Housekeeping Rules

Attendees will be entered into the webcast on mute and will remain muted at all times.

Use the Chat Box on the webcast or the live Q/A feature on the conference app to share a question or comment and to communicate with presenters and moderators during the Summit.

If you have technical issues, please seek assistance from your local technical support.
Case Studies for Use of PPI in Medical Device Decision-Making Processes
SESSION 2
Use of Patient Preference Information in Medical Device Submissions: Setting the Stage

Michelle Tarver, MD, PhD
Director, Patient Science & Engagement (PSE)
Office of Strategic Partnerships & Technology Innovation
Center for Devices and Radiological Health
Opportunity to integrate real-world perspectives into decisional frameworks

Puts healthcare providers’ and regulators’ perspectives in context with patients’ perspectives

Informs patients’ priorities in a list of many outcomes

Illuminates patients’ tolerance for adverse events in exchange for:
- Quality of life benefits
- Earlier access to potentially effective treatments
- Convenience
Use of Patient Preference Information (PPI)

Device Development
- Identify unmet medical need
- Understand what matters most to patients about their disease or treatment

Clinical Trial Design
- Inform endpoint selection
- Inform performance goal
- Inform uncertainty (alpha error) and sample size

Benefit-risk Assessment
- Clarify what matters most to patients about their disease or treatment
- Illuminate patient benefit-risk tradeoffs
- Identification of subgroup preferences

Post-Market Decisions
- Post-market benefit-risk re-assessment for compliance
- Inform studies of new or expanded use populations
Patient (Parent!) Preference Driving Clinical Endpoint

Daniel Harfe
VP, Regulatory
This presentation was prepared by Dan Harfe in my personal capacity. The opinions expressed are my own and do not necessarily reflect the view of Tusker Medical/Smith+Nephew. This information is offered for informational and educational purposes only and is not intended as medical advice.

Dan Harfe is a full-time employee of Smith+Nephew, and otherwise has no other financial disclosures.

Please see www.tulatubes.com for important safety information, including indications, contraindications and risks.
Disease State

RAOM: Recurrent Acute Otitis Media; repeated ear infections/inflammation [otalgia, headache, fever, vomiting, irritability, diarrhea, otorrhea]

- Complications (rare but very serious): meningitis, intracranial or epidural abscess, venous thrombosis

OME: Otitis Media with Effusion; “glue ear” with non-infected fluid in middle ear [hearing loss, tinnitus, vertigo, otalgia]

- Complications (common): difficulty hearing, possibly leading to speech and language developmental issues and central auditory neurodevelopment impact

OM is extremely common

- Most common condition for which antibacterial agents are prescribed for children in the US. By age 2, >60% of children will experience at least one episode of OME.
When conservative therapy fails, tympanostomy procedure is performed. Extremely common pediatric surgery. **In children, the procedure is performed in an operating room using general anesthesia (GA)**. Perioperative risks include (parent & child) separation and induction distress, intra-operative laryngospasm, arrhythmia, emergence delirium, nausea/vomiting. Long term neurodevelopmental risks are an area of significant controversy. Most clinicians agree that if GA can be avoided, this is a benefit for the child.
Tusker Medical’s Tula® System

Device/Drug Combination Product
- TYMBION otic local anesthetic / Iontophoresis System provides child-friendly local anesthesia of the tympanic membrane
- Tube Delivery System deploys a tympanostomy tube in <500msec

Enables In-Office Placement of Tympanostomy Tubes in Children
- No exposure to general anesthesia
- No child/parent separation
- No sedation, anxiolytics, or papoose boards required
- No fasting
- Potential for meaningful health system savings
The In-Office Procedure Won’t Be 100% Successful

In comparison, the traditional procedure in the OR using general anesthesia is virtually 100% successful in inserting tympanostomy tubes.

---

The Challenge of First-of-a-Kind Clinical Evidence Generation

For combination product PMA, everybody expects and prefers an RCT, but...

vs General Anesthesia?

• A priori, Tula will have lower success rate
• AE comparisons are apples/oranges

NOT USEFUL CONTROL ARM
The Challenge of First-of-a-Kind Clinical Evidence Generation

For combination product PMA, everybody expects and prefers an RCT, but...

vs General Anesthesia?
- A priori, Tula will have lower success rate
- AE comparisons are apples/oranges

NOT USEFUL CONTROL ARM

vs office alternative?
- Tula first-of-a-kind, so no alternative techniques/technologies available for comparison

NOT USEFUL CONTROL ARM
The Challenge of First-of-a-Kind Clinical Evidence Generation

For combination product PMA, everybody expects and prefers an RCT, but…

Agreed with FDA to a single-arm study with a Performance Goal of technical success (how often can you insert tympanostomy tubes in all intended ears).

Assume Tula failures are safe failures, and all future options are preserved. **What Tula success rate is acceptable?**
What Success Rate is Acceptable / Approvable?

Benefits of avoiding GA are meaningful, and parents are likely to prefer this option. Technical success rate significantly lower than 100% is acceptable.

