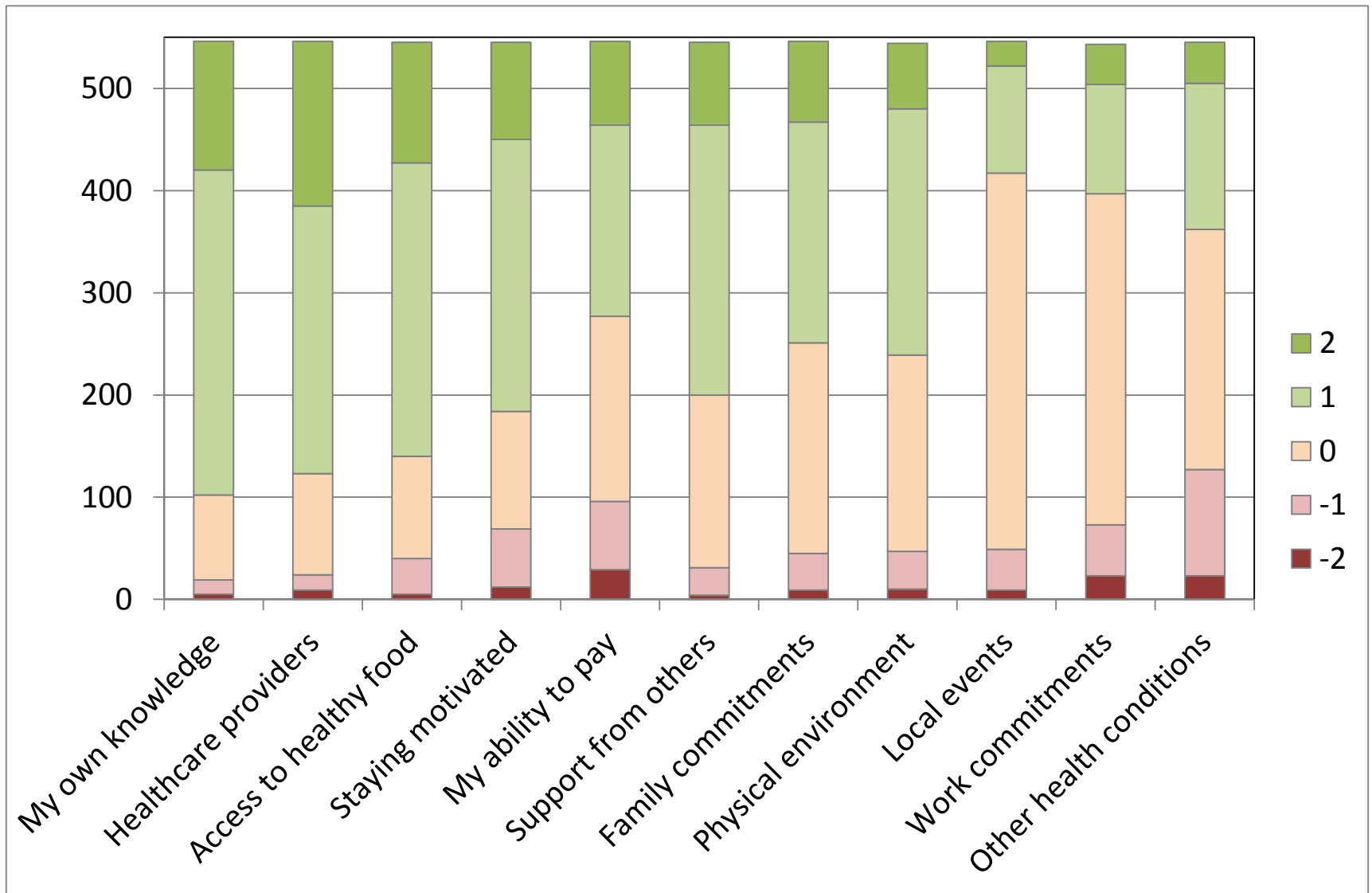
	Strong negative impact -2	Negative impact -1	Neither a positive nor a negative impact 0	Positive impact +1	Strong positive impact +2
Local events	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Support from others	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Access to healthy food	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Healthcare providers	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Physical environment	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Staying motivated	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
My own knowledge	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Family commitments	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Work commitments	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
My ability to pay	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other health conditions	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

