Advancing the Science of Patient Input in the Regulatory Settings

Science of Patient Input (SPI) Team
Office of Biostatistics and Epidemiology
FDA CBER

CERSI Presentation
December 2, 2020
Science of Patient Input @ CBER FDA

When patient inputs meet RWE & digital health technologies

Martin Ho, Associate Director

Patient preference studies for regulatory considerations

Sarah Stothers, RN, MSN, MPH, ORISE Fellow

Pilot study: Natural history study and rare disease RCTs

Ting-Hsuan “Joyce” Lee, MHS, ORISE Fellow

SHAPE: A reconfigurable patient friendly app for site-less study

Hussein Ezzeldin, PhD, Senior Staff Fellow
Patients Driven Regulatory Science

- Benefit-risk ratio
- Digital health tech.
- Rare diseases
- Site-less RCTs
- Real-world data

Patient inputs
Why Collect Patient Input?

Promote Public Health

- Increase therapy access to:
  - Vulnerable populations (e.g., elderly and children)
  - Patients with rare diseases (for advanced therapies)
  - Pregnant women
  - Immunocompromised persons
  - Identify appropriate cohorts by confirming clinical diagnosis

Opportunities

- Novel treatments may come with:
  - High rewards (e.g., potential cure)
  - New risks (e.g., cytokine release syndrome)
    - Uncertainty & unknown unknown’s
  - Unmet medical needs and dire conditions
  - Quantitative patient preferences can inform preference-sensitive decision-making
1. Role of Patient Input in the Regulatory Setting

2010 The Affordable Care Act & PCORI

2012 FDASIA Section 1137 & PDUFA V

2016 PDUFA VI

MDUFA IV

Precision Medicine Initiative

21st Century Cures Act

“…the ideal treatment is personalized to both our cells and our selves”

1 PCORI = Patient-Centered Outcomes Research Institute
2 FDASIA = Food and Drug Administration Safety and Innovation Act
3 PDUFA = Prescription Drug User Fee Act
4 MDUFA = Medical Device User Fee Amendments
5 BMJ Opinion: Berger Z and deBronkart D, “Precision medicine” needs patient partnership
Section 3001. Patient Experience Data
Requires FDA to make public following approval of an NDA or BLA a brief statement regarding patient experience data submitted and reviewed as part of application.

Section 3003. Streamlining Patient Input
Exempts FDA from Paperwork Reduction Act for collections of information under Section 569C of FD&C Act (Patient Engagement), as amended by Section 3001.

Section 3004. Report on Patient Experience Drug Development
Requires FDA to publish report on website about its use of patient experience data in regulatory decisionmaking.
CBER’s Science of Patient Input Program

**Mission:** Advance the science of patient input (SPI) to help inform regulatory decision-making and policy development:

1. Clinical trial design
   - Endpoint development and selection
   - Define clinically meaningful difference
   - Relative importance of Type 1 vs. 2 error

2. Benefit-risk assessments
   - Pre-market licensing
   - Post-market surveillance
Science of Patient Input Team
Office of Biostatistics & Epidemiology (OBE), CBER

Hussein Ezzeldin, PhD
Senior Staff Fellow

Ting-Hsuan “Joyce” Lee, MHS
ORISE Fellow

Xinyi Ng, PhD
Patient Input Scientist

Sarah Stothers, RN, MSN, MPH
ORISE Fellow
### Real World Data (RWD):
Data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.

- Electronic health records (EHRs)
- Claims & billing data
- Data from product & disease registries
- Patient-generated data including in home-use settings
- Data gathered from other sources that can inform on health status e.g. mobile devices

### Real World Evidence (RWE):
Clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD.

- Generated using many different study designs, including but not limited to, randomized trials (e.g., large simple trials, pragmatic clinical trials) and observational studies.
Framework considerations:

I. Are RWD fit for use in regulatory decisions?

II. Can the study design generate adequate scientific evidence to address the regulatory question?

III. Does the study conduct meet FDA regulatory requirements?

FDA RWE Program Framework: https://go.usa.gov/xmQnf
CDRH and CBER

Guidance for Industry and Food
and Drug Administration Staff

Factors to Consider When Making
Benefit-Risk Determinations in
Medical Device Premarket
Approval and De Novo
Classifications

The draft of this document was issued on August 15, 2011.

As of October 22, 2016, this document supersedes
“Factors to Consider When Making Benefit-Risk
Determinations in Medical Device Premarket Approvals
and De Novo Classifications” dated March 28, 2012.

