MDIC PCOR Project: From P-Values to Patient Values in Parkinson's Disease
Workshop Summary

On May 18, 2018, MDIC convened a workshop to discuss the outcomes and next steps for its patient-centered outcomes research (PCOR) project in Parkinson's Disease (PD). The project was a nearly two-year collaboration with the Michael J. Fox Foundation for Parkinson's Research, FDA CDRH, MIT, and RTI Health Solutions to investigate how patient preferences could be used to set statistical significance levels in a clinical trial design.

Download the Project Overview slides here.

Download the Aims 1-3 Results Slides here or read on for more information about specific aims.

Register for the August 15 MDICx Webinar here to learn more about project aims and results.

Why Focus on Significance Levels?

The traditional approach to trial design sets the significance level at a standard threshold. While this threshold is designed to minimize Type 1 error (approving an ineffective therapy), it may not necessarily minimize Type 2 error (rejecting an effective therapy) or consider patients' preferences on the tradeoff between Type 1 and Type 2 errors. In other words, the traditional approach might be too restrictive, potentially denying access to patients who are willing to accept more risks for certain benefits. Setting patient- and therapy-specific significance levels may be a pathway to treatment access for patients with a higher risk tolerance and no effective therapies.

While this project focused on a model for using patient-preferences to set significance levels in a hypothetical clinical trial, the overarching goal of our work in this space is to optimize clinical trial designs to benefit patients.

> **The Expert Perspective**: Moving from *P*-Values to Patient values (*Andrew Lo,* Professor, MIT)
>
> MIT's Andrew Lo discussed the history and meaning of p-values, the role of ethics and trade-offs in clinical trial design and FDA approvals, and a rationale for why we would want to examine how we set p-values. He provided an overview of the Bayesian Decision Analysis model used in this project to design the clinical trial for hypothetical PD device and briefly discussed the patient value results.
>
> Download slides | Download video

Why Parkinson's Disease?

Parkinson's Disease is a chronic, degenerative disease with few good treatment options. The PD patient population is heterogenous in terms of the lived experience of the disease. In other words, each patient experience differs in terms of symptoms, severity, and onset who have varying preferences on the acceptable tradeoffs between treatment benefits and risks. This heterogeneity makes it difficult to recruit enough patients to satisfy the statistical requirements of traditional clinical trial designs and, calls into question whether traditional statistical requirements are unnecessarily lengthening the timeline for promising therapies for certain patient population. For these reasons, PD was a useful test case for exploring the most important benefits and risk to patients and developing a model to design clinical trials based on disease-specific patient preferences.

We partnered with the Michael J. Foundation for Parkinson's Research, which had a tremendous asset for this project, a database of engaged, activated patients ready to share their experience and expertise in life with Parkinson's Disease. The Fox Foundation also introduced our team to the Patient Council.

Though this project focused on Parkinson's Disease, the work may be generalizable to other diseases, in particular, chronic, debilitating diseases with few acceptable treatment options.

Project Details

This project marks the first time MDIC partnered directly with a patient group. We completed the project in four parts (aims) (Figure 1).