# Prioritization via BWS

Things impacting your own diabetes self-management	Best	Worst
Access to healthy food		
Healthcare providers		
My ability to pay		
Local events		
Family commitments		
<p>Consider the following things that can have a positive or negative impact on your own diabetes self-management. Which of the following things is the <b>best</b> and which is the <b>worst</b> in terms of impact on <u>your own</u> diabetes self-management?</p>		

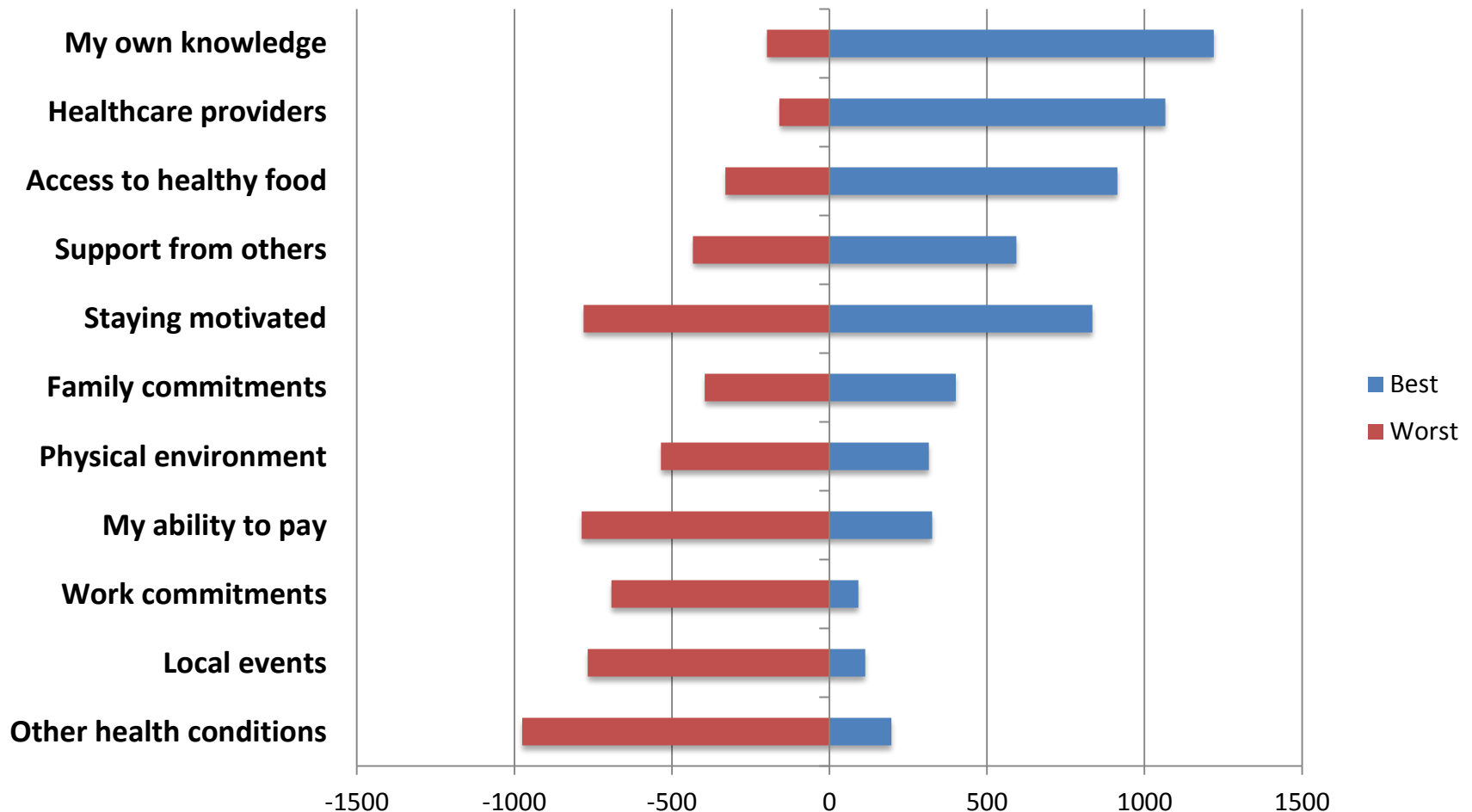


# Frequency of Likert item responses

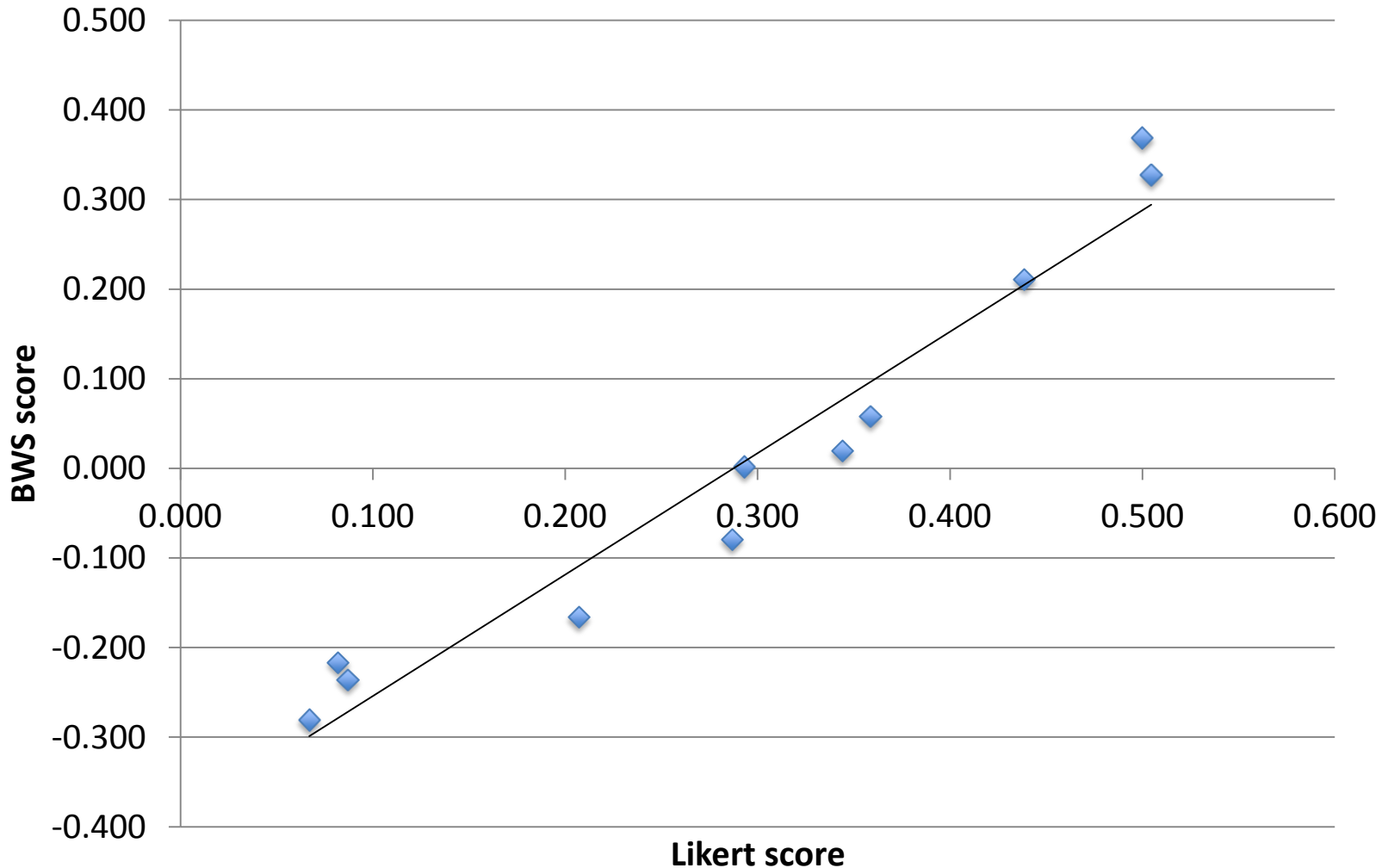


# BWS responses

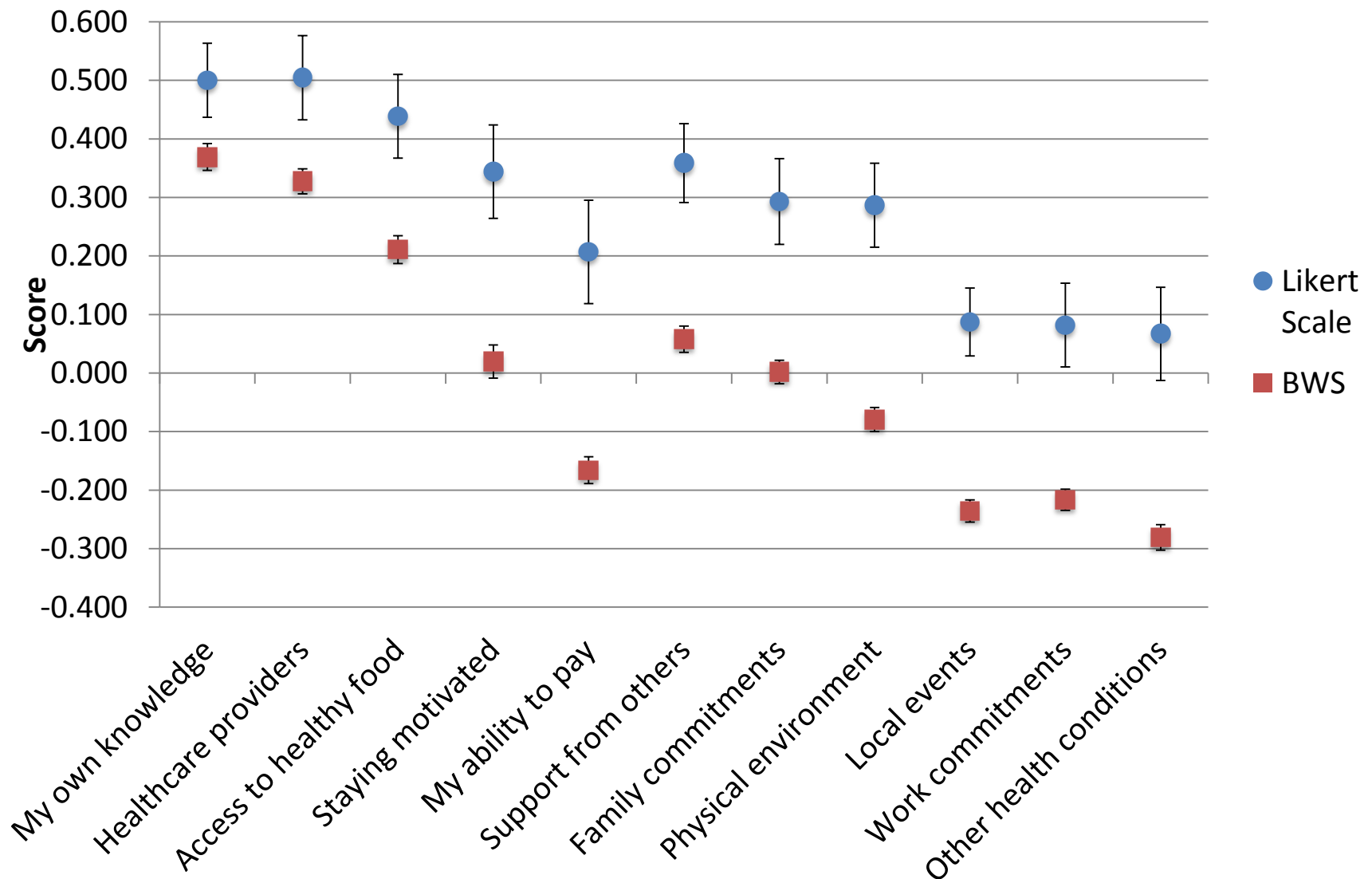
Number of times attribute was chosen as worst or as best