For questions about this document concerning devices regulated by CDRH, contact the
Office of the Center Director at 301-596-5500. For questions about this document concerning
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Development (OCOD) by calling 866-845-4769 or 301-527-1100.

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

CDRH
Center for Devices and Radiological Health

CBER
Center for Biologics Evaluation and Research
Medical Devices (CDRH and CBER)

Factors

Benefits: Type, magnitude, probability, duration
Risks: Severities, types, probabilities, duration, false +ve & -ve

Additional Factors: Context

1. Uncertainty
2. Patient tolerance for risk and perspective on benefit
3. Severity and chronicity of the disease
4. Availability of alternative treatments
5. Risk mitigation
6. Post-market information
7. Novel technology for unmet medical need
4. Patient Tolerance for Risk & Perspective on Benefit

“Risk tolerance will vary among patients, and this will affect individual patient decisions as to whether the risks are acceptable in exchange for a probable benefit. ... FDA would consider evidence relating to patients’ perspective of what constitutes a meaningful benefit.”

However, the guidance did not say how to submit Patient Preference Information to the Agency
CBER Patient Preference Studies

- **Preference Sensitive Decision:** Patients may be willing to tolerate higher risks in exchange for better efficacy
- **Unmet medical needs:**
  1. Dire condition
  2. No effective treatment on market

1 2
Hard-to-control Type 1 Diabetes Mellitus (T1DM)

1 2
Sickle-Cell Disease (SCD)

2
Osteoarthritis of the knee (KOA)

UCSF

DUKE

RTI

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Patients with Type 1 Diabetes Mellitus (T1DM) experience difficulty managing their blood glucose despite optimal insulin therapy and can experience hypoglycemic unawareness.

Islet Cell Transplantation is a treatment strategy for patients with hard-to-control (“brittle”) T1DM.
Questions for islet cell therapy PPI study

• How do patients’ weigh the benefit-risk tradeoff for islet cell therapy?

• What attributes have the greatest relative importance on influencing patients’ treatment preferences?

• How do these findings inform regulatory decision-making?
 Preference Elicitation: Discrete Choice Experiments (DCEs)

- A well-established methodology to elicit and quantify preferences on health-care products and interventions
- Respondents choose between hypothetical treatment profiles
  - Each profile is described in terms of a number of characteristics, or ‘attributes’ that can be related to efficacy, safety, route of administration etc.

<table>
<thead>
<tr>
<th>Attributes</th>
<th>Treatment A</th>
<th>Treatment B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chance of achieving clinical treatment success</td>
<td>60% (60 out of 100 people)</td>
<td>90% (90 out of 100 people)</td>
</tr>
<tr>
<td>Extent of insulin independence (need for monitoring sugars, adjusting insulin)</td>
<td>2 years</td>
<td>5 years</td>
</tr>
<tr>
<td>Risk of treatable procedure-related adverse effects</td>
<td>15% (15 out of 100 people)</td>
<td>40% (40 out of 100 people)</td>
</tr>
<tr>
<td>Risk of serious complications</td>
<td>1% (1 out of 100 people)</td>
<td>5% (5 out of 100 people)</td>
</tr>
<tr>
<td>If these were your only options, which would you choose?</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
</tbody>
</table>

Typically, 12 – 18 questions (i.e., pairs of profiles) are shown.
## T1DM Islet Cell Therapy Study Attributes

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chance of achieving clinical treatment success</td>
<td>normal range HbA1c ($\leq 7.0%$) and elimination of severe hypoglycemia by end of year 1 after final islet cell infusion period</td>
</tr>
<tr>
<td>Success duration</td>
<td>normal range HbA1c and elimination of severe hypoglycemia lasts after the final infusion without additional actions</td>
</tr>
<tr>
<td>Extent of insulin independence</td>
<td>not needing any insulin doses or to monitor sugars or adjust insulin to maintain your blood glucose within the first 5 years after your transplantation procedure</td>
</tr>
<tr>
<td>Expected reduction in the risk of long-term complications</td>
<td>high risk of developing vision loss, or moderate risk of developing kidney damage, or low risk of developing nerve damage</td>
</tr>
<tr>
<td>Risk of Treatable procedure-related adverse effects</td>
<td>nausea, vomiting, diarrhea, moderate bleeding, anemia, pain treated with medications, headache, tremors, confusion, high blood pressure or cholesterol</td>
</tr>
<tr>
<td>Risk of Serious complications</td>
<td>requiring hospital treatment and rare death (serious infections, liver bleeds, kidney damage, development of antibodies making additional transplant more difficult or cytomegalovirus infections or viral heart inflammation.</td>
</tr>
<tr>
<td>Restrictions due to life time immunosuppression</td>
<td>Immunosuppression (anti-rejection) medications required as long as your islet cells are working (up to 5 years or longer)</td>
</tr>
<tr>
<td>Time and support needed</td>
<td>if 1-3 islet cell procedures are required each requiring 3 months of extra time and support to manage your diabetes including 3-5 days hospital stay, 2 weeks intensive monitoring of diabetes, and monthly physician visits each time</td>
</tr>
</tbody>
</table>
### Attribute Levels

