Aim 2 – Patient Preference Survey Breakout Session
Aim 2 Team

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* Presenter in the Aim 2 breakout session
Threshold technique survey:
Development process

Heather Benz, PhD
FDA Center for Devices and Radiological Health
## Attribute List

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Risks</th>
<th>Other considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amount of time your Parkinson’s treatment works each day</td>
<td>Increased risk of depression or anxiety</td>
<td>Number of oral medicines you take each day to treat Parkinson’s disease and the side effects of Parkinson’s medicines</td>
</tr>
<tr>
<td>Movement symptoms of Parkinson’s disease</td>
<td>Risk of bleeding in your brain because of the device</td>
<td>Time until the device is available</td>
</tr>
<tr>
<td>Pain because of Parkinson’s disease</td>
<td>Risk of dying within 1 year of getting the device</td>
<td></td>
</tr>
<tr>
<td>Trouble thinking clearly, getting organized, or making plans because of Parkinson’s disease</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Attribute Level Development Process

1. Patient discussion groups
2. Clinical insight and historical context
3. Patient pretest interviews
Attribute Levels

• Benefits: severity scale

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

No movement symptoms

Very Severe Movement Symptoms

• Risks: probability

6 out of 100 (6%)
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
Threshold Technique

- Respondent presented with 2 alternatives:

<table>
<thead>
<tr>
<th>Reference Treatment</th>
<th>Target Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typically standard of care or Current treatment</td>
<td>Hypothetical or real-world alternative to the existing state of the world</td>
</tr>
</tbody>
</table>

- 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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Option A (Reference)</th>
<th>Option B (Target)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain:</td>
<td>Task 1 to 3 pills, spaced throughout the day</td>
<td></td>
</tr>
<tr>
<td>Pain experienced while walking after taking pills daily, on a 0-10 scale is...</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

**Out-of-pocket cost:**
- Option A: $0
- Option B: $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.
  - Option A: 2%
  - Option B: 2%

- **Dyspepsia:** Nausea, heartburn, stomach pain. These symptoms will disappear if you stop your arthritis medication.
  - Option A: 20%
  - Option B: 20%

- **Fluid Retention:** Swelling ankles or legs, The side effect will disappear if you stop your arthritis medication.
  - Option A: 5%
  - Option B: 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.
  - Option A: 1%
  - Option B: 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.
  - Option A: 10%
  - Option B: 10%

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

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<tbody>
<tr>
<td>Pain:</td>
<td>Task 1 to 3 pills, spaced throughout the day</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Reference Pain (Option A) = 5 on a scale of 0 (none) to 10 (worst)</td>
<td>Reference Pain (Option B) = 3 on a scale of 0 (none) to 10 (worst)</td>
</tr>
<tr>
<td></td>
<td>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.</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>Dyspepsia: Nausea, heartburn, stomach pain. These symptoms will disappear if you stop your arthritis medication.</td>
<td>20%</td>
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<tr>
<td></td>
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<td>10%</td>
</tr>
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- Option B has greater pain relief
- All other levels the same in Option A and Option B
- Everyone should choose Option B
Threshold Technique

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<tr>
<td>Pain experienced while walking after taking pills daily, on a 0-10 scale is...</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Out-of-pocket cost:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$0</td>
<td>$0</td>
<td></td>
</tr>
</tbody>
</table>

**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.
- **Dyspepsia**: Nausea, heartburn, stomach pain. These symptoms will disappear if you stop your arthritis medication.
- **Fluid Retention**: Swelling ankles or legs. The side effect will disappear if you stop your arthritis medication.
- **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.
- **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.

- 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

Threshold technique survey: Analysis

Brennan Mange
RTI Health Solutions

Mo Zhou, PhD
FDA Center for Devices and Radiological Health
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

<table>
<thead>
<tr>
<th>Treatment Benefits</th>
<th>Your current treatment</th>
<th>A new device</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hours of “on time” each day</td>
<td>X hours of “on time” [16-X] hours of “off time”</td>
<td>X hours of “on time” [16-X] hours of “off time”</td>
</tr>
<tr>
<td>Severity of movement symptoms</td>
<td>MS1 (on a scale from 0 to 10)</td>
<td>MS1 ÷ 2 (on a scale from 0 to 10)</td>
</tr>
<tr>
<td>Severity of pain</td>
<td>PS1 (on a scale from 0 to 10)</td>
<td>PS1 (on a scale from 0 to 10)</td>
</tr>
<tr>
<td>Difficulty thinking clearly, getting organized, or making plans</td>
<td>CS1 (on a scale from 0 to 10)</td>
<td>CS1 (on a scale from 0 to 10)</td>
</tr>
<tr>
<td>Number of pills you need to take</td>
<td>PB1 pills each day</td>
<td>PB1 pills each day</td>
</tr>
</tbody>
</table>

New device (target) defined by 50% improvement in self-reported level of one benefit outcome...
Threshold Technique Question

Q# (e.g., 20%)

Q#a (e.g., 10%)

Q#a_1 (e.g., 0%)
Q#a_2 (e.g., 15%)

Q#b (e.g., 40%)

Q#b_1 (e.g., 30%)
Q#b_2 (Max)

current treatment
new device

current treatment
new device

current treatment
new device
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:

\[ \text{Threshold}_i = \beta_1 \text{Benefit} + \beta_2 \text{Non-ambulatory} + \beta_3 \text{Cognitive Impairment} + \beta_4 \text{DBS} \]
\[ + \beta_5 \text{Dyskinesia} + \beta_6 \text{Motor Problems} + \epsilon \]

where \( i \) indexes age subgroups of \( \leq 60, 61-66, 67-71, \) and \( >71 \).