The traditional procedure (GA in OR) has ~100% technical success rate. What is rationale for accepting something meaningfully lower?
It became clear that we needed additional data to resolve what appeared to be a negotiating impasse.
It became clear that we needed additional data to resolve what appeared to be a negotiating impasse.

Rather than have industry (Tusker) or regulators (FDA) determine the acceptable success rate, we asked parents what they would accept (in a highly structured, scientifically valid way).

Rare (only?) example of using Preference Testing to help set an appropriate Performance Goal for a PMA pivotal study.
Preference Study High-Level Design Summary

Design
- Threshold stated-preference
- Fixed Reference (OR) vs Target (Office)

Pre-Test
- 1:1 interviews (n=14)

Testing (n=400)
- Screening Questions
- Informed Consent
- Background Information / Descriptions of Options
- Comprehension Testing
- Threshold Exercise
- Best-Worst Scaling
- Demographics

Threshold Exercise. Note presentation of data in visual, count, and % formats

Every word is critical to avoid bias (or the perception of potential bias) for or against a certain preference option
Preference Testing Usefulness was Questioned
• Initial FDA Response: using “survey respondents” to set clinical performance goal “is not adequate”
FDA Questions (What you should expect)

Preference Testing Usefulness was Questioned
• Initial FDA Response: using “survey respondents” to set clinical performance goal “is not adequate”

Adequacy of the Sample
• Is the sample large enough for statistical confidence?
• Does the sample represent a broad or narrow population of decision maker?

Study Design
• Pre-test interviewing to ensure an understandable survey design
• Within-study comprehension testing of the tradeoff
• Design specifics (in our case, why threshold technique?)

Statistics
• Be prepared to submit analysis datasets and statistical programs so FDA can replicate results and perform additional analysis (as is customary for PMA clinical data)
Lessons Learned

Treat the Preference Study as you would a complex clinical study

- Most of us (in regulatory) do not have prior experience with Health Economic research
- Ensure allocation of budget and timeline appropriate for the complexity of the study
- Proper study design and statistical techniques are essential
- This is NOT a marketing survey, or a homemade Survey Monkey
- Be certain your preference study makes it to the experts within FDA (Patient Science and Engagement Team)
Lessons Learned

Treat the Preference Study as you would a complex clinical study
• Most of us (in regulatory) do not have prior experience with Health Economic research
• Ensure allocation of budget and timeline appropriate for the complexity of the study
• Proper study design and statistical techniques are essential
• This is NOT a marketing survey, or a homemade Survey Monkey
• Be certain your preference study makes it to the experts within FDA (Patient Science and Engagement Team)

Work with the right partners
• We chose RTI Health Solutions primarily because FDA had chosen RTI for FDA’s obesity preference study¹

Lessons Learned

Treat the Preference Study as you would a complex clinical study
• Most of us (in regulatory) do not have prior experience with Health Economic research
• Ensure allocation of budget and timeline appropriate for the complexity of the study
• Proper study design and statistical techniques are essential
• This is NOT a marketing survey, or a homemade Survey Monkey
• Be certain your preference study makes it to the experts within FDA (Patient Science and Engagement Team)

Work with the right partners
• We chose RTI Health Solutions primarily because FDA had chosen RTI for FDA’s obesity preference study

Work with FDA (?)
• Always a difficult decision, particularly in a start-up environment where time=cash burn.
• We conducted our study without FDA input. Study report initially submitted July 2016, FDA alignment in July 2017 with Tusker’s initial proposal for the Performance Goal. This likely would have been accelerated with more robust up-front discussion with FDA.

The Preference Study was instrumental in the design of our pivotal clinical study, leading to approval of PMA P190016.
The Tula System is intended to create a myringotomy and insert a tympanostomy tube using the Tula Tube Delivery System in pediatric (aged 6 months and older) and adult patients indicated to receive tympanostomy tubes. The Tula System is used to deliver a tympanostomy tube under local anesthesia induced using the Tula Iontophoresis System and TYMBION™, a combination of an amide local anesthetic and an alpha and beta-adrenergic agonist. Contraindications include certain abnormal ear anatomy, sensitivity/allergy to lidocaine or other local anesthetics, and reliance on electrically sensitive medical implants such as a pacemaker. Risks may include, but are not limited to, inadequate local anesthesia, dizziness, and common tympanostomy procedure risks. For full prescribing information, see the Tula IFU and TYMBION Drug Package Insert at www.tulatubes.com/IFU. Rx only.
Patient Benefit-Risk Preferences for Treatments for Severe Emphysema: Evidence for a PMA

Christine Poulos, PhD
Senior Economist and Group Head, Health Preference Assessment
RTI Health Solutions
• The opinions expressed are my own and do not necessarily reflect the views of RTI Health Solutions (RTI-HS), PneumRx, or BTG. This information is offered for informational and educational purposes only.