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chance of Achieving clinical treatment success</strong></td>
<td>40 out of 100 people (40 %)</td>
</tr>
<tr>
<td></td>
<td>60 out of 100 people (60 %)</td>
</tr>
<tr>
<td></td>
<td>90 out of 100 people (90 %)</td>
</tr>
<tr>
<td><strong>Success duration</strong></td>
<td>0.5 years or less</td>
</tr>
<tr>
<td></td>
<td>1 year</td>
</tr>
<tr>
<td></td>
<td>2 years</td>
</tr>
<tr>
<td></td>
<td>5 years</td>
</tr>
<tr>
<td><strong>Risk of Treatable procedure-related adverse effects</strong></td>
<td>0 out of 100 people (0 %)</td>
</tr>
<tr>
<td></td>
<td>5 out of 100 people (5 %)</td>
</tr>
<tr>
<td></td>
<td>15 out of 100 people (15 %)</td>
</tr>
<tr>
<td></td>
<td>4 out of 100 people (4 %)</td>
</tr>
<tr>
<td><strong>Risk of Serious complications</strong></td>
<td>0 out of 100 people (0 %)</td>
</tr>
<tr>
<td></td>
<td>1 out of 100 people (1 %)</td>
</tr>
<tr>
<td></td>
<td>5 out of 100 people (5 %)</td>
</tr>
<tr>
<td></td>
<td>15 out of 100 people (15 %)</td>
</tr>
</tbody>
</table>

**Example:**

- **Option 1:**
  - Chance of achieving normal range HbA1c (<7.0%) and elimination of severe hypoglycemia by end of Year 1 after final islet infusion procedure.
  - Duration that normal range HbA1c and elimination of severe hypoglycemia lasts after the final infusion without additional actions.

- **Option 2:**
  - Risk of treatable procedure-related ADVERSE EVENTS.
  - Risk of SERIOUS COMPLICATIONS requiring hospital treatment and rare death.
Recruitment and Patient Characteristics

Recruitment:

- Convenience sampling
- UCSF Diabetes Clinics
- National Diabetes Research Centers
- N = 92

Inclusion Criteria:

- Adults (≥ 18 years)
- English-speaking
- Physician referred Type 1 Diabetics
- Previously experienced a hypoglycemic episode

<table>
<thead>
<tr>
<th>Full Sample (N = 92)</th>
<th>Mean (Range) / n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>42 (20-89)</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>46 (50%)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>71 (77%)</td>
</tr>
<tr>
<td>Black</td>
<td>6 (6%)</td>
</tr>
<tr>
<td>Asian or Pacific Islander</td>
<td>11 (12%)</td>
</tr>
<tr>
<td>Native American</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (3%)</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
</tr>
<tr>
<td>Latino (any race)</td>
<td>5 (5%)</td>
</tr>
<tr>
<td><strong>Education Level</strong></td>
<td></td>
</tr>
<tr>
<td>High School Diploma or GED</td>
<td>6 (6.5%)</td>
</tr>
<tr>
<td>Some College</td>
<td>17 (18%)</td>
</tr>
<tr>
<td>Bachelor's Degree</td>
<td>38 (41%)</td>
</tr>
<tr>
<td>Graduate Degree</td>
<td>31 (34%)</td>
</tr>
<tr>
<td><strong>Employment Status</strong></td>
<td></td>
</tr>
<tr>
<td>Employed Full-Time</td>
<td>53 (57%)</td>
</tr>
<tr>
<td>Employed Part-Time</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Retired</td>
<td>10 (11%)</td>
</tr>
<tr>
<td>Homemaker or student</td>
<td>8 (9%)</td>
</tr>
<tr>
<td>Disabled</td>
<td>11 (12%)</td>
</tr>
<tr>
<td>Unemployed</td>
<td>5 (5%)</td>
</tr>
<tr>
<td><strong>Income Level</strong></td>
<td></td>
</tr>
<tr>
<td>Less than $50,000</td>
<td>20 (22%)</td>
</tr>
<tr>
<td>$50,000 to $74,999</td>
<td>11 (12%)</td>
</tr>
<tr>
<td>$75,000 to $99,999</td>
<td>9 (10%)</td>
</tr>
<tr>
<td>$100,000 to $199,999</td>
<td>18 (19%)</td>
</tr>
<tr>
<td>$200,000 or more</td>
<td>22 (24%)</td>
</tr>
<tr>
<td>Prefer not to answer</td>
<td>12 (13%)</td>
</tr>
<tr>
<td><strong>Health Insurance Type</strong></td>
<td></td>
</tr>
<tr>
<td>Medicare</td>
<td>20 (22%)</td>
</tr>
<tr>
<td>Medicaid</td>
<td>10 (11%)</td>
</tr>
<tr>
<td>Private plan through work</td>
<td>63 (68%)</td>
</tr>
<tr>
<td>VA or other military</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Disability insurance</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Not insured</td>
<td>2 (2%)</td>
</tr>
</tbody>
</table>
Results: preference weights