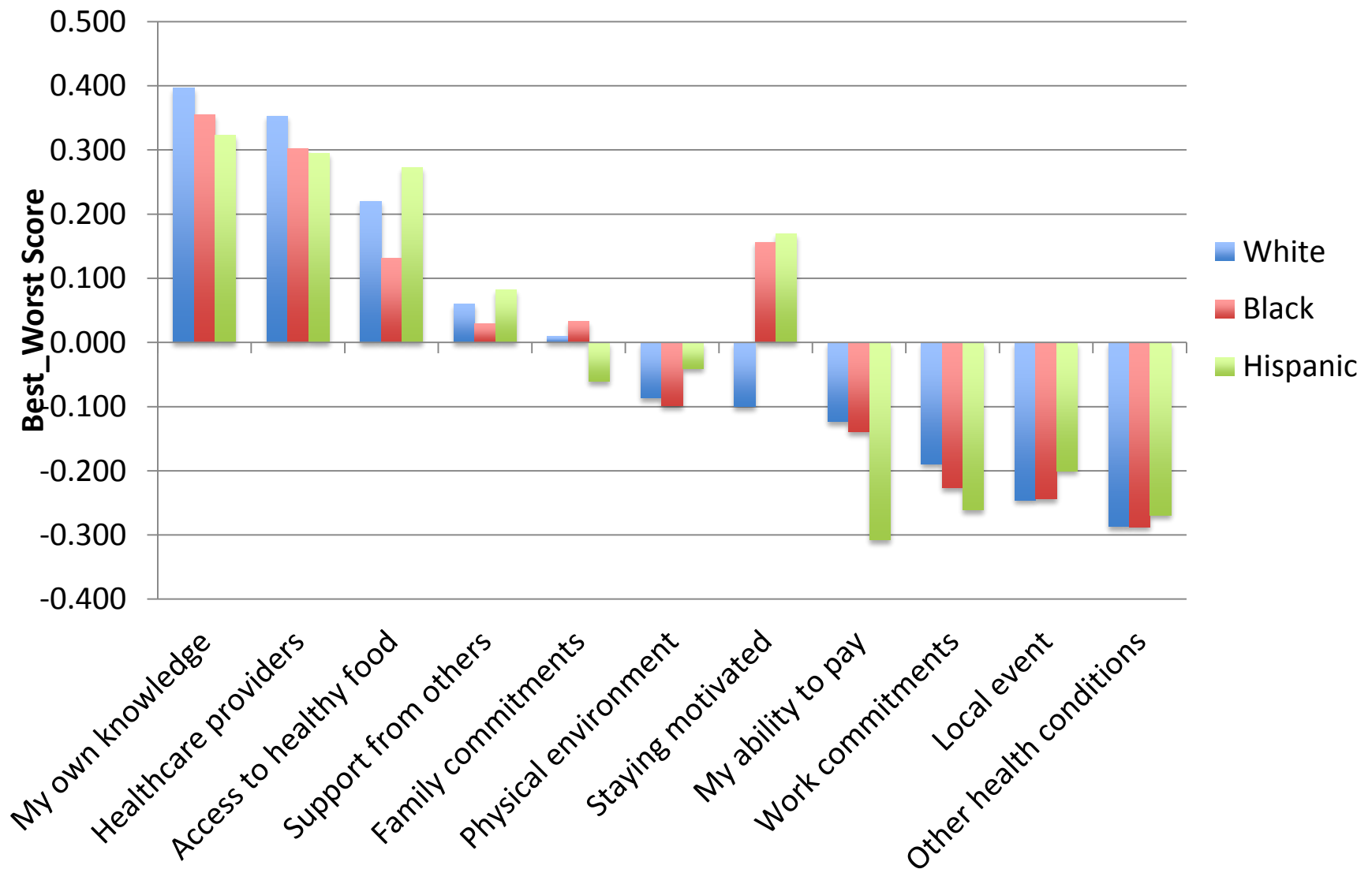
# Likert item vs. BWS (rho=0.97)



# Likert Scores item vs. BWS scores



# Scores by Race and Ethnicity





# Prioritizing endpoints using stated-preference methods

# Parent Project Muscular Dystrophy (PPMD) – Benefit-Risk project

## Benefit-Risk Assessments in Rare Disorders

THE CASE FOR THERAPEUTIC DEVELOPMENT IN DUCHENNE MUSCULAR DYSTROPHY AS THE PROTOTYPE FOR NEW APPROACHES



Parent Project  
Muscular Dystrophy  
LEADING THE FIGHT TO END DUCHENNE

Clinical Therapeutics/Volume 36, Number 5, 2014

### A Community-Engaged Approach to Quantifying Caregiver Preferences for the Benefits and Risks of Emerging Therapies for Duchenne Muscular Dystrophy