• Christine Poulos is a full-time employee of RTI-HS and otherwise has no other financial disclosures.
Severe Emphysema

• Emphysema causes irreversible destruction of alveolar walls and lung hyperinflation

• Breathlessness/dyspnea caused by hyperinflation leads to
  – Significant morbidity
  – Decreased quality of life
  – Poor survival

• PneumRx developed endobronchial coils to address unmet need despite available pharmalogical and surgical options

Source: Adapted from Global Initiative For Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management, and Prevention of COPD. http://goldcopd.org
Benefits and Risks of Treatments for Severe Emphysema

FDA = Food and Drug Administration; LVRS = Lung Volume Reduction Surgery

Source: Adapted from Irony T, Ho M. Incorporating Patient Preferences into Regulatory Decision Making. Society for Medical Decision Making. St. Louis, MO. 2015.
Benefits and Risks of Treatments for Severe Emphysema

FDA = Food and Drug Administration; LVRS = Lung Volume Reduction Surgery
Source: Adapted from Irony T, Ho M. Incorporating Patient Preferences into Regulatory Decision Making. Society for Medical Decision Making. St. Louis, MO. 2015.
Benefits and Risks of Treatments for Severe Emphysema

FDA = Food and Drug Administration; LVRS = Lung Volume Reduction Surgery

Source: Adapted from Irony T, Ho M. Incorporating Patient Preferences into Regulatory Decision Making. Society for Medical Decision Making. St. Louis, MO. 2015.
Benefits and Risks of Treatments for Severe Emphysema

FDA = Food and Drug Administration; LVRS = Lung Volume Reduction Surgery

Source: Adapted from Iony T, Ho M. Incorporating Patient Preferences into Regulatory Decision Making. Society for Medical Decision Making. St. Louis, MO. 2015.
Patient Preference Study

- Intended to support benefit-risk assessment of endobronchial coils relative to MMT and LVRS in PneumRx’s PMA submission to the FDA

- Conducted late 2015–early 2017
  - Initiated before completion of the pivotal trial and analysis of trial results

- One of the first studies conducted after the Center for Devices and Radiologic Health (CDRH) patient preference information guidelines were issued
  - Draft guidelines issued May 2015; Final guidance issued August 2016
  - First patient preference information (PPI) study presented to advisory panel (June 2018)
  - Despite experience in PPI and premarket approval (PMA) process, combination of PPI in the PMA process was unfamiliar territory

- FDA Engagement
  - Presubmission of protocol in 2016 prior to survey pretest
  - Study results submitted with PMA application in 2017
  - Interactive review until panel meeting in June 2018
Patient Preference Study Design

- **Objective**
  - Quantify preferences for benefits and risks of emphysema treatments from the patient perspective

- **Preference study endpoint**
  - Proportion of patients who perceive that the benefit of endobronchial coils outweighs the risks when compared with the benefits and risks of MMT

- **Study participants**
  - 202 Coil-naïve participants recruited through United States (US) clinical centers that treat patients for severe emphysema
  - Eligibility criteria similar to those for the pivotal trial (RENEW) (Criner et al., 2011)

<table>
<thead>
<tr>
<th>TX TYPE</th>
<th>Treatment Feature</th>
<th>Treatment A</th>
<th>Treatment B</th>
</tr>
</thead>
</table>

Example Survey Question

TX = treatment.
<table>
<thead>
<tr>
<th>TX TYPE</th>
<th>Treatment Feature</th>
<th>Treatment A</th>
<th>Treatment B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Type of treatment</td>
<td>Implantable lung device</td>
<td>Medicines</td>
</tr>
<tr>
<td>BENEFIT</td>
<td>Chance of improvement in shortness of breath in the next year</td>
<td>![Graph showing 40% improvement]</td>
<td>![Graph showing 25% improvement]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40 out of 100 people (40%) have improved shortness of breath</td>
<td>25 out of 100 people (25%) have improved shortness of breath</td>
</tr>
</tbody>
</table>

TX = treatment.
### Example Survey Question

#### TX = treatment.

<table>
<thead>
<tr>
<th>TX TYPE</th>
<th>Treatment Feature</th>
<th>Treatment A</th>
<th>Treatment B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BENEFIT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Type of treatment</td>
<td>Implantable lung device</td>
<td>Medicines</td>
</tr>
<tr>
<td></td>
<td>Chance of improvement in shortness of breath in the next year</td>
<td>40 out of 100 people (40%) have improved shortness of breath</td>
<td>25 out of 100 people (25%) have improved shortness of breath</td>
</tr>
<tr>
<td></td>
<td>Difference in flare-ups in the next year</td>
<td>1-2 more flare-ups</td>
<td>No change in flare-ups</td>
</tr>
<tr>
<td></td>
<td>Additional risk of collapsed lung in the next year</td>
<td>Small change (10%)</td>
<td>No chance</td>
</tr>
<tr>
<td></td>
<td>Additional risk of pneumonia requiring hospitalization in the next year</td>
<td>15 additional cases in 100 people (15%)</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Additional risk of dying in the next year</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