- Preference Weights
  - Treatment success
  - Success duration
  - Insulin independence
  - Long-term complications
  - Treatable adverse effects
  - Serious complications
  - Restriction
  - Time and support

- Treatment success:
  - 40% success
  - 60% success
  - 90% success

- Success duration:
  - 0.5 years
  - 1 year
  - 2 years
  - 5 years

- Insulin independence:
  - Never
  - 2 years
  - 5 years

- Long-term complications:
  - Eye
  - Kidney
  - Nerve

- Treatable adverse effects:
  - 0%
  - 5%
  - 15%
  - 40%

- Serious complications:
  - 0%
  - 1%
  - 5%
  - 15%

- Restriction:
  - Time
  - Support

- Treatment success categories:
  - 40%
  - 60%
  - 90%

- Success duration categories:
  - 0.5 years
  - 1 year
  - 2 years
  - 5 years

- Insulin independence categories:
  - Never
  - 2 years
  - 5 years

- Long-term complications categories:
  - Eye
  - Kidney
  - Nerve

- Treatable adverse effects categories:
  - 0%
  - 5%
  - 15%
  - 40%

- Serious complications categories:
  - 0%
  - 1%
  - 5%
  - 15%

- Restriction categories:
  - Time
  - Support

- Treatment success values:
  - 40% success
  - 60% success
  - 90% success

- Success duration values:
  - 0.5 years
  - 1 year
  - 2 years
  - 5 years

- Insulin independence values:
  - Never
  - 2 years
  - 5 years

- Long-term complications values:
  - Eye
  - Kidney
  - Nerve

- Treatable adverse effects values:
  - 0%
  - 5%
  - 15%
  - 40%

- Serious complications values:
  - 0%
  - 1%
  - 5%
  - 15%

- Restriction values:
  - Time
  - Support
Results: preference weights

Better outcomes have significantly larger scores

Worse outcomes have significantly lower scores
Most important attributes

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Preference Weights</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment success</td>
<td>1.09</td>
</tr>
<tr>
<td>Success duration</td>
<td>1.37</td>
</tr>
<tr>
<td>Insulin independence</td>
<td>1.71</td>
</tr>
<tr>
<td>Long-term complications</td>
<td></td>
</tr>
<tr>
<td>Treatable adverse effects</td>
<td></td>
</tr>
<tr>
<td>Serious complications</td>
<td></td>
</tr>
<tr>
<td>Restriction</td>
<td></td>
</tr>
<tr>
<td>Time and support</td>
<td></td>
</tr>
</tbody>
</table>

- **Preference Weights**
  - 40 %
  - 60 %
  - 90 %

- **Treatment success**
  - 0.5 years
  - 1 year
  - 2 years
  - 5 years

- **Success duration**
  - Never
  - 2 years
  - 5 years

- **Insulin independence**
  - Eye
  - Kidney
  - Nerve

- **Long-term complications**
  - 0 %
  - 5 %
  - 15 %
  - 40 %

- **Treatable adverse effects**
  - 0 %
  - 1 %
  - 5 %

- **Serious complications**
  - 0 %
  - 15 %

- **Restrictions**
  - 3 months
  - 6 months
  - 9 months

- **Time and support**
  - 2 months
  - 3 months
  - 4 months

- **Adverse effects**
  - Serious
  - Restriction
  - Time and support
Relative importance of attributes

