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Aim 2 – Patient Preference Survey Breakout Session

Aim 2 Team

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Threshold technique survey: Development process

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Heather Benz, PhD
FDA Center for Devices and Radiological Health

Attribute List

Benefits	Risks	Other considerations
Amount of time your Parkinson's treatment works each day	Increased risk of depression or anxiety	Number of oral medicines you take each day to treat Parkinson's disease and the side effects of Parkinson's medicines
Movement symptoms of Parkinson's disease	Risk of bleeding in your brain because of the device	Time until the device is available
Pain because of Parkinson's disease	Risk of dying within 1 year of getting the device	
Trouble thinking clearly, getting organized, or making plans because of Parkinson's disease		

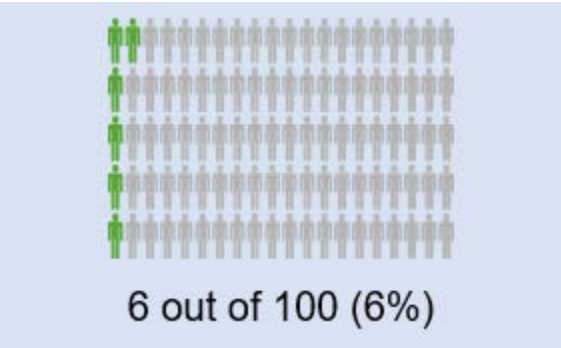
Attribute Level Development Process

Attribute Levels

- Benefits: severity scale

No movement symptoms										Very Severe Movement Symptoms
0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

- Risks: probability



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Pretest Interviews

One-on-one conversations to ensure the survey is interpreted as intended.

Key considerations:

- Diversity of background and experiences among pretest participants, including disease stage and duration
- Are participants able to answer the survey questions?

Some updates as a result of pretesting:

- Risk of developing depression
- Daytime sleepiness and sleep problems
- Maximum wait time for a new device

Threshold technique survey: The method

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Threshold Technique

- Respondent presented with 2 alternatives:

Reference Treatment	Target Treatment
Typically standard of care or Current treatment	Hypothetical or real-world alternative to the existing state of the world

- Respondent asked to choose between reference and target treatment
- The level of one attribute of the target alternative is varied systematically until the respondent switches his or her preferred alternative
  - Target made systematically better (more attractive) if reference treatment chosen first
  - Made systematically worse (less attractive) if target is chosen first

Threshold Technique

	Option A (Reference)	Option B (Target)
Treatment	Task 1 to 3 pills, spaced throughout the day	
Pain: Pain experienced while walking after taking pills daily, on a 0-10 scale is…	5	3
Out-of-pocket cost:	$0	$0
Risks and Side Effects		
Stomach Bleed: Feeling unwell, Vomiting blood. Treatment involves hospitalization, sedation for tests, a tube inserted down the throat, and blood transfusion. Hospital stay will be for 2-7 days. You will be tired for about 3-4 weeks, on medication for 6 months. A small proportion of people may die from stomach bleeding.	2%	2%
Dyspepsia: Nausea, heartburn, stomach pain. These symptoms will disappear if you stop your arthritis medication.	20%	20%
Fluid Retention: Swelling ankles or legs, The side effect will disappear if you stop your arthritis medication.	5%	5%
Heart Attack or Stroke: These conditions usually require hospitalization and may cause long-term disability. About 1 in 10 to 1 in 5 patients will die after heart attack or stroke.	1%	1%
High Blood Pressure: Increase in blood pressure. This may be more severe in patients who already have high blood pressure, heart disease or kidney problems. Treatment usually requires long-term medication, but will disappear if you stop your arthritis medication.	10%	10%

Option B (Target)

Option A (Reference)

Source: Kopec et al., (2007) J Clin Epidemiol

Threshold Technique

	Option A (Reference)	Option B (Target)
Treatment	Task 1 to 3 pills, spaced throughout the day	
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High Blood Pressure: Increase in blood pressure. This may be more severe in patients who already have high blood pressure, heart disease or kidney problems. Treatment usually requires long-term medication, but will disappear if you stop your arthritis medication.	10%	10%

Reference Pain (Option A) = 5 on a scale of 0 (none) to 10 (worst)

Reference Pain (Option B) = 3 on a scale of 0 (none) to 10 (worst)

- Option B has greater pain relief
- All other levels the same in Option A and Option B
- Everyone should choose Option B

Source: Kopec et al., (2007) J Clin Epidemiol

Threshold Technique

	Option A (Reference)	Option B (Target)
Treatment	Task 1 to 3 pills, spaced throughout the day	
Pain: Pain experienced while walking after taking pills daily, on a 0-10 scale is…	5	3
Out-of-pocket cost:	$0	$0
Risks and Side Effects		
Stomach Bleed: Feeling unwell, Vomiting blood. Treatment involves hospitalization, sedation for tests, a tube inserted down the throat, and blood transfusion. Hospital stay will be for 2-7 days. You will be tired for about 3-4 weeks, on medication for 6 months. A small proportion of people may die from stomach bleeding.	2%	2%
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High Blood Pressure: Increase in blood pressure. This may be more severe in patients who already have high blood pressure, heart disease or kidney problems. Treatment usually requires long-term medication, but will disappear if you stop your arthritis medication.	10%	10%

- Option A is the reference treatment
- Option B is the target treatment
- Option B has greater pain relief
- In this example, everyone should choose Option B
- Rate of high blood pressure is the threshold of interest

Rate of high blood pressure for Option B is increased systematically until respondent chooses Option A

Source: Kopec et al., (2007) J Clin Epidemiol

Threshold technique survey: Analysis

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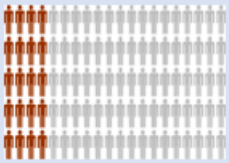
The Survey Data

- The survey elicited respondents' maximum acceptable risk threshold of 3 treatment risks for 5 different treatment benefits
  - There were 15 versions of the threshold technique questions (one for each benefit-risk pairing)
- The survey elicited respondents' maximum acceptable wait time for 5 different treatment benefits
  - There were 5 version of the time tradeoff questions
- Respondents evaluated benefits that were conditional on their self-reported baseline of benefit outcomes

Threshold Technique Question

5 treatment benefit outcomes

3 treatment risks

	Your current treatment	A new device
Hours of "on time" each day	**X** hours of "**on time**" **[16-X]** hours of "**off time**"	**X** hours of "**on time**" **[16-X]** hours of "**off time**"
Severity of movement symptoms	**MS1** (on a scale from 0 to 10)	**MS1 ÷ 2** (on a scale from 0 to 10)
Severity of pain	**PS1** (on a scale from 0 to 10)	**PS1** (on a scale from 0 to 10)
Difficulty thinking clearly, getting organized, or making plans	**CS1** (on a scale from 0 to 10)	**CS1** (on a scale from 0 to 10)
Number of pills you need to take	**PB1** pills each day	**PB1** pills each day
Risk of getting depression or anxiety after getting the device	None	 20 out of 100 (20%)
Risk of having bleeding in the brain after getting the device	None	None
Risk of dying within 1 year after getting the device	None	None
Which option would you choose?	☐	☐