### TX = treatment.
### Example Survey Question

<table>
<thead>
<tr>
<th>TX TYPE</th>
<th>Treatment Feature</th>
<th>Treatment A</th>
<th>Treatment B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BENEFIT</strong></td>
<td>Type of treatment</td>
<td>Implantable lung device</td>
<td>Medicines</td>
</tr>
<tr>
<td>Chance of improvement in shortness of breath in the next year</td>
<td>40 out of 100 people (40%) have improved shortness of breath</td>
<td>25 out of 100 people (25%) have improved shortness of breath</td>
<td></td>
</tr>
<tr>
<td>Difference in flare-ups in the next year</td>
<td>1-2 more flare-ups</td>
<td>No change in flare-ups</td>
<td></td>
</tr>
<tr>
<td>Additional risk of collapsed lung in the next year</td>
<td>Small change (10%)</td>
<td>No chance</td>
<td></td>
</tr>
<tr>
<td>Additional risk of pneumonia requiring hospitalization in the next year</td>
<td>15 additional cases in 100 people (15%)</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Additional risk of dying in the next year</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td><strong>RISK</strong></td>
<td>Which treatment would you choose?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TX = treatment.
Example
Survey Question

<table>
<thead>
<tr>
<th>TX TYPE</th>
<th>Treatment Feature</th>
<th>Treatment A</th>
<th>Treatment B</th>
</tr>
</thead>
<tbody>
<tr>
<td>BENEFIT</td>
<td>Type of treatment</td>
<td>Implantable lung device</td>
<td>Medicines</td>
</tr>
<tr>
<td></td>
<td>Chance of improvement in shortness of breath in the next year</td>
<td>40 out of 100 people (40%) have improved shortness of breath</td>
<td>25 out of 100 people (25%) have improved shortness of breath</td>
</tr>
<tr>
<td>RISK</td>
<td>Difference in flare-ups in the next year</td>
<td>1-2 more flare-ups</td>
<td>No change in flare-ups</td>
</tr>
<tr>
<td></td>
<td>Additional risk of collapsed lung in the next year</td>
<td>Small change (10%)</td>
<td>No chance</td>
</tr>
<tr>
<td></td>
<td>Additional risk of pneumonia requiring hospitalization in the next year</td>
<td>15 additional cases in 100 people (15%)</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Additional risk of dying in the next year</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Which treatment would you choose?</td>
<td>✔️</td>
<td>❌</td>
</tr>
</tbody>
</table>

TX = treatment.
The selection and definition of the treatment benefit attribute were challenging.

According to CDRH guidelines and good practices, attributes should be:
- Relevant (aligned with trial endpoints) and patient centered.

Patients do not understand the improvements in 6MWT and FEV1.

**Primary Endpoint in RENEW**
- Change in 6MWT at 12 months

**Secondary Endpoints in RENEW**
- 6MWT responder rate
- Change in FEV1
- Change in St. George’s Respiratory Questionnaire (SGRQ)

SGRQ is a 16-question quality of life instrument with 3 domains: symptoms, activities, impact.
- Minimum clinically important difference is a 4-point change in total score.

FEV1 = forced expiratory volume in 1 second; 6MWT = 6-minute walk test.
Treatment Benefit Attribute

- In survey development, patients and physicians indicated that improving breathlessness with activity is a common and important treatment goal.

Quotes from qualitative interviews:

- “Everything else is related to shortness of breath.”
- “If I didn’t have shortness of breath, I’d be OK.”
- “The shortness of breath thing for me is the whole thing.”
- “[breathlessness] is the manifestation of the disease that most concerns me.”

Quotes from qualitative interviews.
### Treatment Benefit Attribute

<table>
<thead>
<tr>
<th>SGRQ Item 11 measures breathlessness with activity</th>
<th>Benefit attribute characterized as the chance of improvement in shortness of breath in the next year (a 1-step improvement in modified SGRQ Item 11)</th>
</tr>
</thead>
</table>

**SGRQ Item 11 measures breathlessness with activity**

<table>
<thead>
<tr>
<th>Activity</th>
<th>True</th>
<th>False</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting or lying still</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Getting washed or dressed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walking around the home</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walking outside on the level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walking up a flight of stairs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walking up hills</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Playing sports or games</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Benefit attribute**

- **Baseline**: I don't feel out of breath doing these activities
- **With improvement**: I do feel out of breath doing these activities

**Activities**

- Sitting or lying still
- Getting washed or dressed
- Walking around the house
- Walking outside on the level
- Walking up a flight of stairs
- Walking up hills
- Playing sports or games
Treatment Benefit Attribute

SGRQ item 11 measures breathlessness with activity

Benefit attribute characterized as the chance of improvement in shortness of breath in the next year (a 1-step improvement in modified SGRQ Item 11)

Correlation between a 1-step improvement in SGRQ Item 11 and the likelihood of achieving the MCID (secondary endpoint) = 93.5%
FDA Comments

• Benefit attribute
  – Preference endpoint is not representative of the secondary endpoint
  – 1-step improvement is not correlated with change in FEV\textsubscript{1}

• Additional comments on range of pneumonia risk levels and pooling data from different sites, attribute descriptions
Outcomes

- PPI Study: There is a group of patients in the target population for whom the benefit of a coil treatment likely outweighs the risk when compared with MMT.