Holly L. Peay, MS<sup>1</sup>; Ilene Hollin, MPH<sup>2</sup>; Ryan Fischer, BA<sup>1</sup>; and John F.P. Bridges, PhD<sup>2</sup>

<sup>1</sup>Parent Project Muscular Dystrophy, Hackensack, New Jersey; and <sup>2</sup>Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland

#### ABSTRACT

**Background:** There is growing agreement that regulators performing benefit-risk evaluations should take patients' and caregivers' preferences into consideration. The Patient-Focused Drug Development Initiative at the US Food and Drug Administration offers patients and caregivers an enhanced opportunity to contribute to regulatory processes by offering direct testimonials. This process may be advanced by providing scientific evidence regarding treatment preferences through engagement of a broad community of patients and caregivers.

**Objective:** In this article, we demonstrate a community-engaged approach to measure caregiver preferences for potential benefits and risks of emerging therapies for Duchenne muscular dystrophy (DMD).

**Methods:** An advocacy oversight team led the community-engaged study. Caregivers' treatment preferences were measured by using best-worst scaling (BWS). Six relevant and understandable attributes describing potential benefits and risks of emerging DMD therapies were identified through engagement with advocates (n = 5), clinicians (n = 9), drug developers from pharmaceutical companies and academic centers (n = 11), and other stakeholders (n = 5). The attributes, each defined across 3 levels, included muscle function, life span, knowledge about the drug, nausea, risk of bleeds, and risk of arrhythmia. Cognitive interviewing with caregivers (n = 7) was used to refine terminology and assess acceptability of the BWS instrument. The study was implemented through an online survey of DMD caregivers, who were recruited in the United States through an advocacy group and snowball sampling. Caregivers were presented with 18 treatment profiles, identified via a main-effect orthogonal experimental design, in which the dependent variable was the respondents' judgment as to the best and worst feature in each

profile. Preference weights were estimated by calculating the relative number of times a feature was chosen as best and as worst, which were then used to estimate relative attribute importance.

**Results:** A total of 119 DMD caregivers completed the BWS instrument; they were predominately biological mothers (67.2%), married (89.9%), and white (91.6%). Treatment effect on muscle function was the most important among experimental attributes (28.7%), followed by risk of heart arrhythmia (22.4%) and risk of bleeding (21.2%). Having additional postapproval data was relatively the least important attribute (2.3%).

**Conclusions:** We present a model process for advocacy organizations aiming to promote patient-centered drug development. The community-engaged approach was successfully used to develop and implement a survey to measure caregiver preferences. Caregivers were willing to accept a serious risk when balanced with a noncurative treatment, even absent improvement in life span. These preferences should inform the Food and Drug Administration's benefit-risk assessment of emerging DMD therapies. This study highlights the synergistic integration of traditional advocacy methods and scientific approach to quantify benefit-risk preferences. (*Clin Ther.* 2014;36:624–637) © 2014 The Authors. Published by Elsevier HS Journals, Inc. All rights reserved.

**Key words:** benefit-risk assessment, caregiver, choice behavior, Duchenne muscular dystrophy, patient preferences.

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<http://dx.doi.org/10.1016/j.clinthera.2014.04.011>  
0149-2918/\$ - see front matter

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# Drafting Duchenne FDA guidance

## Guidance for Industry Duchenne Muscular Dystrophy Developing Drugs for Treatment over the Spectrum of Disease

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## Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment Guidance for Industry

### *DRAFT GUIDANCE*

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For questions regarding this draft document contact Colleen Locicero 301-796-1114.

