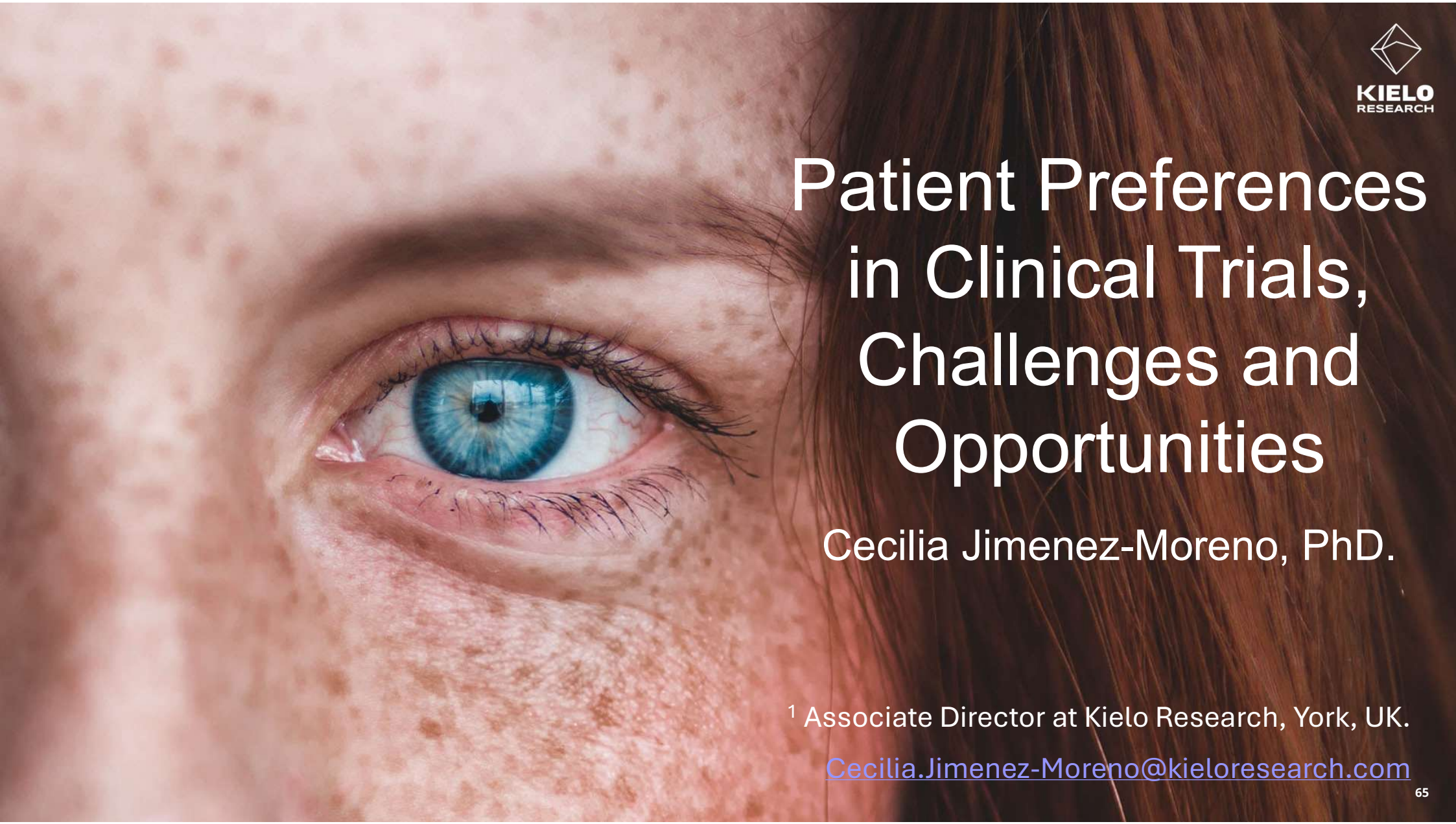


Patient Preferences in Clinical Trials, Challenges and Opportunities

Cecilia Jimenez-Moreno, PhD.

[1] Associate Director at Kielo Research, York, UK.

Cecilia.Jimenez-Moreno@kieloresearch.com

Background

Use of Patient Experience Data (PED) in Clinical Trials

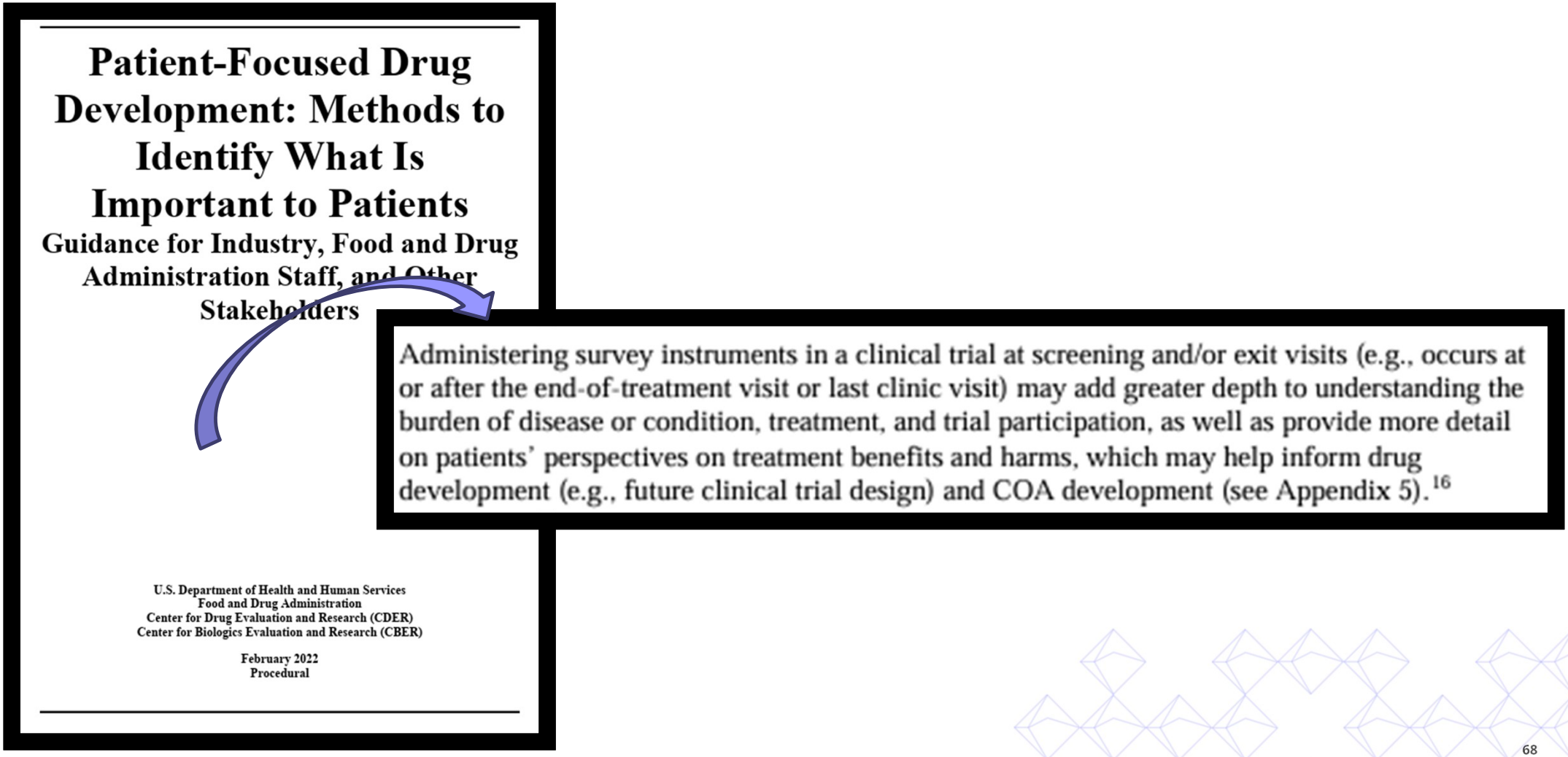
Different **qualitative and quantitative methods in clinical trials** are used not only to assess disease progression within the clinical trial but also to gain deeper insights into patient perspectives on treatment benefits and harms.