- **Chance of treatment success**: Improvement from 40% to 90%
- **Success duration**: Improvement from 0.5 to 5 years
- **Insulin independence**: Improvement from never to 5 years
- **Long-term complications**: Change from high risk of developing vision loss to moderate risks of developing kidney damage
- **Treatable adverse effects**: Increase from 0% to 40%
- **Serious Complications**: Increase from 0% to 15%
- **Restrictions**: Change from meds to prevent mouth sores/anemia to constant renal monitoring
- **Times and support**: Increase from 3 to 9 months
Key Findings

• Three most influential attributes to patients’ choices for islet cell treatments are:
  1. How risky of experiencing serious complications (from 0 to 15%)
  2. How independent from insulin (improvement from never to 5-years)
  3. How long treatment success lasts (improvement from 0.5 to 5-years)

• This study has demonstrated that patients are willing to make benefit-risk tradeoff when choosing islet cell treatments

• PPI data can inform regulatory considerations of islet cell treatments by attaching patients’ preference weights to the outcomes observed in the clinical studies
Osteoarthritis
- Characterized by degradation of knee cartilage & bone
- Patients experience increasing pain & functional impairment

Treatment options
- Avail. treatments. offer symptomatic relief; not slow OA progression
- New therapies (cell therapies, cell or tissue-engineered products, & gene therapies) may slow OA progression

Question: Relative value of improvements in pain vs. function to patients?
# KOA Study Attributes

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Attribute Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement in pain</td>
<td>No improvement</td>
</tr>
<tr>
<td></td>
<td>30% improvement in pain score</td>
</tr>
<tr>
<td></td>
<td>50% improvement in pain score</td>
</tr>
<tr>
<td></td>
<td>100% improvement (no pain)</td>
</tr>
<tr>
<td>Improvement in function</td>
<td>No improvement</td>
</tr>
<tr>
<td></td>
<td>30% improvement in activity score</td>
</tr>
<tr>
<td></td>
<td>50% improvement in activity score</td>
</tr>
<tr>
<td></td>
<td>100% improvement (no difficulty)</td>
</tr>
<tr>
<td>How long improvements last</td>
<td>6 months</td>
</tr>
<tr>
<td></td>
<td>1 year (12-months)</td>
</tr>
<tr>
<td></td>
<td>2 years (24-months)</td>
</tr>
<tr>
<td></td>
<td>5 years (60-months)</td>
</tr>
<tr>
<td>Risk of developing too much tissue inside the knee</td>
<td>3 out of 100 people (3%)</td>
</tr>
<tr>
<td></td>
<td>5 out of 100 people (5%)</td>
</tr>
<tr>
<td></td>
<td>8 out of 100 people (8%)</td>
</tr>
<tr>
<td></td>
<td>10 out of 100 people (10%)</td>
</tr>
<tr>
<td>Treatment Feature</td>
<td>Treatment A</td>
</tr>
<tr>
<td>--------------------------------------------------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>Improvement in pain</td>
<td>Improve pain from 88 to 62</td>
</tr>
<tr>
<td>Improvement in ability to do day-to-day activities</td>
<td>Improve from 79 to 0 (no difficulty)</td>
</tr>
<tr>
<td>How long improvements last</td>
<td>5 years</td>
</tr>
<tr>
<td>Risk of developing too much tissue inside the knee</td>
<td>8 out of 100 people (8%)</td>
</tr>
</tbody>
</table>

Which treatment would you choose? [ ] [ ] [ ] [ ]
PROM to PPI

- Select a Patient-reported outcome measure (PROM) for adaptation to PPI attributes

- Translate pain and function domains from *Western Ontario and McMaster Universities Osteoarthritis Index* (WOMAC) into pre-defined attributes
  - 5-item Pain
  - 17 item Function

- Two Discrete Choice Experiments (DCEs) were developed to facilitate comparison between domain score version and single-item score version of DCE
  - Selection for single-item: “walking on a flat surface”

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Research Questions

- Gene therapy offers a potential cure for sickle cell disease but poses high risks for patients.
  - How would patients make tradeoffs?
  - Do patients with more severe symptoms view the benefit-risk tradeoffs differently?
### Sickle Cell Disease Study Attributes