New device (target) defined by 50% improvement in self-reported level of one benefit outcome…

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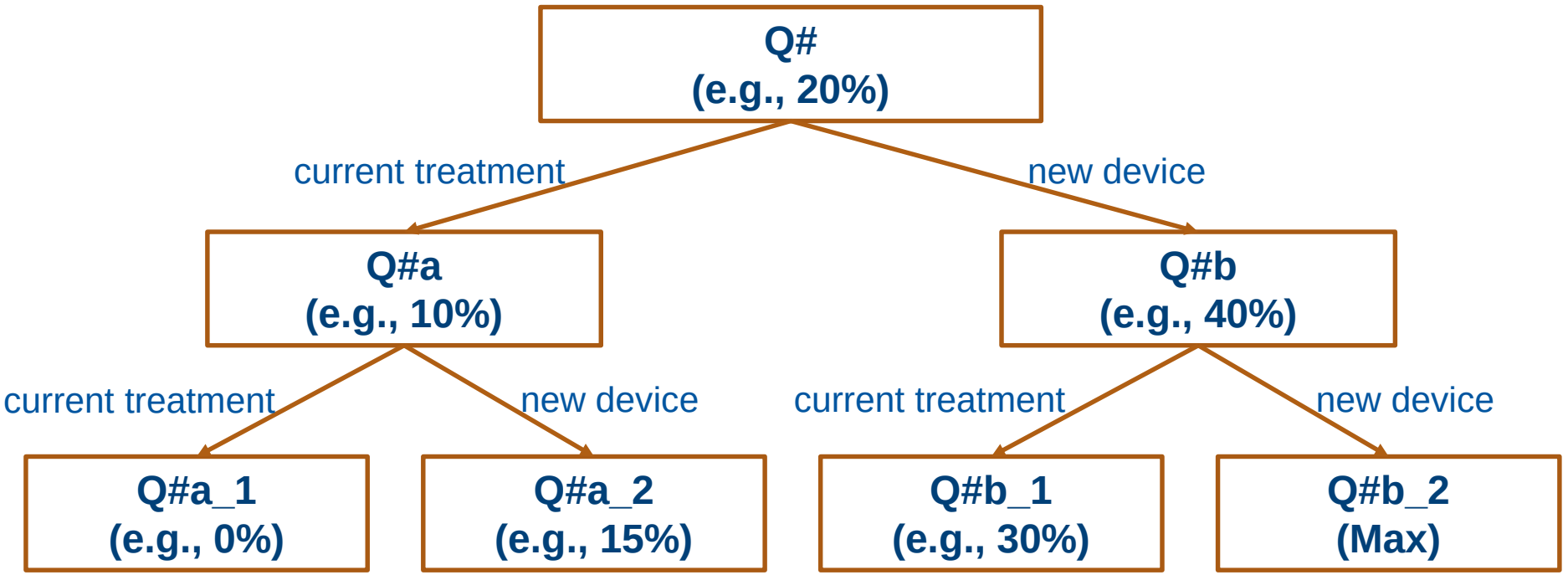
Threshold Technique Question



Analyzing the Threshold Technique Data

- Interval regression without constants on narrow threshold intervals
- Separate regression for each benefit-risk tradeoff
- Include age, ambulation, cognitive impairment, DBS experience, dyskinesia, and motor problems as covariates
- Use four age groups defined by sample quartiles
- Estimate two models:
  - Model with age group interacted with benefit
  - Separate models for each age group with covariates

Final Threshold Technique Models

1.) Individual model:

$$Threshold_i = \beta 1_i\, Benefit + \beta 2_i\, Non{-}ambulatory + \beta 3_i\, Cognitive\ Impairment + \beta 4_i\, DBS + \beta 5_i\, Dyskinesia + \beta 6_i\, Motor\ Problems + \epsilon$$

where i indexes age subgroups of ≤60, 61-66, 67-71, and >71.

2.) Aggregated model:

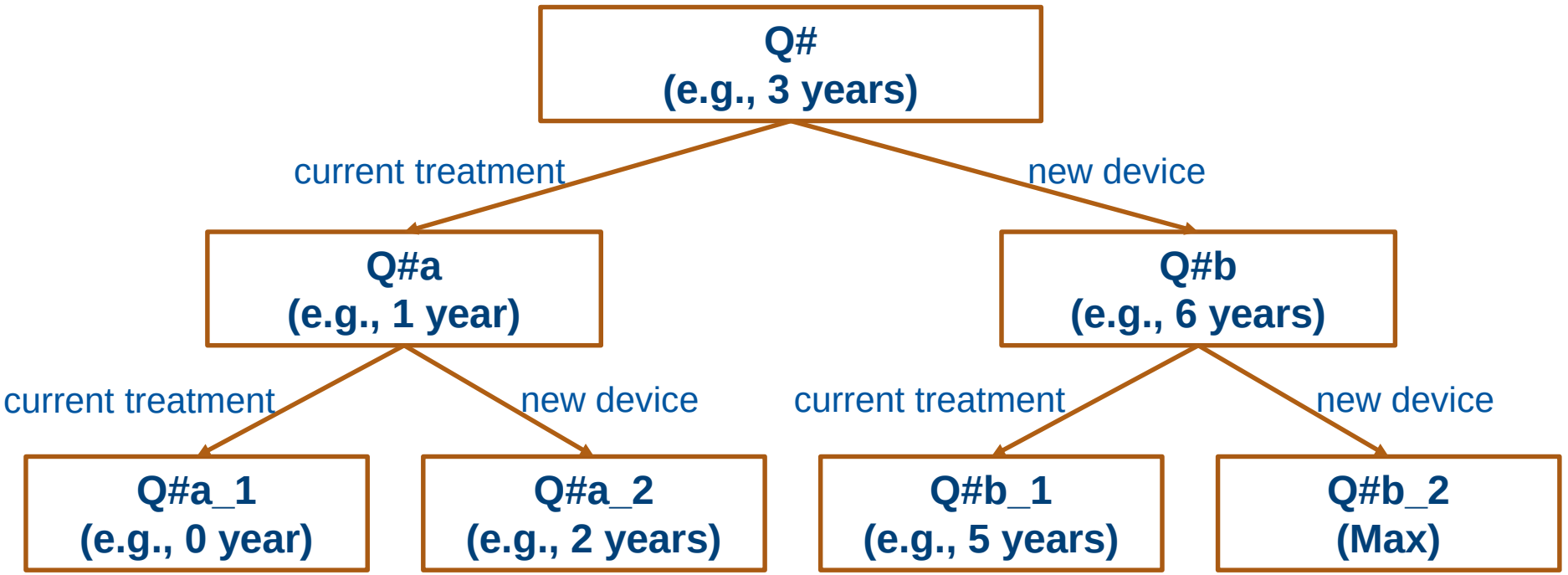
$$Threshold = \beta 1\, Benefit + \beta 2(Benefit * age\ 61{-}66) + \beta 3(Benefit * age\ 67{-}71) + \beta 4(Benefit * age{>}71) + \beta 5\, Non{-}ambulatory + \beta 5\, Cognitive\ Impairment + \beta 7\, DBS + \beta 8\, Dyskinesia + \beta 9\, Motor\ Problems + \epsilon$$