- This information can be used to:
  - inform clinical trial design
  - the development of clinical outcome assessments
  - and ultimately, regulatory decision-making

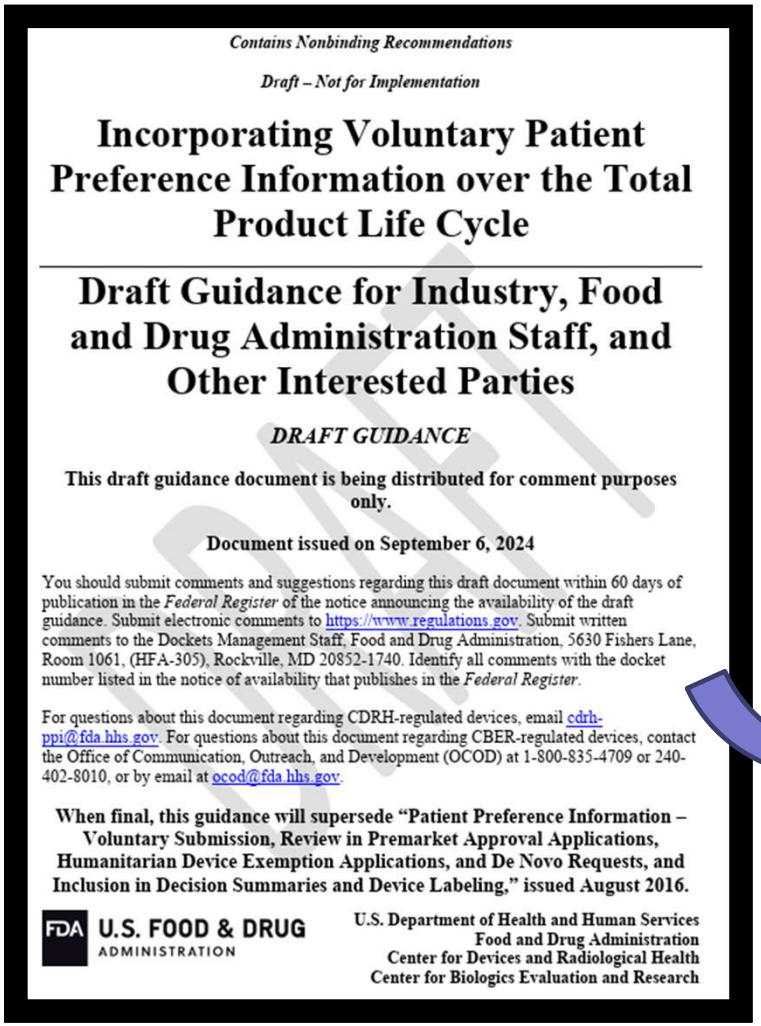
So far…

- **Byron** – published PPI influencing endpoint choices in a Phase 2 trial.
  - Value: ensuring inclusion of patient-relevant endpoints – from early stages in the drug development.
- **Michael** – questioned whether (de-novo) PP studies are always needed
  - Value: identified diseases (and health attributes within each disease) with extensive published PP
- **Divya** – assessed the generalizability of estimates obtained in PP studies
  - Value: evidence suggesting that PP conclusions from one study to be generalised to a broader population
- **Now…***Where and How do PP studies directly fit with Clinical Trials?*

Rationale


Patient-Focused Drug Development: Methods to Identify What Is Important to Patients
Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
February 2022
Procedural
Administering survey instruments in a clinical trial at screening and/or exit visits (e.g., occurs at or after the end-of-treatment visit or last clinic visit) may add greater depth to understanding the burden of disease or condition, treatment, and trial participation, as well as provide more detail on patients' perspectives on treatment benefits and harms, which may help inform drug development (e.g., future clinical trial design) and COA development (see Appendix 5).[16]

Rationale



Contains Nonbinding Recommendations

Draft – Not for Implementation

Incorporating Voluntary Patient Preference Information over the Total Product Life Cycle

Draft Guidance for Industry, Food and Drug Administration Staff, and Other Interested Parties

DRAFT GUIDANCE

This draft guidance document is being distributed for comment purposes only.

Document issued on September 6, 2024

You should submit comments and suggestions regarding this draft document within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD 20852-1740. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions about this document regarding CDRH-regulated devices, email cdrh-ppi@fda.hhs.gov. For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach, and Development (OCOD) at 1-800-835-4709 or 240-402-8010, or by email at ocod@fda.hhs.gov.