<table>
<thead>
<tr>
<th>Attributes</th>
<th>Attribute Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chance of no symptoms of SCD</td>
<td>• 90% (9 out of 10)</td>
</tr>
<tr>
<td></td>
<td>• 80% (8 out of 10)</td>
</tr>
<tr>
<td></td>
<td>• 40% (4 out of 10)</td>
</tr>
<tr>
<td>Increase in life years</td>
<td>• None</td>
</tr>
<tr>
<td></td>
<td>• 4 years</td>
</tr>
<tr>
<td></td>
<td>• 8 Years</td>
</tr>
<tr>
<td>Chance of dying within first year after treatment</td>
<td>• No chance</td>
</tr>
<tr>
<td></td>
<td>• 10% (1 out of 10)</td>
</tr>
<tr>
<td></td>
<td>• 30% (3 out of 10)</td>
</tr>
<tr>
<td>Increase in lifetime risk of cancer</td>
<td>• No increase</td>
</tr>
<tr>
<td></td>
<td>• Not expected</td>
</tr>
<tr>
<td></td>
<td>• Not known</td>
</tr>
</tbody>
</table>
SCD Study Question Example

### Chance of no symptoms of SCD after treatment (for some patients this takes up to 2 years)
- **Gene Therapy A**: 8 out of 10 (80%)
- **Gene Therapy B**: 6 out of 10 (60%)
- **No Gene Therapy**: No chance

### Expected increase in life years after treatment
- Gene Therapy A: No increase
- Gene Therapy B: 8 more years
- No Gene Therapy: No increase

### Chance of death within 1 year after treatment
- Gene Therapy A: No chance
- Gene Therapy B: 3 out of 10 (10%)
- No Gene Therapy: No chance

### Increase in lifetime cancer risk after treatment
- Gene Therapy A: No Increase
- Gene Therapy B: Not known
- No Gene Therapy: No increase
PPI Contributions

• Patient preference information is an important complement to clinical and statistical evidence to make benefit-risk assessments
• Evidence on patient preference can be scientifically obtained
• Patient preference information can provide insights to reviewers who may have limited experience with patients of some rare diseases
• The Science of Patient Input is evolving
CBER Pilot Natural History Study
What is a Natural History Study (NHS)?

• Follows a group of people over time who have, or are at risk of developing, a specific medical condition or disease.

• Collects health information to provide understanding on how the medical condition or disease develops and how to treat it.

Source: The National Cancer Institute Dictionary of Cancer Terms (go.usa.gov/xvvXb)
CBER Pilot Natural History Study

Purpose of the study

Develop a pilot of a natural history study, which is designed to serve as a potential source of external controls to augment the concurrent controls of future RCTs
Why Augment Concurrent Controls for Rare Disease?

1. Patients are reluctant to enroll in clinical trials when their chance of being randomized to the treatment is 50%.
2. Patients in dire conditions face an opportunity cost from being randomized to a control arm; they may become ineligible for other studies.
3. Ethical considerations.
4. Small population size means limited sample pool; [Tradeoff] A smaller control arm allows for a larger treatment arm.
Collaborators and Selected Disease for Pilot NHS

Collaborators: National Organization for Rare Disorders (NORD) and IBM

Disease Area: Metachromatic leukodystrophy (MLD)
   a. It is a rare disease that needs an external control for single-arm trials.
   b. A product is already in the pipeline, anticipating a marketing application submission in about 2-3 years.
What is Metachromatic Leukodystrophy (MLD)?

**Background**
- Rare hereditary *progressive* disease
- Prevalence rate is estimated to be between 1 in 40,000 and 1 in 160,000

**Symptoms**
- Difficulty talking
- Difficulty walking
- Seizures
- Personality & behavior changes

**Cause**
Accumulation of sulfatides (fats) causes destruction of the myelin sheath of nerves in the CNS and PNS

**Types (age of symptom onset)**
- Late-infantile MLD (≤ 3 yrs.)
- Juvenile MLD (4–12 & 14 yrs.)
- Adult MLD (>14 yrs.)
Key Significances of the project

1. Use multi-stakeholder approach (including patients and caregivers, clinicians and FDA) to design and conduct study

2. Learn **good research practices** for designing and conducting natural history studies to augment concurrent controls

3. Explore innovative data collection methods to mitigate drawbacks of traditional natural history studies
Key Significance 1: Collaboration

1. CBER actively collaborates with multi-stakeholders (e.g., product review office, NORD, patient groups) to design study and to strive for study results that can inform regulatory decision making.