where age 61-66, age 67-71, and age >71 are dummy coded and age ≤60 is used as the reference category.

Time Tradeoff Question

	Device A	Device B
Severity of movement symptoms	**MS1-1** (on a scale from 0 to 10)	**MS1 ÷ 2** (on a scale from 0 to 10)
Time until you get the device	Now	3 years
Which option would you choose?	☐	☐

Time Tradeoff Question



Analyzing the Time Tradeoff Data

- Interval regression without constants on narrow intervals
- Separate regression for each benefit-time tradeoff
- Use natural logarithm transformation of benefit to estimate the discount rate
- Interact all covariates (age, ambulation, cognitive impairment, DBS experience, dyskinesia, and motor problems) with natural logarithm of benefit

Rationale for Log Transformation

The relationship we want to estimate is as follows:

$$1 = e^{-rt}\, x$$

i.e., the benefit x occurring t years from today discounted at rate r equals to 1 unit of benefit today.

Rearranging we get: $t = \frac{1}{r} \ln(x)$

Final Time Tradeoff Models

1.) Individual model(s):

$$Threshold_i = \beta 1_i \ln(Benefit) + \beta 2_i\ Non{-}ambulatory * \ln(Benefit) + \beta 3_i\ Cognitive\ Impairment * \ln(Benefit) + \beta 4_i\ DBS * \ln(Benefit) + \beta 5_i\ Dyskinesia * \ln(Benefit) + \beta 6_i\ Motor\ Problems * \ln(Benefit) + \epsilon$$

where i indexes age subgroups of ≤60, 61-66, 67-71, and >71.

2.) Aggregated model:

$$Threshold = \beta 1 \ln(Benefit) + \beta 2 \ln(Benefit) * [age\ 61{-}66] + \beta 3 \ln(Benefit) * [age\ 67{-}71] + \beta 4 \ln(Benefit) * [age > 71] + \beta 5\ Non{-}ambulatory * \ln(Benefit) + \beta 5\ Cognitive\ Impairment * \ln(Benefit) + \beta 7\ DBS * \ln(Benefit) + \beta 8\ Dyskinesia * \ln(Benefit) + \beta 9\ Motor\ Problems * \ln(Benefit) + \epsilon$$

where age 61-66, age 67-71, and age >71 are dummy coded and age ≤60 is used as the reference category.

Threshold technique survey: Results

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Demographic Characteristics

Demographics	n=2,740
Mean Age (SD)	65.4 (9.01)
Female, n (%)	1,279 (46.7%)
Employed outside the home, n (%)	680 (24.8%)
Caucasian, n (%)	2,593 (94.6%)
4-year college degree or higher, n (%)	1,912 (69.7%)

Parkinson's Symptoms

Symptom	Number reporting symptom (%)	Symptom Level Mean (SD)
Average hours of on time*	1,677 (61.2%)	10.8 (3.78)
Severity of movement symptoms **	2,649 (96.7%)	4.3 (2.06)
Severity of pain**	1,348 (49.2%)	4.5 (2.23)
Severity of cognitive symptoms**	1,217 (44.4%)	4.4 (2.17)

*symptom was off time; respondents reporting off time were asked how many hours of on time they had in a 16 waking hours each day