- Panel: The advisory committee voted to reject a pre-market approval application
  - Most of the panel questioned effectiveness and did not agree that benefits outweighed risks.

**Survey Sample with RV ≥ 225%**

- Benefit > Risk: 49%
- Risk > Benefit: 51%

**Full Survey Sample**

- Benefit > Risk: 32%
- Risk > Benefit: 68%
Lessons Learned and Considerations

• Balance the benefits of FDA engagement and input with time and budget resources
  – More engagement may have resolved the FDA’s concerns with PPI study design and analysis

• The adaptation of the SGRQ-related endpoint to the preference study endpoint was systematic and evidence based
  – No guidelines in the literature or regulatory guidance on adapting PRO for PPI
  – Use of PRO in PPI was focus of 2 recent ISPOR workshops
  – RTI-HS is working with CBER on a pilot study and 2 manuscripts that focus on these issues
Agenda

- Background
- Why Patient Preference?
- Study Design and Results
- Summary and Lessons Learned
Background
Overview - NxStage Medical

- Founded in 1998
  - Based in Lawrence MA
  - IPO 2005 (NASDAQ: NXTM)
  - History of innovation and patents

- Key Medical Device Businesses:
  - Home Hemodialysis (HHD) – portable NxStage System One hemodialysis system cleared for home use. Class II life-sustaining, home use device.
  - Critical Care – acute renal care and fluid overload therapies in a hospital environment using the NxStage System One.

- HHD – 90+% of all US treatments prior to FMC merger

- Purchased by Fresenius Medical Care – Feb 2019
The NxStage System One – Over 19 Million HHD Treatments

- Simple to learn and operate
  - Drop-in cartridge
  - Simple interface
  - No significant home modifications

- Portable and flexible
  - Compact
  - Modular
  - No unique electrical requirements

- Attention to safety
  - Comprehensive self-tests automatically performed before each treatment
The NxStage System One is indicated for the treatment of acute and chronic renal failure, or fluid overload using hemofiltration, hemodialysis, and/or ultrafiltration, in an acute or chronic care facility.

The System is also indicated for home hemodialysis, including home nocturnal hemodialysis.

All treatments must be administered under a physician’s prescription and must be observed by a trained and qualified person, considered to be competent in the use of this device by the prescribing physician.
Why Solo HHD?

- Substantial clinical and quality of life benefits to Home Hemodialysis (HHD), particularly when done more frequently.

- Significantly lower penetration of HHD (1.7% of US) than believed clinically appropriate (10-12%) by proponents of the therapy.
  - Patients unable to identify partner not offered therapy due to clear restriction in US labeling.
  - Patients who lose partner or if partner becomes unwilling often must stop home therapy and return to center.

- HHD partner standard is a higher bar vs. in other life sustaining therapies, and in other markets.
  - Peritoneal Dialysis (According to a 2015 Dialysis Patients Citizens survey of PD patients, 30% did not have a partner that could assist them with PD and 12% lived alone).
  - Insulin-Dependent Diabetes.
  - Solo HHD is accepted internationally as the standard of care (and access is higher in those markets).

- Patient groups (including HDU) have been vocal advocates of individual dialysis patients being able to make their own informed choice on whether to perform Solo HHD.
Why Patient Preference?
Why Patient Preference for Solo HHD?

- Relatively little is known about home hemodialysis without a care partner ("Solo HHD") in the US.
  - Current use of Solo HHD
  - Patient attitudes about Solo HHD, including its perceived risks

- To determine if experienced home hemodialysis patients would perform Solo HHD after considering the **benefits** and **risks** of treatment

- To identify risk tolerance thresholds for which experienced home hemodialysis patients would remain willing to perform Solo HHD
Study Design and Results
Engaged Interaction with the FDA

- Care partner requirements are a widely accepted barrier to home hemodialysis (HHD)
  - Lack of a care partner may disqualify HHD as a therapy option for otherwise, qualified patients
  - Care partner burden, or loss of a partner, may increase risk of therapy attrition for patients on HHD therapy

- FDA Patient Preference Workshop conducted with dialysis device manufacturers, renal disease patients, and FDA to understand barriers to home treatments

- As part of a follow-on series of interactions between NxStage and the FDA, NxStage conducted a survey of 142 HHD patients to better understand patient risk tolerance and preference to perform Solo home hemodialysis (Solo)
- NxStage internal risk file review identified unique Solo HHD risks and mitigations which can not be completely eliminated

- Initial plan to submit 510k for indication expansion with supplemental labeling

- NxStage-FDA Discussions
  - ‘Informed consent’ versus ‘decision support tool’ labeling – agreed on a ‘discussion guide’ to inform patients and clinicians of Solo HHD risk
Study Objectives

- To identify risk tolerance thresholds for which experienced home hemodialysis patients would remain willing to perform Solo HHD.

- To determine if experienced home hemodialysis patients would perform Solo HHD after considering the benefits and risks of treatment.
Survey participants

- 1049 current HHD patients in 129 dialysis clinics were contacted electronically by a third party.

- All patients must have been in a dialysis clinic with ≥5 current HHD patients.