2. Listen to the patient’s voice: Promote patient-focused research and product development
Key Significance 2: Report on Good Research Practices for a Natural History Study (NHS)

a. Good practices in:
   I. Designing and conducting a NHS to serve as external control
   II. Combining and analyzing data from:
      • NHS external control, and
      • Future concurrent data from the prospective RCT
   III. Mimicking an RCT using analytical methods in the study design phase to control for confounding and biases

b. Pilot of a longitudinal registry that incorporates CBER’s clinical data requirements
Conducting the NHS

- Study Coordinator to conduct video assessments with patients and caregivers

  1. Coordinator can answer any questions the families may have
  2. Less patient burden and more accuracy in data collection
  3. Scheduled data entry which may reduce missing data
  4. The primary endpoint (GMFC-MLD) designed to be collected by clinicians. This enables comparison with a patient reported endpoint
NORD Pilot NHS Homepage

https://rarediseases.org/mld-home-study/
Key Significance 3: Innovative Data Collection

- This study will use innovative patient-centered methods (e.g., mobile & web-based app) to collect longitudinal data and patient perspectives on their disease status and potential treatments.
Introducing... Biologics Effectiveness and Safety Initiative (BEST)’s SHAPE

Survey of Clinical Health and Patient Experience App
Integrate FDA/IBM Patient Experience App

Survey of Health & Patient Experience (SHAPE) App

1. Collect various endpoints:
   • Scheduled: Gross Motor Function Classification (primary endpoint)
   • Unscheduled: Relevant health events

2. Increase compliance; reduce missing data

3. Compare clinician- & caregiver-reported outcome measures (via video assessment study visits)

4. Explore linking EHR data
Integrate FDA/IBM Patient Experience App

SHAPE App

App tabs/components
Integrate FDA/IBM Patient Experience App

SHAPE App

Respondent

Participant
Integrate FDA/IBM Patient Experience App

SHAPE App

Survey/Study

Participant

Event Type
Integrate FDA/IBM Patient Experience App
SHAPE App
Integrate FDA/IBM Patient Experience App

SHAPE App
Innovative Data Collection enhancing Clinical Trial Design

Healthcare System

Electronic Health Record (EHR) Data

Natural History Study

SHAPE

Patient

Clinical Trial Design

Augmenting Clinical Trial control group with external control from natural history study

Regulatory Decision-Making
SHAPE Application

NORD and CBER
Creates & Deploys Surveys

Email survey invitation & link to App

SHAPE
Study participants access the App to complete consent & surveys

Consent
Answers sent to NORD NHS

NORD Natural History Study
Store survey, consent, non-PI ID & security questions for enrollment
Analysis by NORD

SHAPE Creates & Deploys Surveys

Email survey invitation & link to App

Study participants access the App to complete consent & surveys

Consent
Answers sent to NORD NHS

NORD Natural History Study
Store survey, consent, non-PI ID & security questions for enrollment
Analysis by NORD
Patient preference information plays an increasingly important role to benefit patients and other stakeholders in the clinical trial enterprise.

Emerging breakthroughs of biologic products bring hope to address unmet medical needs; they also introduce new challenges for benefit-risk assessments.

Patient preference studies can be the key to address new challenges and make biologic innovations accessible to patients safely and efficiently.

Successfully harnessing advances in novel types of patient input requires close collaborations between patients, investigators, sponsors, and FDA.
Discussion and Questions?
Science of Patient Input Team
Office of Biostatistics & Epidemiology (OBE), CBER