**symptoms rated on a 10-point scale in which 0 indicated no symptoms and 10 indicated very severe symptoms

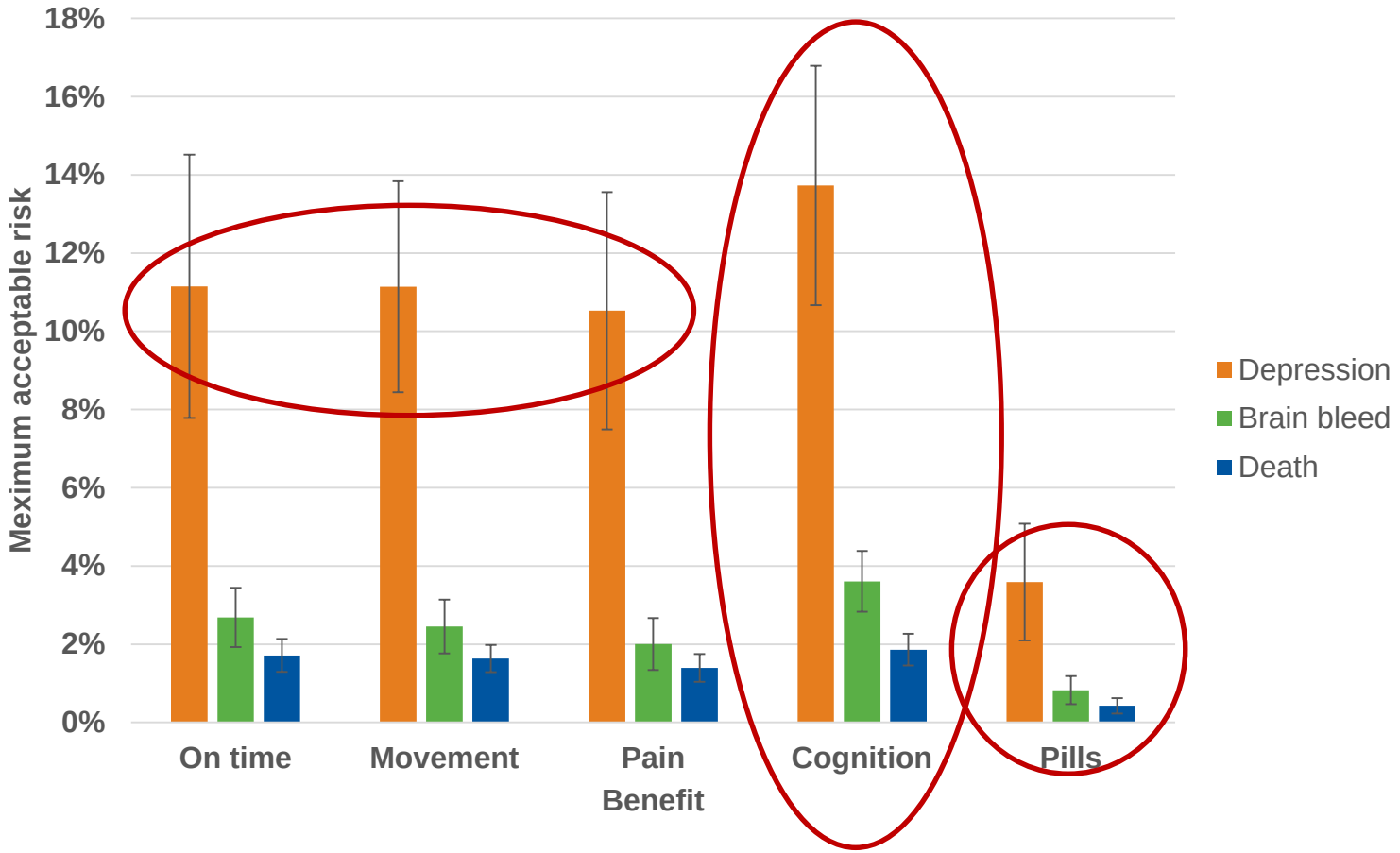
Other Characteristics

Parkinson's Related Characteristic		n=2,740
Number of daily pills	mean (SD)	7.6 (5.39)
Years since diagnosis	mean (SD)	5.3 (4.91)
Prior deep brain stimulation	n (%)	219 (8%)
Biological relative with PD	n (%)	569 (20.8%)

Experience with Risk Outcomes	n	mean (SD)
Severity of current depression or anxiety**	1,118	4.4 (2.09)
Prior brain bleed	67 (2.4%)	
Known someone who died after an operation	922 (33.6%)	

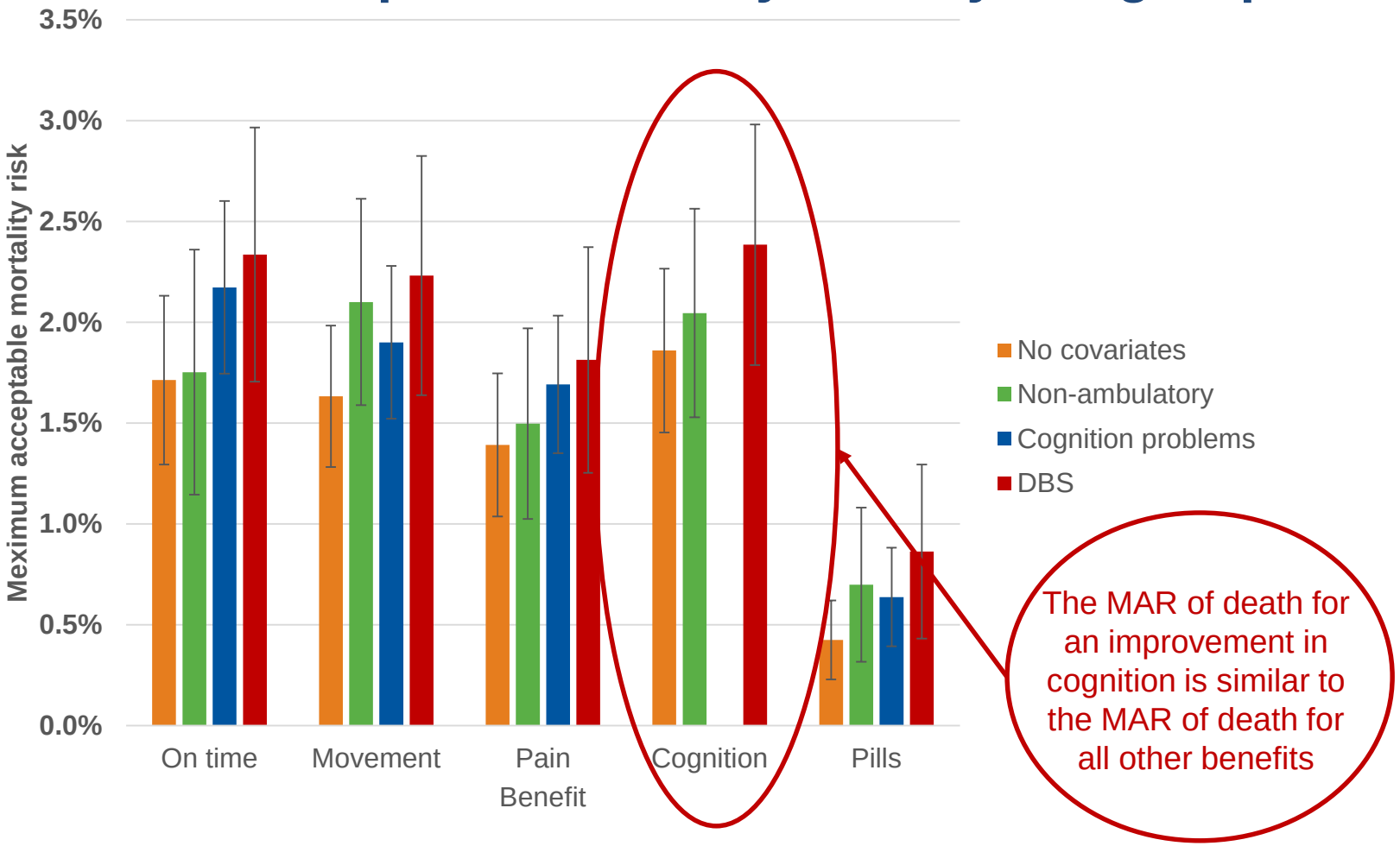
**symptoms rated on a 10-point scale in which 0 indicated no symptoms and 10 indicated very severe symptoms

Maximum Acceptable Risk of Each Risk for Each Benefit for Respondents with Median Sample Age (66 years)