- 142 respondents (response rate, 13.5%)
Survey Techniques

- Patients were asked about their experience with Solo HHD, the role of care partners, and the frequency of adverse events during treatment.

- Patients were asked to consider preferences for Solo HHD vs. in-center HD under a variety of scenarios with equal or higher risks of adverse events on Solo HHD.

- After further information about potential risks on Solo HHD, patients with a care partner were asked to state a preference for either Solo HHD or in-center HD.
Patient Preference Survey **Key Findings**

Overall, patients expressed **confidence in their ability** to handle issues during solo treatments.

**61% of patients** *with a care partner* would choose **Solo HHD** over **in-center HD**.*

Solo preference is strong despite concerns of increased risk.

*NxStage data on file
2 in 3 patients prefer Solo HHD to in-center HD, even if risk of death were to be 50% higher.

When risk of death is equal, the vast majority of patients prefer solo HHD.
3 in 4 patients prefer Solo HHD to in-center HD, even if risk of needle dislodgement were to be 1000 times higher.

When risk of needle dislodgement is equal, the vast majority of patients prefer solo HHD.
Patients perceive numerous benefits from HHD, but they remain concerned about risks.

Many patients experience intradialytic hypotension and some have experienced needle dislodgement.

Despite these risks, the majority of current HHD patients would prefer Solo HHD over in-center HD, even if Solo HHD were to confer higher risks of death and needle dislodgement.
NxStage Proposed Pathway ...

... Based on 14 million HHD treatments, a previously cleared nocturnal study and indication expansion, and complaint handling/reporting history (since 2005)
Solo Clearance for NxStage System One

NxStage receives FDA clearance for Solo during waking hours with the NxStage System One

Indications for Use

The NxStage System One is indicated for the treatment of acute and chronic renal failure or fluid overload using hemofiltration, hemodialysis, and/or ultrafiltration, in an acute or chronic care facility.

The system is also indicated for home hemodialysis, including home nocturnal hemodialysis and solo home hemodialysis during waking hours.

All treatments must be administered under physician’s prescription, and must be performed by a trained and qualified person, considered to be competent in the use of this device by the prescribing physician.
Summary and Lessons Learned
Challenges and Lessons Learned

- Determining technology/patient risk assessment trade-off
  - Difficult to do without post-market experience
  - Determining technology ‘state of the art’

- Determining the complexity of the patient preference study for clearance
  - Started with ‘limited’ qualitative assessment
  - Discrete choice model used for clearance

- Assessing patient preference prior to investing in a larger, more complex patient preference study – utilized a pilot

- Understanding patient comprehension of the discrete choice model – utilized graphical models created by FDA to assist patient understanding of the survey
Advice for Other Medical Device Companies

- Plan on a discrete choice model for the patient preference survey – secure the statistical and market research expertise

- Know your audience – make sure the patient preference survey is understandable to the patient

- Make sure you understand your device risk – are there existing technologies today that can address the risks?

- Seek patient feedback prior to the survey – pilots may help you understand qualitative patient risk, survey comprehension, and potential demographic differences

- Involve the FDA Branch and the Patient Science & Engagement program up front
Thank You
Severe Aortic Stenosis: Symptoms & Prognosis

American Heart Association: Symptoms

- Chest pain
- Rapid, fluttering heartbeat
- Trouble breathing or feeling short of breath
- Feeling dizzy or light-headed, even fainting
- Difficulty walking short distances
- Swollen ankles or feet
- Difficulty sleeping or needing to sleep sitting up
- Decline in activity level

After the onset of symptoms, patients with severe aortic stenosis have a survival rate as low as 50% at 2 years and 20% at 5 years without aortic valve replacement.*

Severe Aortic Stenosis: Treatment Options

- Watchful waiting & medical management
- Surgical replacement (SAVR)
- Balloon valvuloplasty
- Transcatheter replacement (TAVR)
Patient Preference Study of TAVR v SAVR

Conducted by Evidera in 2019
- 219 Severe Aortic Stenosis patients (unconfirmed diagnosis)
- Adjusted Swing-Weighting Model
- 12 Attributes tested

For Edwards Lifesciences (sponsor) and Heart Valve Voice (patient group)

Purpose: inform reimbursement decision-making
- US CMS TAVR NCD: coverage constraints warranted?
- Shared Decision-Making (SDM) Tool design

Study Objectives:
- What matters most to patients?
- Quantify the relative weights of each outcome
- Evaluate PCORI SDM Tool attributes
Patients Recruited in Partnership with Patient Groups
Sources for Attribute Selection

**Previous preference studies**: A review of attributes highlighted in previous preference studies with patients, clinical studies, and regulators assessments of related products

**Expert/patient consultation**: Consultation with Edwards staff, who provided input based on their knowledge from conducting interviews with patients, valve clinic coordinators and clinicians

**Clinical literature review**: A review of relevant published meta-analyses and clinical studies to determine the attributes that differentiated SAVR and TAVR
### Attribute Selection and Comparison