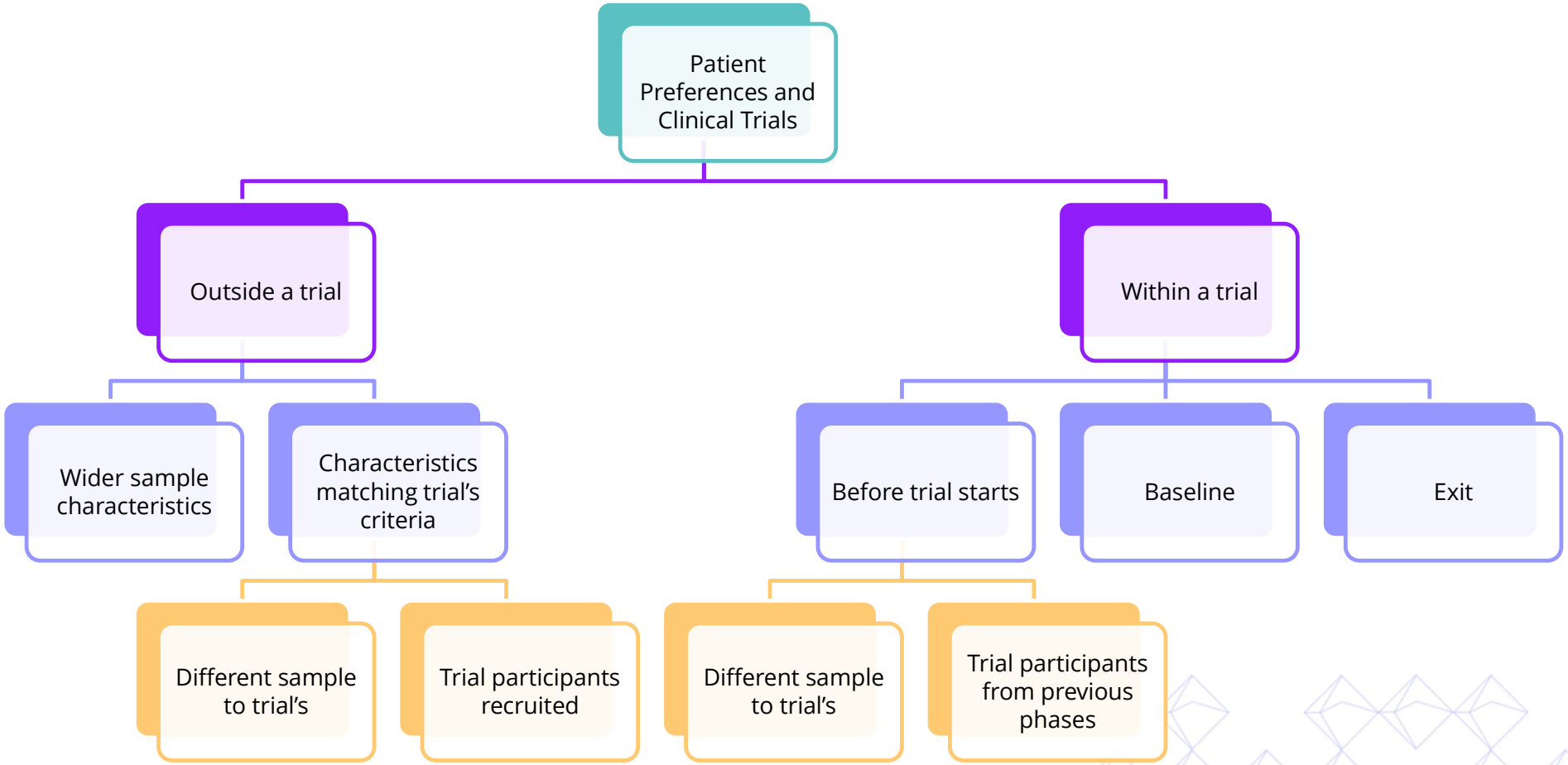
When final, this guidance will supersede "Patient Preference Information – Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and De Novo Requests, and Inclusion in Decision Summaries and Device Labeling," issued August 2016.

FDA U.S. FOOD & DRUG ADMINISTRATION

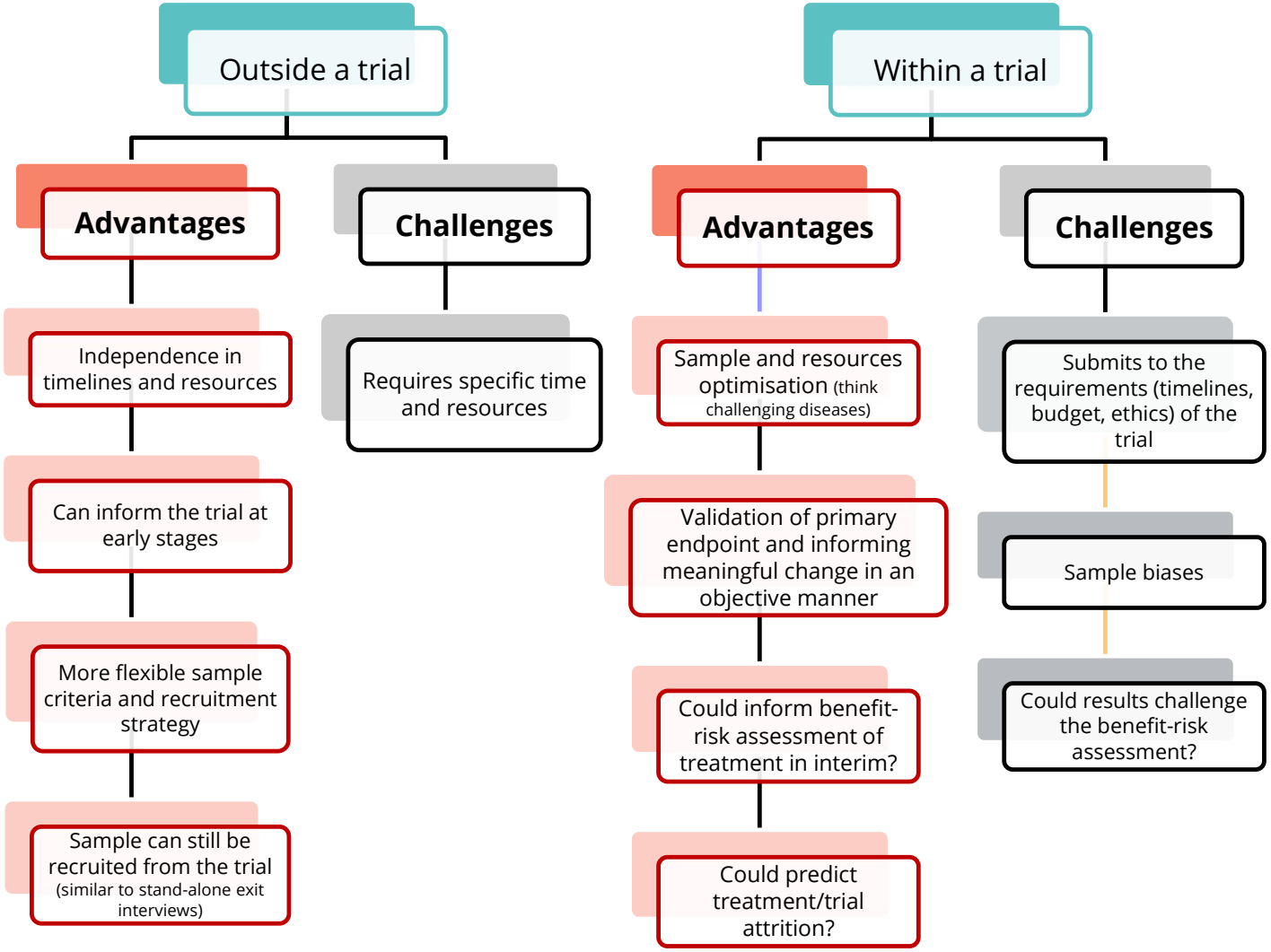
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