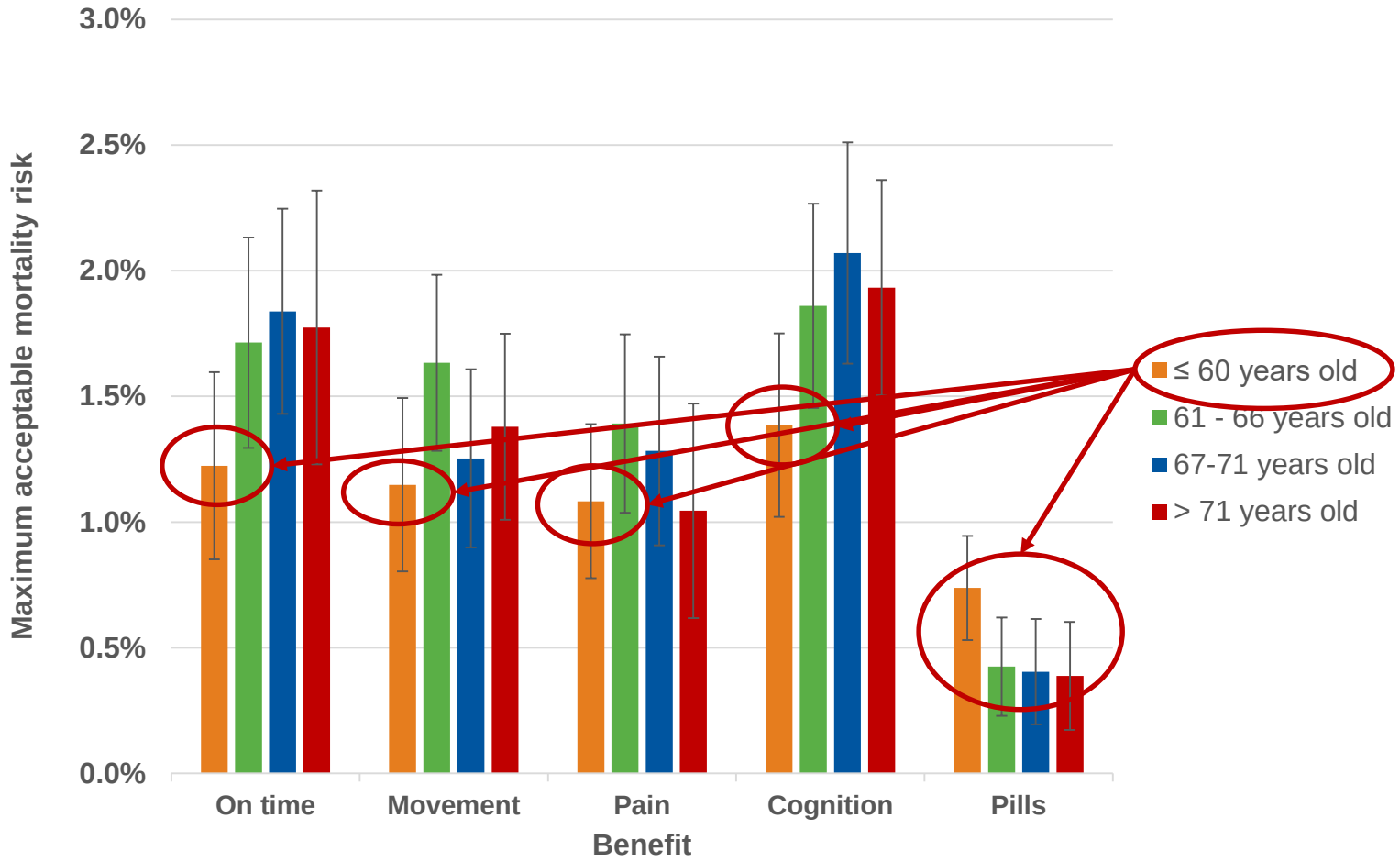
- The benefit levels were set as the midpoint of the benefits offered in the threshold questions. They are an improvement of 4.625 hours of on time, a reduction in movement, pain, or cognition of 3.25, and a reduction of 4.5 pills per day.

Maximum Acceptable Mortality Risk by Subgroup



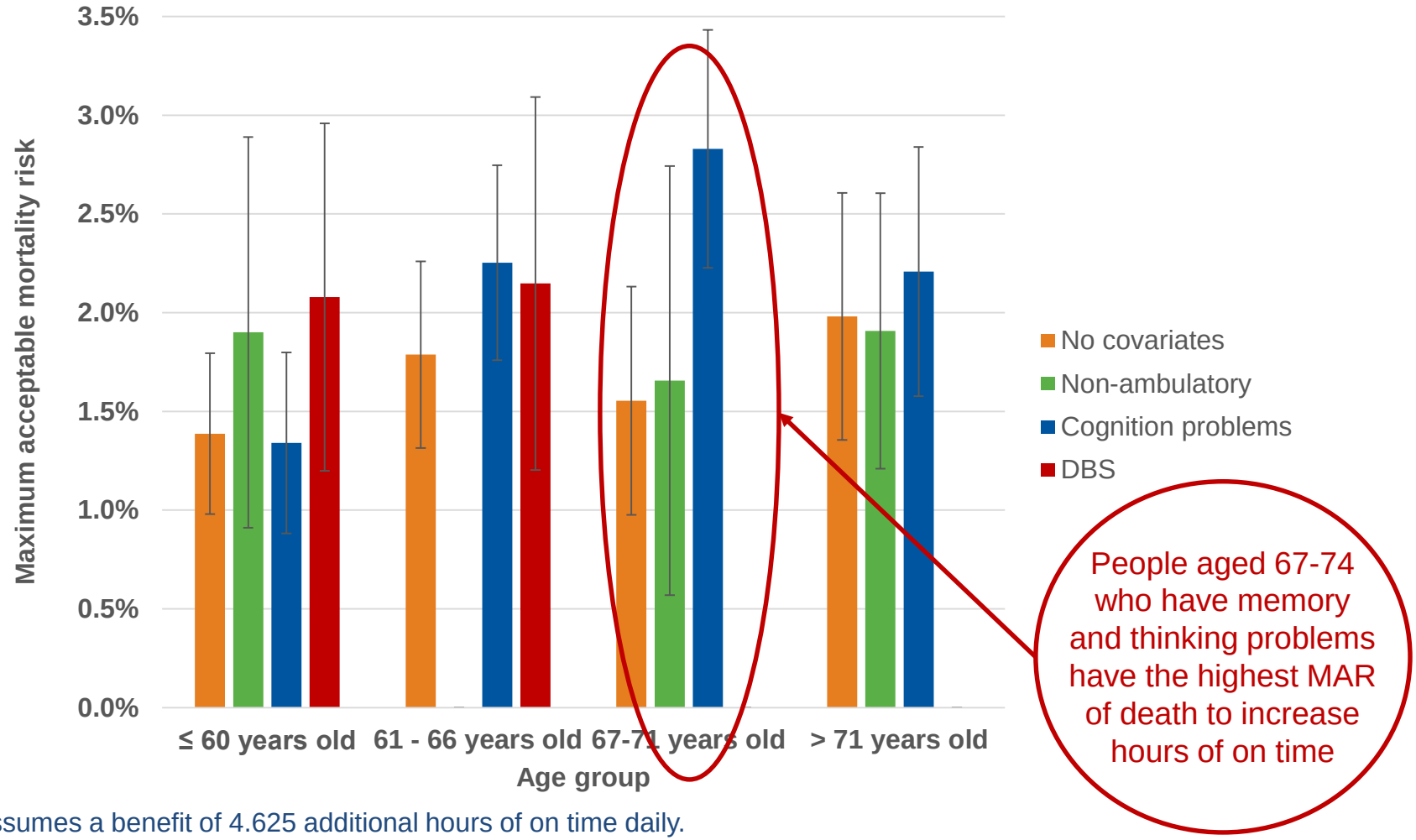
- The benefit levels were set as the midpoint of the benefits offered in the threshold questions. They are an improvement of 4.625 hours of on time, a reduction in movement, pain, or cognition of 3.25, and a reduction of 4.5 pills per day.
- Cognition was not included as a covariate in any of the models in which the benefit was an improvement in cognition, because all respondents who saw those versions of the threshold exercise reported cognition problems.