**Did the PCOR SDM Tool choose the right attributes?**

<table>
<thead>
<tr>
<th>Attribute Type</th>
<th>PCORI Model</th>
<th>Expanded Attribute Model</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Procedure</strong></td>
<td></td>
<td>The invasiveness of the procedure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>The number of years the procedure has been proven to work</td>
</tr>
<tr>
<td></td>
<td>The probability of being discharged to home</td>
<td></td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td>The probability of having a stroke (1m)</td>
<td>The probability of having a non-fatal disabling stroke (1m)</td>
</tr>
<tr>
<td></td>
<td>The probability of having a stroke (1yr)</td>
<td></td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>The probability of dying (1yr)</td>
<td>The probability of dying (1m)</td>
</tr>
<tr>
<td></td>
<td>The proportion of days alive and out of the hospital (1yr)</td>
<td></td>
</tr>
<tr>
<td><strong>Independence</strong></td>
<td></td>
<td>The probability of having greater independence (1m)</td>
</tr>
<tr>
<td><strong>Other Risks</strong></td>
<td></td>
<td>The probability of needing dialysis (1yr)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>The probability of needing a pacemaker (1yr)</td>
</tr>
</tbody>
</table>
Preference Elicitation Instrument: *Adapted Swing Weighting*

1. Patients **compare** the ‘procedure’ attribute and one ‘other’ attribute

2. They were then asked to **select** which of the attributes they would choose to improve
Preference Elicitation Instrument: *Adapted Swing Weighting*

1. Patients **compare** the ‘procedure’ attribute and one ‘other’ attribute

   ![Example Choice Question Diagram]

2. They were then asked to **select** which of the attributes they would choose to improve

3. Do it again 300 times
Results
Selected Sociodemographic & Clinical Characteristics (N=219)

Procedure Experience
- TAVR: 58%
- SAVR: 13%
- None: 28%
- Other: 1%

Education
- Secondary/High School
- Some College
- College Degree
- Postgraduate Degree
Benefit-Risk Analysis: Threshold analysis

- Older patients generally more tolerant of risk
- Patients willing to tolerate risks much greater than TAVR may provide

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Maximum Acceptable Risk / Minimum Acceptable Benefit</th>
<th>Actual TAVR Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Whole Population</td>
<td>&lt;60 years old</td>
</tr>
<tr>
<td>Mortality (1 Month)</td>
<td>12.6%</td>
<td>11.6%</td>
</tr>
<tr>
<td>Disabling Non-fatal Stroke</td>
<td>20.7%</td>
<td>21.0%</td>
</tr>
<tr>
<td>Independence</td>
<td>6.5%</td>
<td>6.0%</td>
</tr>
<tr>
<td>New Permanent Pacemaker</td>
<td>33.0%</td>
<td>30.6%</td>
</tr>
<tr>
<td>Requirement for Dialysis</td>
<td>21.6%</td>
<td>19.9%</td>
</tr>
<tr>
<td>Proven to Work</td>
<td>0yrs</td>
<td>0yrs</td>
</tr>
</tbody>
</table>
Benefit-Risk Analysis: Relative Weights

- Independence is most important
- 1-month survival is important, but not as important as long-term “durability”
- Disabling stroke not as nearly as important as independence or type of procedure

Independence is most important
1-month survival is important, but not as important as long-term “durability”
Disabling stroke not as nearly as important as independence or type of procedure
Benefit-Risk Analysis: Relative Weights

- Independence is most important
- 1-month survival is important, but not as important as long-term “durability”
- Disabling stroke not as nearly as important as independence or type of procedure

Independence is most important
1-month survival is important, but not as important as long-term “durability”
Disabling stroke not as nearly as important as independence or type of procedure
The heterogeneity in patient preferences supports the need for a SDM framework to support patients’ choices between TAVR and SAVR; patients’ ages were associated with their preferences, but did not explain all the preference heterogeneity.
# Does Size Matter in Patient Preference Studies?