Describes how, by incorporating patient preferences, researchers can inform the clinically meaningful value of their endpoints.

When and How can patient preferences be implemented to complement clinical trials?



What are the perceived advantages and challenges?



CASE STUDIES

Patient Preferences Supporting Clinical Trials

Case study 1

Surg Endosc (2015) 29:2984–2993
DOI 10.1007/s00464-014-4044-2

Incorporating patient-preference evidence into regulatory decision making

Martin P. Ho · Juan Marcos Gonzalez · Herbert P. Lerner · Carolyn Y. Neuland · Joyce M. Whang · Michelle McMurry-Heath · A. Brett Hauber · Telba Irony

Received: 5 September 2014 / Accepted: 9 November 2014 / Published online: 1 January 2015

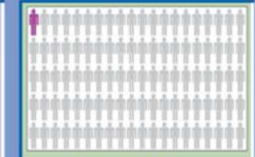
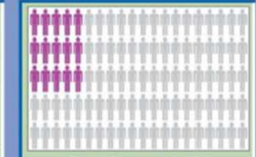
- **Objective:** quantify the relative importance of safety, effectiveness, and other attributes of weight-loss devices for obesity.
- **Methods:** a DCE (with eight attributes) was utilised.
  - The sample was recruited outside a Clinical Trial but with similar eligibility criteria (e.g., BMI and willing to loose weight)
- **Results:** identified that for participants to accept a device with a 0.01 % mortality risk, a risk-tolerant patient will require about 10 % total body weight loss lasting 5 years.

Ho MP, Gonzalez JM, Lerner HP, Neuland CY, Whang JM, McMurry-Heath M, Hauber AB, Irony T. Incorporating patient-preference evidence into regulatory decision making. Surg Endosc. 2015 Oct;29(10):2984-93. doi: 10.1007/s00464-014-4044-2. Epub 2015 Jan 1. PMID: 25552232.

Case study 1

Cont…

- Example of the trade-off questions

Feature	Device A	Device B
Type of operation	Open surgery	Open surgery
Recommended diet restrictions	Wait 4 hours between eating	Can't eat sweets or foods that are hard to digest
Average amount of weight loss	30 lbs.	15 lbs.
On average, how long the weight loss lasts	Weight loss lasts 5 years	Weight loss lasts 6 months
Average reduction in dose of prescription drugs for Diabetes at the lower weight	Eliminate need for prescription drugs to treat Diabetes	Half the current dose to treat Diabetes
On average, how long side effects last (Remember that side effects will limit your ability to do daily activities several times a month)	1 year	1 month
Chance of side effects requiring hospitalization	5% chance of going to hospital with no surgery	5% chance of going to hospital with no surgery
Chance of dying from getting the weight loss device	 1% (10 out of 1,000)	 15% (150 out of 1,000)

Which weight-loss device do you think is better for people like you?	Device A	Device B

[If Device A is chosen as shown]