Maximum Acceptable Mortality Risk by Age Group



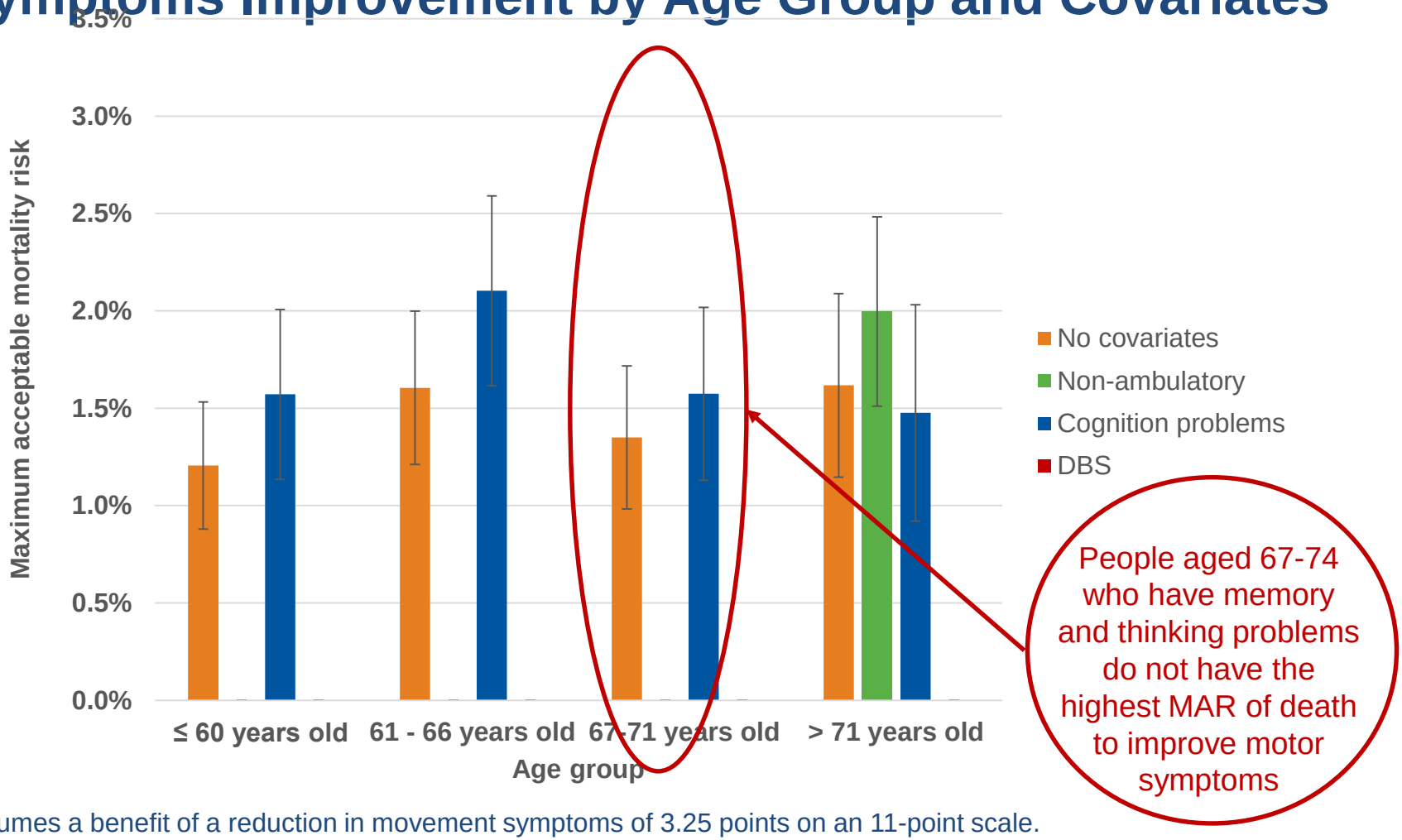
- The benefit levels were set as the midpoint of the benefits offered in the threshold questions. They are an improvement of 4.625 hours of on time, a reduction in movement, pain, or cognition of 3.25, and a reduction of 4.5 pills per day.
- Cognition was not included as a covariate in any of the models in which the benefit was an improvement in cognition, because all respondents who saw those versions of the threshold exercise reported cognition problems.

Maximum Acceptable Mortality Risk for On Time Improvement by Age Group and Covariates



- Assumes a benefit of 4.625 additional hours of on time daily.
- Covariates for ambulation, cognition, and DBS experience were only included in the individual age group models if more than 15 observations had the characteristic expressed by the covariate.

Maximum Acceptable Mortality Risk for Movement Symptoms Improvement by Age Group and Covariates



- Assumes a benefit of a reduction in movement symptoms of 3.25 points on an 11-point scale.
- Covariates for ambulation, cognition, and DBS experience were only included in the individual age group models if more than 15 observations had the characteristic expressed by the covariate.