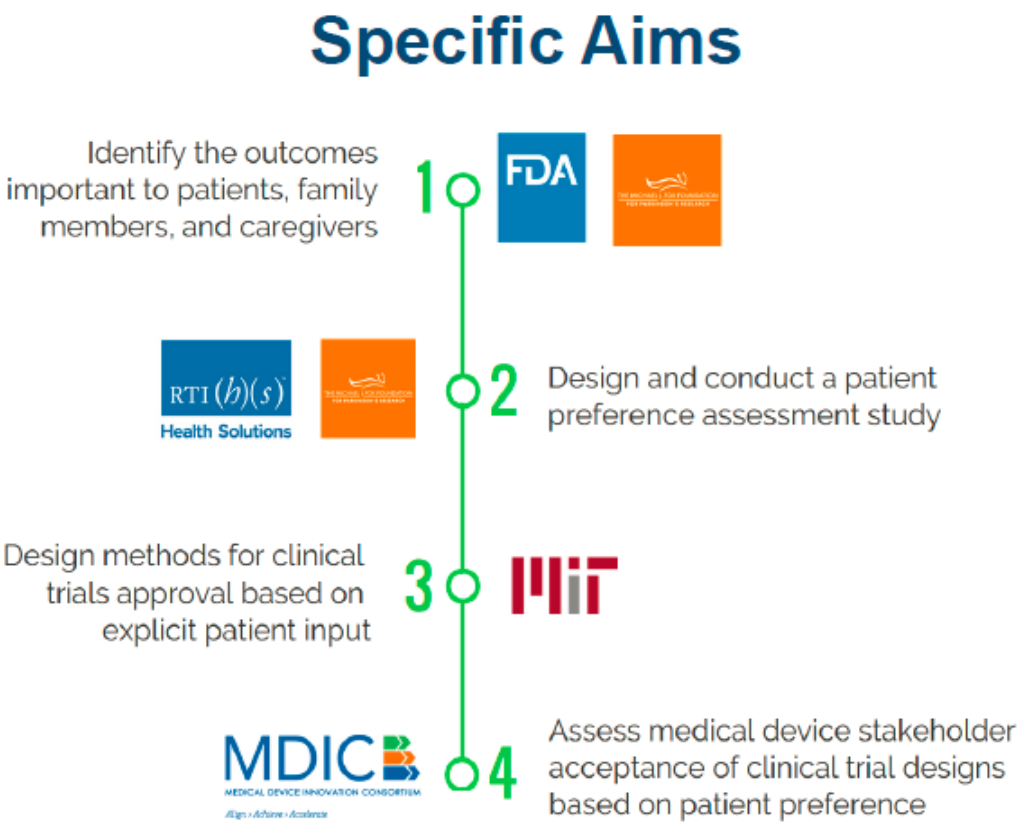

Figure 1. PCOR Project Aims and Collaborators

Project Aim 1: Identify the outcomes important to patients, family members, and caregivers

Collaborators: FDA, MJFF

Approach: We reviewed relevant literature and previous clinical studies, interviewed MJFF Patient Scientists – a small group of volunteers from the MJFF Patient Council – and surveyed the entire MJFF Patient Council to identify important outcomes. FDA reviewers participated in this aim to help ensure that the outcomes also took into consideration the concerns FDA might have in making benefit-risk decisions in this context.

> **The Expert Perspective**: A Vision for Partnering with Patients (*Sohini Chowdhury*, Deputy CEO, Michael J. Fox Foundation for Parkinson's Research)
>
> MJFF's Deputy CEO Sohini Chowdhury discussed MJFF's mission and vision and how the organization partners with patients. She explained the history of the partnership between MJFF and MDIC shared key learnings from the project's Parkinson's patient preference study. In the second half of her talk, she interviewed MJFF Patient Council co-chairs, Margaret Sheehan and Anne Cohn Donnelly, about their motivation for

participating in this project, their experiences as Patient Scientists, and their advice for other teams interested in conducting similar projects.

Download slides | Download video

Project Aim 2: Design and conduct a patient preference assessment study

Collaborators: MJFF, RTI Health Solutions

Approach: Using the results from Aim 1, we further refined the benefits and risks that mattered most to patients. After an iterative interview process with the MJFF Patient Council, we arrived at the final list of the most meaningful benefits and least acceptable risks of this hypothetical PD treatment (Table 1).

Table 1. Final Benefits and Risks

Most Meaningful Benefits	Least Acceptable Risks
Increase in daily "on time" Decrease in motor symptoms Decrease in PD pain Decrease in cognitive impairment Decrease in medication and side effect burden	(Worsening) depression or anxiety Serious brain bleed Increase in one-year mortality risk Increase in wait time

We then sought to understand the benefit-risk preferences in a larger PD population by deploying the survey to more than 10,000 Parkinson's patients via the Fox Insight platform. After six weeks, we received 2,752 responses and began analysis.

Download the Aim 2 Slides here for more information about this process.

Project Aim 3: Design methods for clinical trials based on explicit patient input

Collaborators: MIT

Approach: We incorporated the patient-generated benefit-risk preferences into the design of a clinical trial. Using a Bayesian Decision Analysis Framework, we arrived at patient-generated p-values for several subpopulations of PD patients based on their risk tolerance (Figure 2).