U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)

June 2015  
Clinical/Medical

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# Pulmonary Therapy Study

- Study objectives
  - To what extent do parents and patients assess **pulmonary outcomes** as meaningful benefits?
  - To inform the **regulatory process** and disseminate to patient community
  - To facilitate **patient focused drug development**
- Utilized BWS to prioritize **pulmonary and other possible endpoints** not included in our original study
- Sampled patients (n=59) and caregivers (n=96)



# Sample task

**Most important  
to treat**

**Least important  
to treat**

Headaches



Depression



Feeling tired



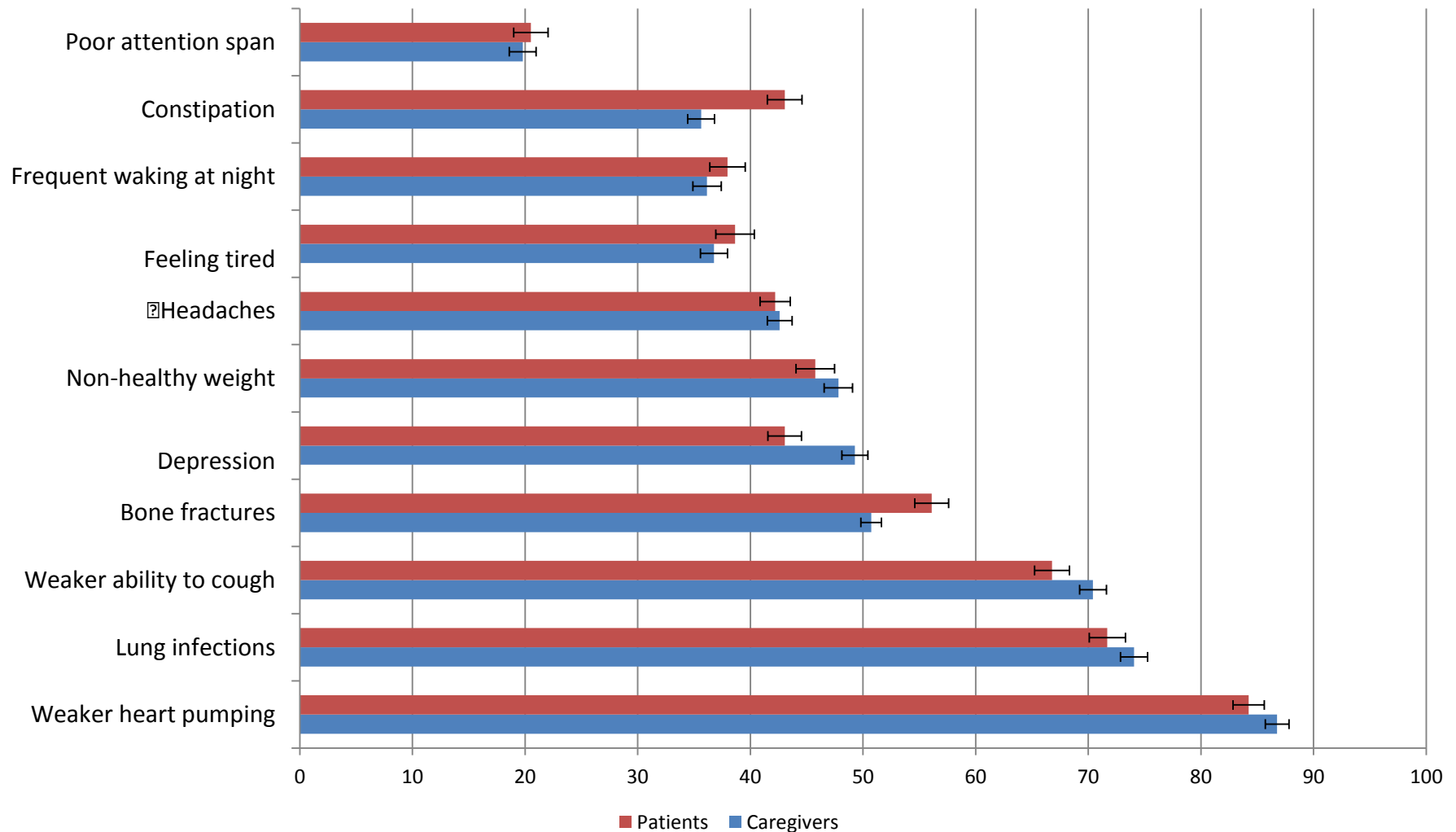
Constipation



Poor attention span



# Endpoint prioritization



Protecting Health,  
Saving Lives—  
*Millions at a Time*



JOHNS HOPKINS  
BLOOMBERG SCHOOL  
of PUBLIC HEALTH