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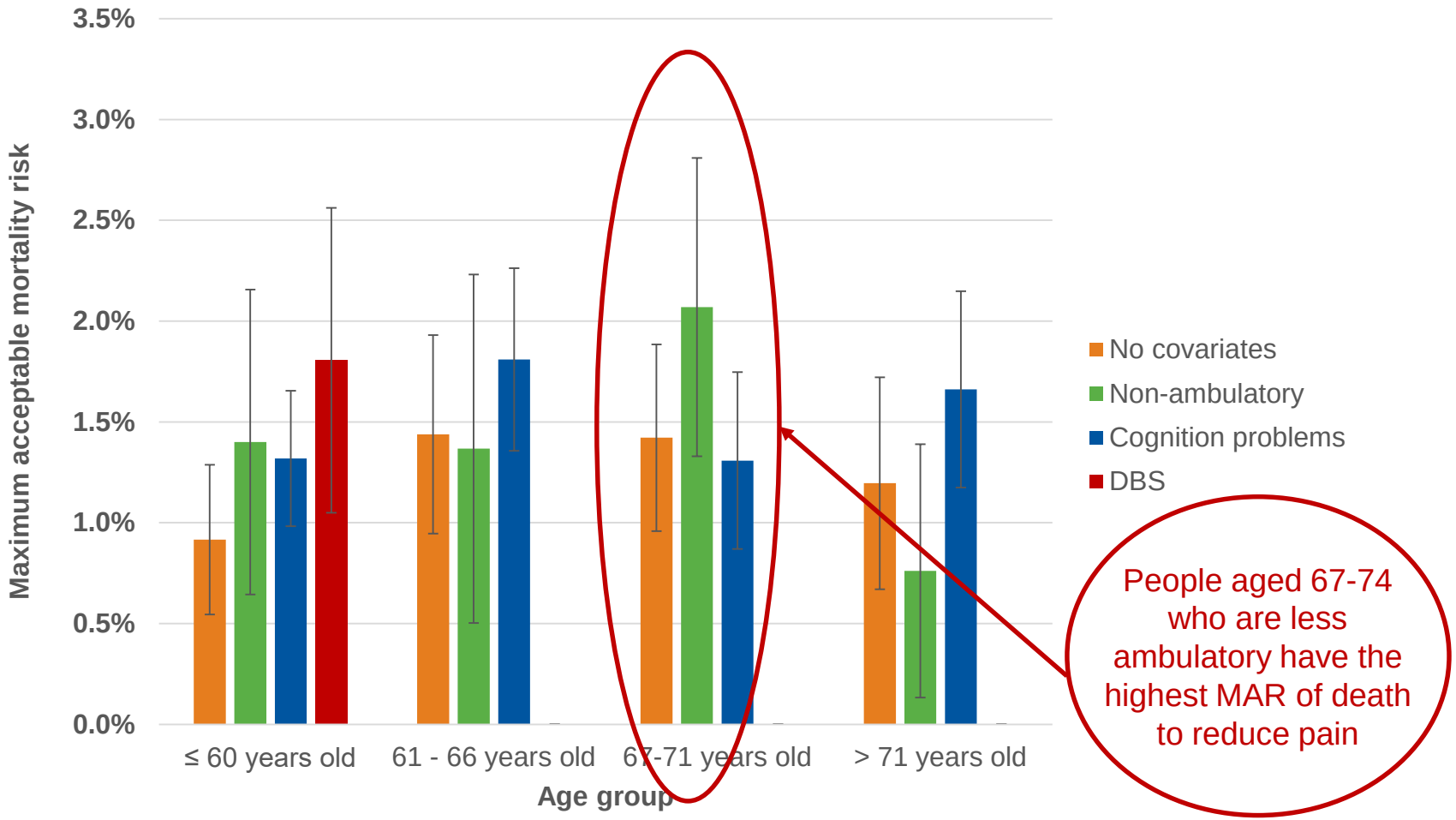
Maximum Acceptable Mortality Risk for Pain Improvement by Age Group and Covariates



- Assumes a benefit of a reduction in pain of 3.25 points on an 11-point scale.
- Covariates for ambulation, cognition, and DBS experience were only included in the individual age group models if more than 15 observations had the characteristic expressed by the covariate.