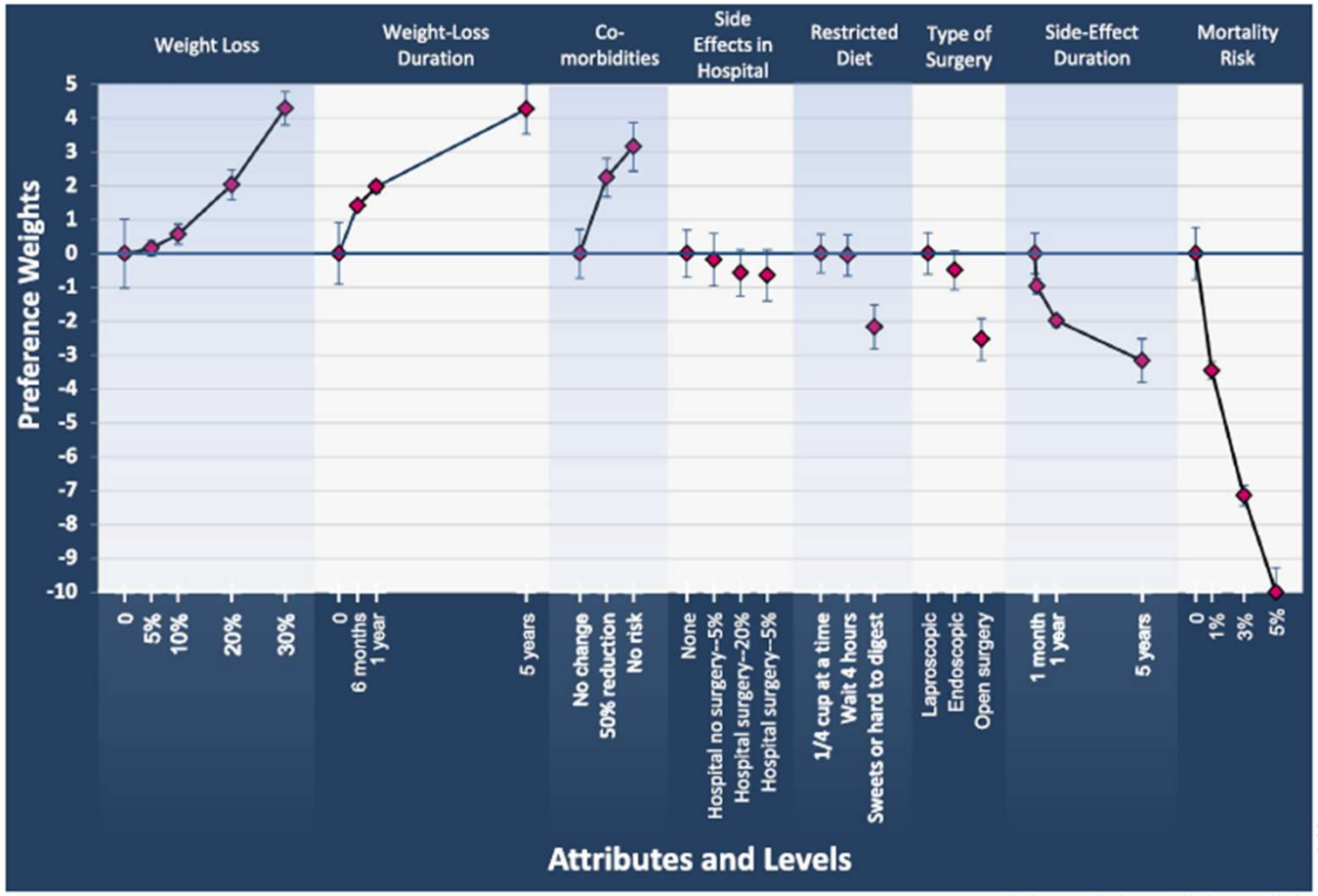
Would you get Device A if it was available?

- O Yes
- O No
- O Not sure or don't know

Ho MP, Gonzalez JM, Lerner HP, Neuland CY, Whang JM, McMurry-Heath M, Hauber AB, Irony T. Incorporating patient-preference evidence into regulatory decision making. Surg Endosc. 2015 Oct;29(10):2984-93. doi: 10.1007/s00464-014-4044-2. Epub 2015 Jan 1. PMID: 25552232.

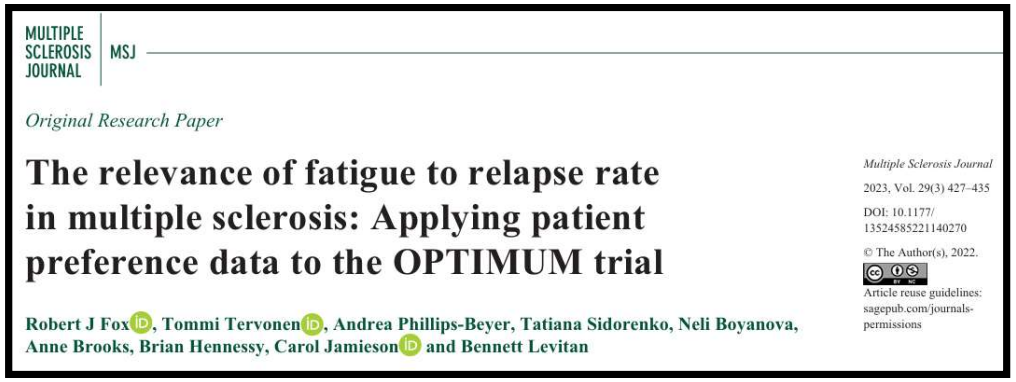
Case study 1

Cont…



Ho MP, Gonzalez JM, Lerner HP, Neuland CY, Whang JM, McMurry-Heath M, Hauber AB, Irony T. Incorporating patient-preference evidence into regulatory decision making. Surg Endosc. 2015 Oct;29(10):2984-93. doi: 10.1007/s00464-014-4044-2. Epub 2015 Jan 1. PMID: 25552232.

Caste study 2



MULTIPLE SCLEROSIS JOURNAL | MSJ

Original Research Paper

The relevance of fatigue to relapse rate in multiple sclerosis: Applying patient preference data to the OPTIMUM trial

Robert J Fox, Tommi Tervonen, Andrea Phillips-Beyer, Tatiana Sidorenko, Neli Boyanova, Anne Brooks, Brian Hennessy, Carol Jamieson and Bennett Levitan

Multiple Sclerosis Journal
2023, Vol. 29(3) 427–435
DOI: 10.1177/13524585221140270

- **Objective:** to understand the clinical relevance of the difference in fatigue scores between ponesimod and teriflunomide in the OPTIMUM (phase III) trial.
- **Method:** combining data from OPTIMUM and a DCE study to determine the number of relapses per year and the change in time to MS progression that patients regarded as equal in importance to the treatment difference in fatigue observed in OPTIMUM.
  - Sample recruited independent of the trial – and characteristics represented a slightly more severe cohort
- Results:

Fox RJ, Tervonen T, Phillips-Beyer A, et al. The relevance of fatigue to relapse rate in multiple sclerosis: Applying patient preference data to the OPTIMUM trial. Multiple Sclerosis Journal. 2022;29(3):427-435. doi:10.1177/13524585221140270