2.) Aggregated model:

\[ \text{Threshold} = \]
\[ \beta_1 \text{Benefit} + \beta_2 (\text{Benefit} \times \text{age 61–66}) + \beta_3 (\text{Benefit} \times \text{age 67–71}) \]
\[ + \beta_4 (\text{Benefit} \times \text{age} \geq 71) + \beta_5 \text{Non-ambulatory} + \beta_6 \text{Cognitive Impairment} + \beta_7 \text{DBS} \]
\[ + \beta_8 \text{Dyskinesia} + \beta_9 \text{Motor Problems} + \epsilon \]

where age 61-66, age 67-71, and age \( >71 \) are dummy coded and age \( \leq 60 \) is used as the reference category.
## Time Tradeoff Question

<table>
<thead>
<tr>
<th>Severity of movement symptoms</th>
<th>Device A</th>
<th>Device B</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS1-1 (on a scale from 0 to 10)</td>
<td>Now</td>
<td>MS1 ÷ 2 (on a scale from 0 to 10)</td>
</tr>
<tr>
<td>Time until you get the device</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Now</td>
<td>3 years</td>
<td></td>
</tr>
</tbody>
</table>

Which option would you choose?
Time Tradeoff Question

Q# (e.g., 3 years)

Q#a (e.g., 1 year)
  - Q#a_1 (e.g., 0 year)
  - Q#a_2 (e.g., 2 years)

Q#b (e.g., 6 years)
  - Q#b_1 (e.g., 5 years)
  - Q#b_2 (Max)

current treatment

new device
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\(_i\) = 
\[ \beta_1 \ln(\text{Benefit}) + \beta_2 \text{Non-ambulatory} \times \ln(\text{Benefit}) + \beta_3 \text{Cognitive Impairment} \times \ln(\text{Benefit}) + \beta_4 \text{DBS} \times \ln(\text{Benefit}) + \beta_5 \text{Dyskinesia} \times \ln(\text{Benefit}) + \beta_6 \text{Motor Problems} \times \ln(\text{Benefit}) + \epsilon \]

where \(i\) indexes age subgroups of \(\leq 60\), 61-66, 67-71, and >71.

2.) Aggregated model:

Threshold = 
\[ \beta_1 \ln(\text{Benefit}) + \beta_2 \ln(\text{Benefit}) \times [\text{age 61–66}] + \beta_3 \ln(\text{Benefit}) \times [\text{age 67–71}] + \beta_4 \ln(\text{Benefit}) \times [\text{age > 71}] + \beta_5 \text{Non-ambulatory} \times \ln(\text{Benefit}) + \beta_6 \text{Cognitive Impairment} \times \ln(\text{Benefit}) + \beta_7 \text{DBS} \times \ln(\text{Benefit}) + \beta_8 \text{Dyskinesia} \times \ln(\text{Benefit}) + \beta_9 \text{Motor Problems} \times \ln(\text{Benefit}) + \epsilon \]

where age 61-66, age 67-71, and age >71 are dummy coded and age \(\leq 60\) is used as the reference category.
Threshold technique survey: Results
Demographic Characteristics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>n=2,740</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (SD)</td>
<td>65.4 (9.01)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>1,279 (46.7%)</td>
</tr>
<tr>
<td>Employed outside the home, n (%)</td>
<td>680 (24.8%)</td>
</tr>
<tr>
<td>Caucasian, n (%)</td>
<td>2,593 (94.6%)</td>
</tr>
<tr>
<td>4-year college degree or higher, n (%)</td>
<td>1,912 (69.7%)</td>
</tr>
</tbody>
</table>
# Parkinson’s Symptoms

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

*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

<table>
<thead>
<tr>
<th>Parkinson’s Related Characteristic</th>
<th>n=2,740</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of daily pills</td>
<td>mean (SD) 7.6 (5.39)</td>
</tr>
<tr>
<td>Years since diagnosis</td>
<td>mean (SD) 5.3 (4.91)</td>
</tr>
<tr>
<td>Prior deep brain stimulation</td>
<td>n (%) 219 (8%)</td>
</tr>
<tr>
<td>Biological relative with PD</td>
<td>n (%) 569 (20.8%)</td>
</tr>
</tbody>
</table>

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

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

The MAR of death for an improvement in cognition is similar to the MAR of death for all other benefits.
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.

People aged 67-74 who have memory and thinking problems have the highest MAR of death to increase hours of on time.
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.

People aged 67-74 who have memory and thinking problems do not have the highest MAR of death to improve motor symptoms.
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.

People aged 67-74 who are less ambulatory have the highest MAR of death to reduce pain.
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.
• 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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FDA Center for Devices and Radiological Health

Margaret Sheehan
Michael J Fox Foundation Patient Council
Acknowledgements and Thanks

• The patient preference survey team is indebted to

  − Dawn Bardot (formerly of MDIC), Murray Sheldon (FDA), Kathryn O’Callaghan (FDA), and Andrew Lo (MIT) for initiating this project and making it happen
  − The MDIC Board for Directors for funding this project
  − Reviewers at FDA who contributed to the identification and definition of the survey attributes
  − The Michael J Fox Foundation for constant investments of time and resources throughout the project
  − 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