Hussein Ezzeldin, PhD
Senior Staff Fellow

Ting-Hsuan “Joyce” Lee, MHS
ORISE Fellow

Xinyi Ng, PhD
Visiting Scientist

Sarah Stothers, RN, MSN, MPH
ORISE Fellow
APPENDICES
# Patient Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Full Sample (N = 92) Mean (Range) / n (%)</th>
<th>High Hypoglycemic Risk Sample (N=78) Mean (Range) / n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diabetes Status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years with diabetes</td>
<td>22 (1-61)</td>
<td>23 (1-61)</td>
</tr>
<tr>
<td>Latest HbA1c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 6.5%</td>
<td>18 (19%)</td>
<td>15 (19%)</td>
</tr>
<tr>
<td>6.5% to 8%</td>
<td>58 (63%)</td>
<td>48 (62%)</td>
</tr>
<tr>
<td>Greater than 8%</td>
<td>14 (15%)</td>
<td>14 (18%)</td>
</tr>
<tr>
<td>Don’t know</td>
<td>2 (2%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td><strong>Severe Hypoglycemia Episodes (SHE)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In the past 6 months</td>
<td>0.79 (0-20)</td>
<td>1 (0-20)</td>
</tr>
<tr>
<td>In the past 12 months</td>
<td>1.6 (0-40)</td>
<td>1.9 (0-40)</td>
</tr>
<tr>
<td><strong>Diabetes Management</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>92 (100%)</td>
<td>78 (100%)</td>
</tr>
<tr>
<td>Oral medications</td>
<td>4 (4%)</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Diet</td>
<td>37 (40%)</td>
<td>28 (36%)</td>
</tr>
<tr>
<td>Physical activity</td>
<td>32 (35%)</td>
<td>26 (33%)</td>
</tr>
<tr>
<td>Pancreas transplant</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Islet cell transplant</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (3%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td><strong>Ever Considered Islet Cell Transplant</strong></td>
<td>25 (27%)</td>
<td>22 (28%)</td>
</tr>
<tr>
<td><strong>Device Used for Insulin Injection</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vial &amp; Syringe</td>
<td>10 (11%)</td>
<td>8 (10%)</td>
</tr>
<tr>
<td>Pen (Self-Injecting)</td>
<td>39 (42%)</td>
<td>26 (33%)</td>
</tr>
<tr>
<td>Insulin Pump Single Loop</td>
<td>22 (24%)</td>
<td>22 (28%)</td>
</tr>
<tr>
<td>Insulin Pump Closed Loop</td>
<td>21 (23%)</td>
<td>21 (27%)</td>
</tr>
<tr>
<td>Self-Programmed Insulin Pump</td>
<td>8 (9%)</td>
<td>8 (10%)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (3%)</td>
<td>3 (4%)</td>
</tr>
<tr>
<td><strong>Frequency of Blood Glucose Check</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rarely or never</td>
<td>7 (8%)</td>
<td>6 (8%)</td>
</tr>
<tr>
<td>Several times a week</td>
<td>18 (20%)</td>
<td>14 (18%)</td>
</tr>
<tr>
<td>1-3 times a day</td>
<td>20 (22%)</td>
<td>15 (19%)</td>
</tr>
<tr>
<td>4-6 times a day</td>
<td>18 (19%)</td>
<td>14 (18%)</td>
</tr>
<tr>
<td>More than 6 times a day</td>
<td>29 (31%)</td>
<td>29 (37%)</td>
</tr>
</tbody>
</table>
Results: preference weights – overall sample versus high-risk hypoglycemic group

- **Preference Weights**
  - Overall sample
  - High-risk hypoglycemic group

- **Treatment success**
  - 0.5 years
  - 1 year
  - 2 years
  - 5 years

- **Success duration**
  - Never
  - 2 years
  - 5 years

- **Insulin independence**
  - Eye
  - Kidney
  - Nerve

- **Long-term complications**
  - 0%
  - 5%
  - 15%
  - 40%

- **Treatable adverse effects**
  - 0%
  - 5%
  - 15%
  - 40%

- **Serious complications**
  - 0%
  - 1%
  - 5%
  - 15%

- **Restrictions**
  - 3-months
  - 6-months
  - 9-months

- **Time and support**
  - 0
d  - 0.4
  - 0.8
  - 1.2
  - 1.6
  - 2
  - 2.4
  - 2.8
  - 3.2
  - 3.6

- **Overall**
  - High-risk
Relative importance of attributes – overall sample versus high-risk hypoglycemic group

- **Chance of treatment success** (Improvement from 40% → 90%)
  - Overall: 5.0
  - High-risk group: 4.9

- **Success duration** (Improvement from 0.5 → 5 years)
  - Overall: 6.3
  - High-risk group: 6.7

- **Insulin independence** (Improvement from never → 5 years)
  - Overall: 7.9
  - High-risk group: 8.1

- **Long-term complications** (Change from high risk of developing vision loss → moderate risks of developing kidney damage)
  - Overall: 0.1
  - High-risk group: 1.1

- **Treatable adverse effects** (Increase from 0% → 40%)
  - Overall: 4.2
  - High-risk group: 5.0

- **Serious Complications** (Increase from 0% → 15%)
  - Overall: 10.0
  - High-risk group: 10.0

- **Restrictions** (Change from meds to prevent mouths sores/anemia → constant renal monitoring)
  - Overall: 2.8
  - High-risk group: 2.9

- **Times and support** (Increase from 3 → 9 months)
  - Overall: 1.1
  - High-risk group: 1.5