Caste study 2

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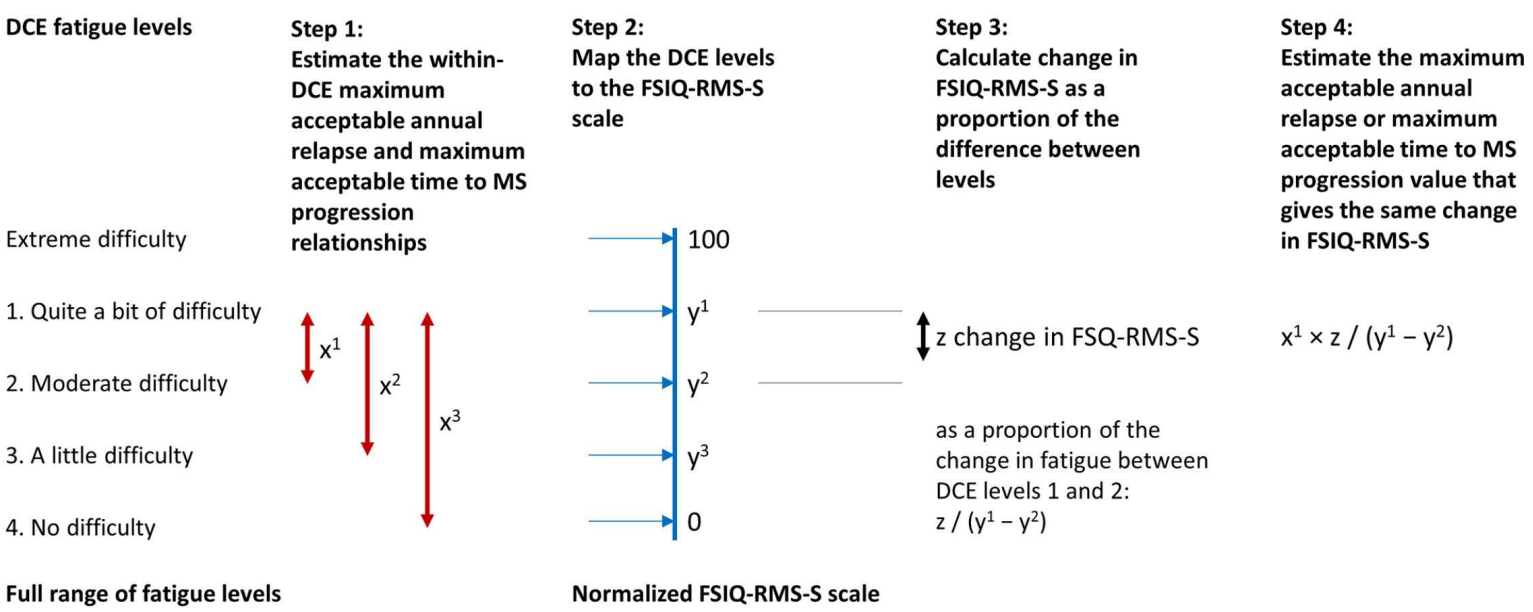

x^1, x^2, and x^3 represent the maximum acceptable annual relapse and maximum acceptable time to MS progression values for changes in levels of fatigue (physical or cognitive) within the DCE. For example, x^1 represents the maximum acceptable annual relapse or maximum acceptable time to MS progression value for a change from "Quite a bit of difficulty" to "Moderate difficulty", and x^3 represents the maximum acceptable annual relapse or maximum acceptable time to MS progression value for a change from "Quite a bit of difficulty to" "No difficulty".

The mapping estimates change y^i in FSQI-RMS-S score corresponding to a particular change in DCE fatigue level. The DCE fatigue levels are approximately equispaced along the FSIQ-RMS-S scale.

For change z in FSIQ-RMS-S, the corresponding proportion of the difference in fatigue levels is determined. For example, using levels 1 and 2 as anchors, the proportion is $z / (y^1 - y^2)$.

The change in maximum acceptable annual relapses or maximum acceptable time to MS progression that is equally as important as change z in FSIQ-RMS-S is estimated. For example, using levels 1 and 2 as anchors, the maximum acceptable annual relapse and maximum acceptable time to MS progression values are $x^1 \times z / (y^1 - y^2)$.

Fox RJ, Tervonen T, Phillips-Beyer A, et al. The relevance of fatigue to relapse rate in multiple sclerosis: Applying patient preference data to the OPTIMUM trial. Multiple Sclerosis Journal. 2022;29(3):427-435. doi:10.1177/13524585221140270

Caste study 2

Cont…

Table 3. Maximum acceptable increase in annual relapses and maximum acceptable decrease in time to MS progression for a 3.57-point improvement in FSIQ-RMS-S score.

Fatigue level	Corresponding FSIQ-RMS-S score	Maximum acceptable increase in annual relapses (95% CI)		Maximum acceptable decrease in time to MS progression in years (95% CI)	
		Physical fatigue	Cognitive fatigue	Physical fatigue	Cognitive fatigue
A little difficulty	25	0.06 (0.02–0.10)	0.09 (0.05–0.13)	0.17 (0.05–0.28)	0.24 (0.13–0.35)
Moderate difficulty	50	0.06 (0.03–0.09)	0.10 (0.07–0.13)	0.15 (0.07–0.23)	0.28 (0.19–0.36)
Quite a bit of difficulty	75	0.21 (0.18–0.25)	0.15 (0.12–0.18)	0.57 (0.48–0.66)	0.40 (0.32–0.49)
Average across all levels	–	0.12 (0.10–0.13)	0.12 (0.10–0.13)	0.32 (0.28–0.36)	0.32 (0.27–0.36)

CI: confidence interval; FSIQ-RMS-S: Fatigue Symptoms and Impacts Questionnaire–Relapsing Multiple Sclerosis, symptom domain; *SD*: standard deviation.

Fox RJ, Tervonen T, Phillips-Beyer A, et al. The relevance of fatigue to relapse rate in multiple sclerosis: Applying patient preference data to the OPTIMUM trial. Multiple Sclerosis Journal. 2022;29(3):427-435. doi:10.1177/13524585221140270

Caste study 3

OXFORD

Sleep Research Society®

SLEEP, 2022, 1–12

https://doi.org/10.1093/sleep/zsac204
Advance Access Publication Date: 2 September 2022
Original Article

ORIGINAL ARTICLE

Preferences of patients for benefits and risks of insomnia medications using data elicited during two phase III clinical trials

Sebastian Heidenreich[1], Melissa Ross[2], Gin Nie Chua[1], Dalma Seboek Kinter[3] and Andrea Phillips-Beyer[4,*]

[1]Patient Centered Research, Evidera, London, UK, [2]Patient Centered Research, Evidera, Bethesda, MD, USA, [3]Idorsia, Allschwil, Switzerland and [4]Innovus Consulting, London, UK