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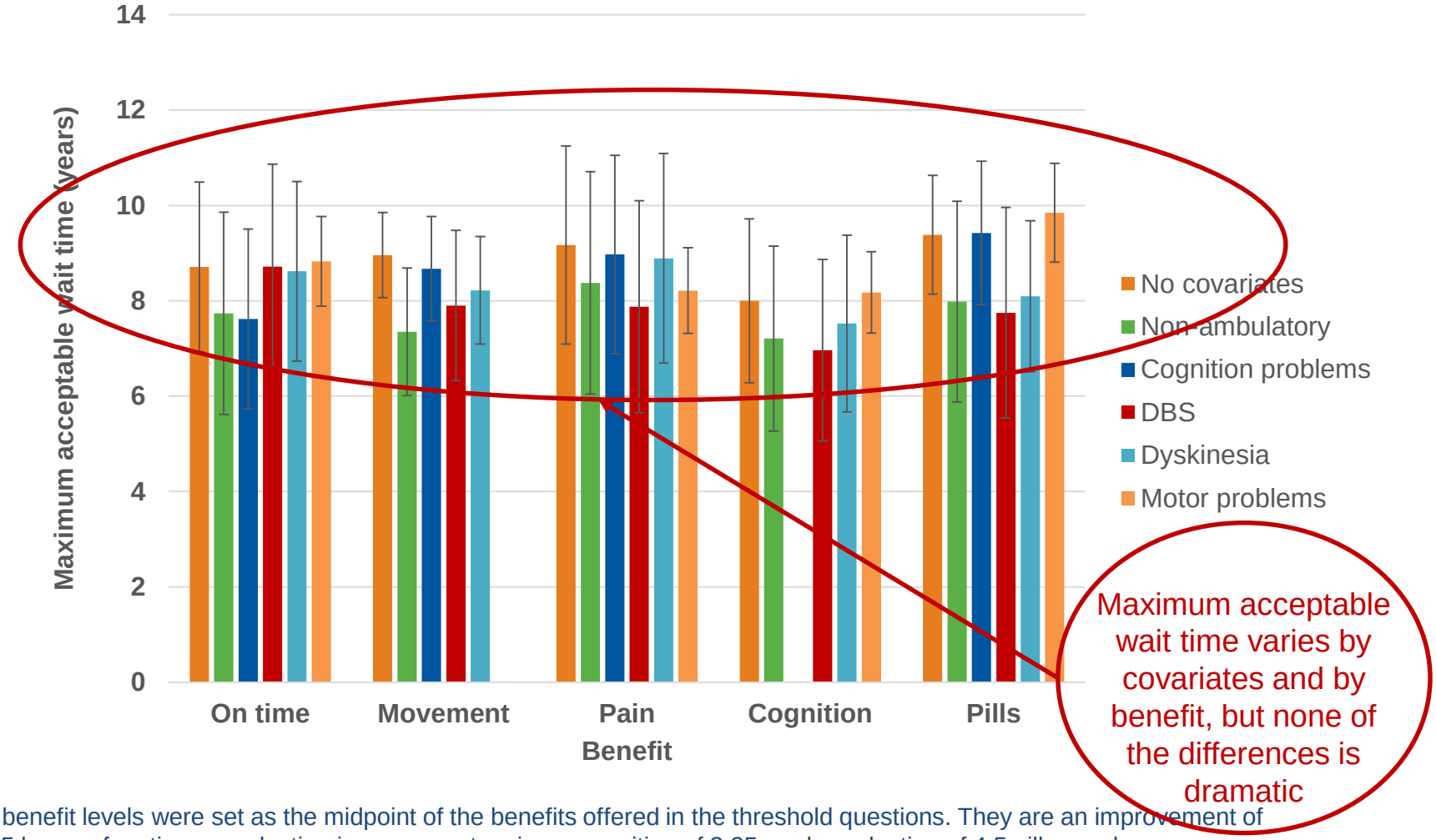
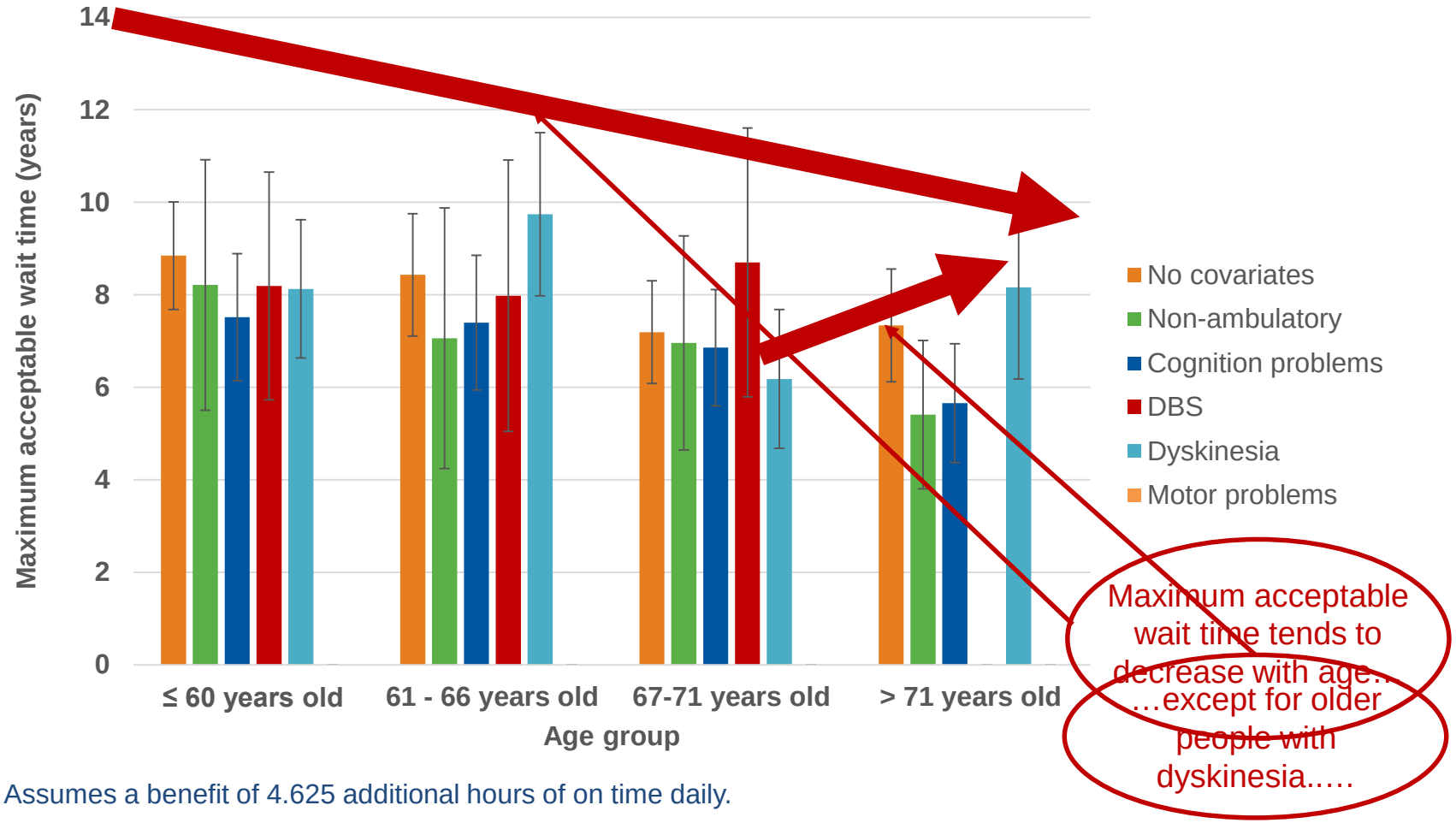
Maximum Acceptable Wait Time by Covariates



- The benefit levels were set as the midpoint of the benefits offered in the threshold questions. They are an improvement of 4.625 hours of on time, a reduction in movement, pain, or cognition of 3.25, and a reduction of 4.5 pills per day.
- Cognition was not included as a covariate in any of the models in which the benefit was an improvement in cognition, because all respondents who saw those versions of the threshold exercise reported cognition problems. For the same reason, motor problems was not included as a covariate in any of the models in which the benefit was an improvement in movement symptoms.

Maximum Acceptable Wait Time for On Time Improvement by Age Group



- Assumes a benefit of 4.625 additional hours of on time daily.
- Cognition was not included as a covariate in any of the models in which the benefit was an improvement in cognition, because all respondents who saw those versions of the threshold exercise reported cognition problems. For the same reason, motor problems was not included as a covariate in any of the models in which the benefit was an improvement in movement symptoms.

Conclusions

- Preference results have face validity
  - Maximum acceptable risk of (worsening) depression and anxiety is greater than that of brain bleed which is higher than that of death for all benefits
- Risk tolerance varies depending on the type of benefit and the level of benefit
- Risk tolerance varies across different types of patients
- Age is the respondent characteristic that is the most significant predictor of risk tolerance for any given type or level of benefit

Threshold Technique – Advantages and Limitations

- Advantages
  - Estimates risk tolerance for individual tradeoffs directly
  - Can be used for n=1 if
    - Threshold series continues until indifference is reached
    - Threshold is imputed within interval
  - Risk tolerance can be related directly to individual characteristics
  - Does not require an experimental design
- Limitations
  - Individual tradeoffs assumed independent
  - Requires multiple threshold series to achieve full coverage of tradeoffs
  - Potentially sensitive to bias from baseline level of risk if baseline level does not reflect actual or expected level

Threshold technique survey: What does this mean to patients?

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  - Members of the MJFF Patient Council who provided feedback and insight at critical steps in the project and participated in focus groups to refine the attributes and attribute descriptions
  - 20 incredible people with Parkinson's disease who participated in the telephone pretest interviews
  - The over 2700 people with Parkinson's disease who participated in the survey