<table>
<thead>
<tr>
<th>Attributes</th>
<th>Survey Round 1</th>
<th>Survey Round 2</th>
<th>p-value</th>
<th>Pooled</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean(SD) (n46-56)</td>
<td>Mean(SD) (n63-76)</td>
<td></td>
<td>Mean(SD) n (n109-132)</td>
</tr>
<tr>
<td>Mortality (1 Month)</td>
<td>4.0 (3.2)</td>
<td>4.3 (2.8)</td>
<td>0.6218</td>
<td>3.86% (2.95)</td>
</tr>
<tr>
<td>Mortality (1 Year)</td>
<td>7.7 (6.6)</td>
<td>9.5 (5.1)</td>
<td>0.1082</td>
<td>7.26% (5.81)</td>
</tr>
<tr>
<td>Stroke (1 Month)</td>
<td>9.9 (5.6)</td>
<td>9.2 (5.5)</td>
<td>0.4937</td>
<td>6.35% (5.63)</td>
</tr>
<tr>
<td>Stroke (1 Year)</td>
<td>10.0 (5.9)</td>
<td>9.4 (5.4)</td>
<td>0.5577</td>
<td>6.53% (5.54)</td>
</tr>
<tr>
<td>Disabling Non-fatal Stroke</td>
<td>9.4 (5.9)</td>
<td>9.2 (5.6)</td>
<td>0.8549</td>
<td>6.69% (5.73)</td>
</tr>
<tr>
<td>Independence</td>
<td>39.3 (12.4)</td>
<td>36.9 (11.2)</td>
<td>0.2594</td>
<td>13.94% (11.77)</td>
</tr>
<tr>
<td>New Permanent Pacemaker</td>
<td>7.7 (6.2)</td>
<td>10.0 (5.2)</td>
<td>0.0205</td>
<td>6.98% (5.71)</td>
</tr>
<tr>
<td>Requirement for Dialysis</td>
<td>9.5 (6.3)</td>
<td>10.0 (5.1)</td>
<td>0.5801</td>
<td>6.21% (5.62)</td>
</tr>
<tr>
<td>Proven to Work</td>
<td>19.9 (16.8)</td>
<td>24.3 (16.8)</td>
<td>0.1394</td>
<td>17.42 (16.86)</td>
</tr>
<tr>
<td>Days Alive and Out of the Hospital</td>
<td>92.1 (6.4)</td>
<td>91.3 (5.1)</td>
<td>0.4470</td>
<td>7.64% (5.70)</td>
</tr>
<tr>
<td>Discharge Location</td>
<td>59.9 (12.6)</td>
<td>61.3 (12.1)</td>
<td>0.5389</td>
<td>16.70% (12.27)</td>
</tr>
</tbody>
</table>

- The table above shows the indifference points derived from each of the survey rounds. The indifference point on only one attribute varied significantly between the two samples – ‘new permanent pacemaker’.

- The standard deviations of the indifferent points do not narrow substantially between each round and the pooled analysis. This would normally be expected, as the larger sample size allows estimation with greater certainty. This isn’t the case because of the bimodal distribution seen in the data.

* n varies between attributes as not all participants provided data on all attributes.
SDM Tools Need to Address Preference-Sensitive Outcomes

Four of the five attributes included in the PCORI model fail to differentiate between TAVR and SAVR
US CMS TAVR National Coverage Determination

National Coverage Determination (NCD) for Transcatheter Aortic Valve Replacement (TAVR) (20.32)

Select the Print Complete Record, Add to Basket or Email Record Buttons to print the record, to add it to your basket or to email the record.

Tracking Information

- Publication Number: 166-3
- Manual Section Number: 20.32
- Effective Date of this Version: 6/21/2019
- Manual Section Title: Transcatheter Aortic Valve Replacement (TAVR)
- Implementation Date: 6/12/2020
Ontario Health HTA Recommendation

“... Marsh et al conducted a benefit–risk analysis of patient preferences for TAVI or SAVR.”

“Committee members agreed that... given the lived experience of patients with aortic stenosis and their caregivers, most older adults with severe aortic valve stenosis who are at low surgical risk would likely choose transcatheter aortic valve implantation (TAVI) over surgical aortic valve replacement (SAVR; the conventional treatment in this patient population).”
Relevant Lessons Learned

*Ask patients what matters to them most*

Clinical studies not the best source of attributes!!

*Recruiting patients is extremely challenging*

*Work with decision-makers upfront*

*Sample size not as important in preference studies*
Helping Patients is Our Life’s Work, and

life is now
Use of Patient Preference Information in Medical Device Submissions: Lessons Learned

Michelle Tarver, MD, PhD
Director, Patient Science & Engagement (PSE)
Office of Strategic Partnerships & Technology Innovation
Center for Devices and Radiological Health
Caution: Consideration for PPI Studies

- Language that is not patient-friendly or that may bias patient responses
- Omitting key regulatory considerations from the preference study
- Unclear mapping between preference study attributes and the clinical investigation outcomes
- Providing insufficient information for FDA to assess the preference study for recommended study qualities and determine that the PPI is valid scientific evidence
Solid qualitative work grounds a patient-centric quantitative preference study

- Informs attribute selection
- Ensures patient comprehension of attributes and levels

Consult FDA early when designing PPI studies for a regulatory context

- Ask for the Patient Science & Engagement Team Members to be consulted
- Be clear about the regulatory question you want your study to answer

Develop a plan for recruiting patients

- Ensure heterogeneity & generalizability of sample
- Include under-represented populations
- Determine criteria for disease validation

Ensure PPI benefit and risk attributes align with outcomes of interest in clinical studies to inform benefit-risk decision

Lessons Learned
Resources

FDA CDRH Websites:


Contacts for Medical Devices

- For Patient-Reported Outcome Questions: CDRH-PRO@fda.hhs.gov
- For Patient Preference Information Questions: CDRH-PPI@fda.hhs.gov
- For Patient Engagement Questions: CDRH_PatientEngagement@fda.hhs.gov
- If you are not sure: michelle.tarver@fda.hhs.gov
Thank You
To ask a question, either:

1. Use the live Q&A feature in the app
2. Click on the thought bubble icon in the webcast window
Virtual ISPOR-FDA Summit 2020

BREAK
PROGRAM WILL RETURN AT 3:15PM EDT