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Sleep Epidemiology 5 (2025) 100108

Contents lists available at ScienceDirect

Sleep Epidemiology

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sleep epidemiology

A patient-centric benefit-risk assessment of daridorexant for the treatment of insomnia disorder using patient preference data collected in two phase 3 clinical trials

Sebastian Heidenreich [a], Melissa Ross [b,*], Bruno Flamion [c], Andrea Phillips-Beyer [d]

- **Objective:** to determine whether, relative to placebo, the benefits of daridorexant 25 mg and 50 mg outweigh their risks from the patient's perspective.
- **Methods:** data from an optional DCE administered to a subset of subjects recruited from Germany and the US who participated in the two phase 3 clinical trials of *daridorexant* (insomnia Tx).
- **Results:** both daridorexant 25 mg and daridorexant 50 mg had a significantly higher net benefit than placebo (both $p < 0.001$)

Heidenreich, Sebastian, et al. "Preferences of patients for benefits and risks of insomnia medications using data elicited during two phase III clinical trials." Sleep 45.11 (2022): zsac204.
Heidenreich S., Ross M., Flamion B., Phillips-Beyer A., A patient-centric benefit-risk assessment of daridorexant for the treatment of insomnia disorder using patient preference data collected in two phase 3 clinical trials, Sleep Epidemiology, Volume 5, 2025, 100108, ISSN 2667-3436,

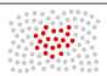
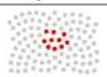
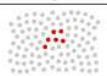
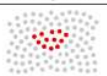
Caste study 3

Cont…

As in the practice question, your doctor asks you to decide between two treatments for your sleeping problems, treatment A and treatment B. The outcomes you will experience after taking either treatment A or treatment B are described in the table below.

Take a moment to review the outcomes produced by each treatment, and then indicate which treatment you would choose at the bottom of the table.

To see the description of each outcome, hover your mouse over the name of the outcome in the left column.

Outcomes	Treatment A	Treatment B
Time it takes to fall asleep		
	30 minutes to fall asleep	45 minutes to fall asleep
Total time asleep		
	5 hours	7 hours
Daytime functioning		
	Restricted functioning	Difficulty functioning
Likelihood of next morning dizziness/ grogginess		
	20 out of 100 patients (20%)	10 out of 100 patients (10%)
Likelihood of abnormal thoughts and behavioural changes		
	6 out of 100 patients (6%)	12 out of 100 patients (12%)
Likelihood of falls in the night		
	5 out of 100 patients (5%)	0 out of 100 patients (0%)
Treatment withdrawal		
	Moderate withdrawal	Severe withdrawal
Choice:	○	○

Heidenreich, Sebastian, et al. "Preferences of patients for benefits and risks of insomnia medications using data elicited during two phase III clinical trials." Sleep 45.11 (2022): zsac204.
Heidenreich S., Ross M., Flamion B., Phillips-Beyer A., A patient-centric benefit-risk assessment of daridorexant for the treatment of insomnia disorder using patient preference data collected in two phase 3 clinical trials, Sleep Epidemiology, Volume 5, 2025, 100108, ISSN 2667-3436,

Caste study 3

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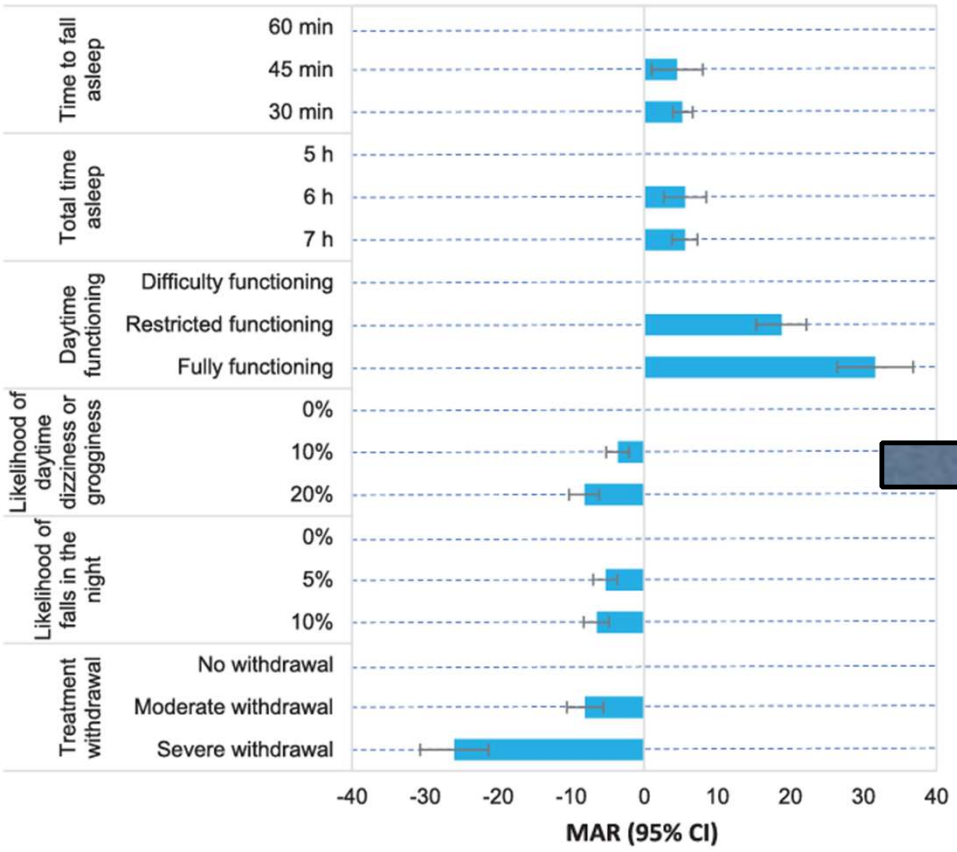