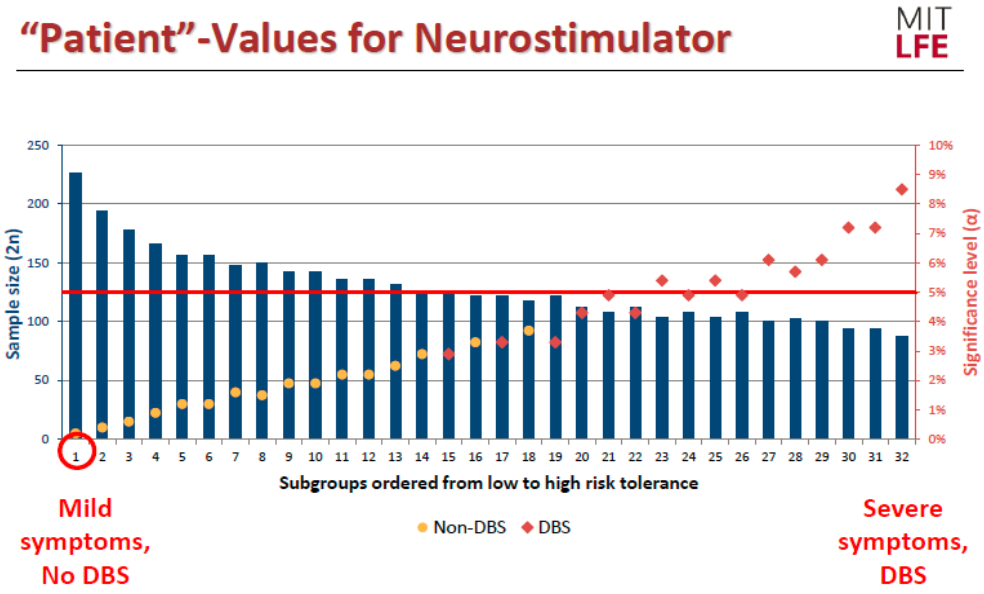

Figure 2. Aim 3 Results (Courtesy of Shomesh Chaudhuri, MIT)

Key findings:

- A fixed significance level of 5 percent does not always maximize patient value
- For risk-tolerant subpopulations (experience with DBS, severe cognitive and motor function impairment), clinical trials are overly conservative
- For patients with less severe symptoms, traditional thresholds of 5 percent may be too permissive

The Expert Perspective: Clinical Trial Design Based on Explicit Patient Input

Download the Aim 3 slides and watch the Aim 3 Breakout Session with MIT, FDA, MJFF, and industry scientists for a thorough background and a discussion of the results:

Watch the Aim 3 Breakout Session here | Download the Aim 3 slides here

Download a detailed summary of the Aim 3 Breakout Session here

Project Aim 4: Assess medical device stakeholder acceptance of clinical trial designs based on patient preference

Collaborators: MDIC, Medical Device Stakeholders

Approach: This PCOR workshop was the first step of many in Aim 4. We will continue to promote the project at conferences and in trade publications. As we spread the word, we will facilitate discussion among all stakeholders to better understand the implications of the patient-centered approach to clinical trials.

The Expert Perspective: Closing Panel – What does this all mean?
Owen Faris, FDA CDRH; *Margaret Sheehan*, Patient Scientist; *Anne Cohn Donnelly*, Patient Scientist; Lauren McLaughlin, MJFF; *Brett Hauber*, RTI Health Solutions; *Andrew Lo*, MIT; *Greg Molnar,* MDIC

Experts took questions from the audience and discussed the implications of this project, how CDRH might handle submissions that mirror the work of this project, and the path to shifting culture toward an optimized, patient-centric approach to clinical trial design.

Watch a recap of the breakout sessions and the closing panel/Q&A here

---

Next Steps:
The collaborative study team is continuing to share the results of this project through conferences and journal publications. In July 2018, MDIC launched a new collaborative patient preference study in patients with heart failure. The output from this collaboration will also be used to test the MIT model for designing clinical trials based on patient preference information. We will be discussing our Science of Patient Input program efforts at the MDIC Annual Public Forum on September 5, 2018. View the agenda and register at http://www.mdic.org/2018apf. To learn more about this project visit **http://mdic.org/spi/pcor** or contact MDIC Science of Patient Input (SPI) Program Director, Stephanie Christopher at **schristopher@mdic.org.**

Media Coverage for this Project:
Read our workshop summary in Medical Device Online and Clinical Leader
The Science Of Patient Preferences In Med Device Clinical Trial Design

Medical Device + Diagnostics Industry
Patients with Parkinson's Get Their Say on Device Trial Design

How Much Risk Will Patients Accept?

Medtech Insight
MDIC Project Looks to New P-Value Possibilities

New Clinical Trial Approach for Urgently Needed Therapies Could Be On Horizon

Mass Device
Patients with Parkinson's Disease Help to Shape Clinical Trial Design

Prioritizing Patient Preference & Risk in Device Trials

Upcoming Conference Appearances:

NYC Neuromodulation Conference
Date: Aug 24-26, 2018
Location: New York City, NY, USA

MDIC 5th Annual Public Forum
Date: Sept 5, 2018
Location: Washington, DC, USA

American Neurological Association (ANA)
Date: Oct 21-23, 2018
Location: Atlanta, GA, USA