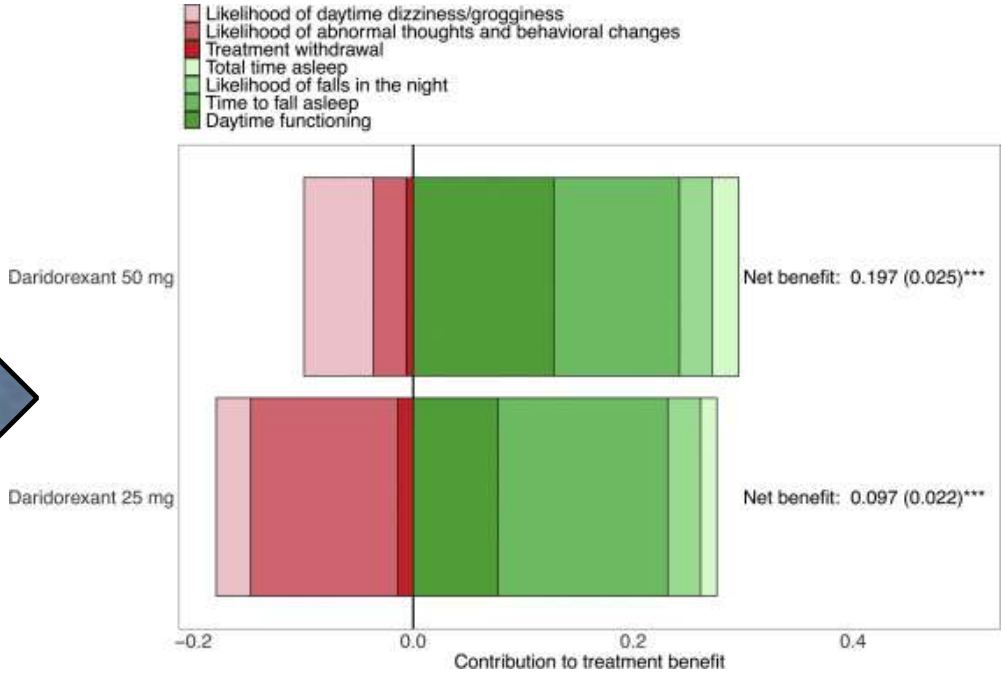

Figure 4. MAR of abnormal thoughts and behavioral changes. MAR normalizes the impact of changes in attributes on preferences using risk equivalences as a common and comparable unit of measurement. CI, confidence interval; MAR, maximum acceptable risk of abnormal thoughts and behavioral changes.

Heidenreich, Sebastian, et al. "Preferences of patients for benefits and risks of insomnia medications using data elicited during two phase III clinical trials." Sleep 45.11 (2022): zsac204.

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Caste study 3

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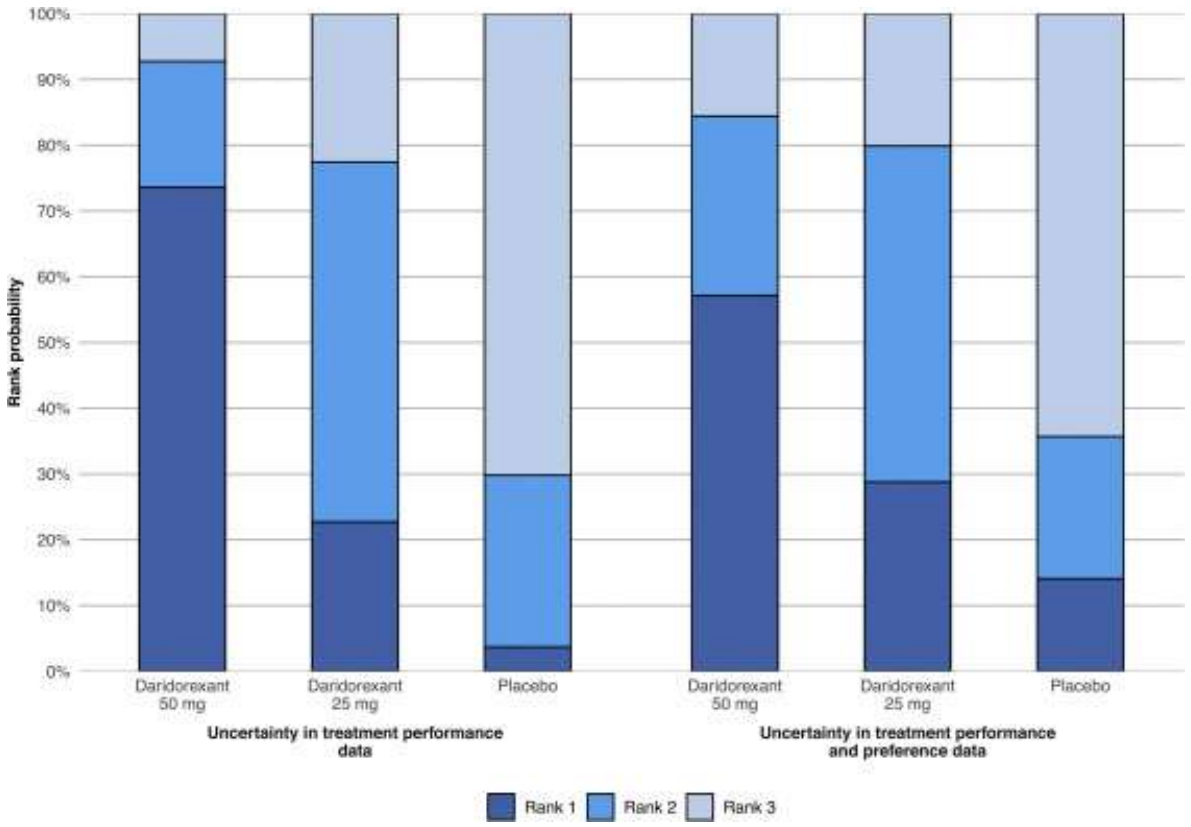

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Conclusions and Next Steps

1. There has been proven value from Patient Preferences information informing decision-making related to clinical trials
2. Patient Preferences information can complement Clinical Trial findings – but it seems to be more efficient and accurate when considered in advance
3. Further research is required to establish advantages that surpass the challenges and ultimately provide best practices for Patient Preferences studies designed for/with Clinical Trials

Research collaborators are members from the PREFER EN: Byron Jones[1], Michael Bui[2], Janine van Til[2], Karin Oudshoorn[2], Jorien Veldwijk[3], Barry Liden [4], Conny Berlin[1]

[1]Novartis, Basel, Switzerland, [2]University of Twente, Enschede, The Netherlands, [3]Erasmus University Rotterdam, Netherlands, [4]USC Schaeffer Institute, Washington, US