

**Outcomes Summary:**  
**Regulatory Roundtable for Cognitive Impairment in Parkinson's Disease**  
**Lona Vincent, MPH and Jamie Eberling, PhD**

*Views expressed represent those of the authors and do not formally represent guidance from the FDA.*

Cognitive impairment, defined as gradual deficits in executive functioning or memory, is a common feature of Parkinson's disease. The severity and symptomatology, however, vary across patients. Cognitive impairment may follow a benign course and never significantly progress or it may progress over time first to a transition state, termed mild cognitive impairment (PD-MCI), and eventually to dementia (PDD). It has been estimated that up to 80% of PD patients will eventually develop PDD, although the underlying cause has not been well-defined and may be attributable to a mixture of pathologies including PD, Alzheimer's disease (AD) and vascular disease. With the approval of rivastigmine (Exelon Patch®), the treatment landscape, though limited, diagnostic criteria and regulatory path for PDD are well-defined.

The same cannot be said for PD-MCI. There are currently no marketed therapeutic options for cognitive impairment in PD. Estimates suggest that while most PD patients will experience benign symptoms of cognitive impairment, about 30% of PD patients will go on to experience PD-MCI. The true prevalence, however, may be underestimated because the condition is often not recognized in clinical practice in part due to insensitive screening instruments and vaguely defined diagnostic criteria. Better understanding of who PD-MCI patients are, how to recognize PD-MCI through diagnosis, and how to measure improvement in these patients are critical steps to filling an unmet need so that treatments can be tested in the clinic and ultimately approved by regulatory agencies.

### **Regulatory Meeting Overview**

In April of this year, the Michael J. Fox Foundation for Parkinson's Research staffers Jamie Eberling, PhD, and Lona Vincent, MPH and Karl Kiebertz, PhD, of the University of Rochester, co-chaired the "Regulatory Roundtable for Cognitive Impairment in PD", a consensus workshop of more than 40 key opinion leaders. In attendance were representatives from industry, the AD community, Movement Disorders Society (MDS), National Institute for Neurological Disorders and Stroke (NINDS), Parkinson's Action Network (PAN), Parkinson's Progression Markers Initiative (PPMI), Coalition against of Major Diseases (CAMD), and 16 representatives from the U.S. Food and Drug Administration (FDA). The goals of the meeting were to gather consensus among the attendees and to identify the regulatory requirements for pursuing a therapeutic indication for PD-MCI. The discussion focused on the following topics:

- Review of the PD-MCI diagnostic criteria and plans for validation
- Existing outcome measures for cognitive impairment and unmet needs in the field
- Study design for future cognitive impairment trials

### **Figure 1. Characteristics of Cognitive Impairment in PD**

- Deficits in executive functioning (i.e. problems with planning, multi-tasking, attention, and problem solving) associated with frontal brain regions
- Memory loss and visuospatial impairment associated with posterior brain regions and more severe forms of cognitive impairment
- Although progression of symptoms typically begins with frontal lobe functions and progresses to more posterior functions, the course varies greatly between patients

## **Review of the MDS Taskforce PD-MCI Diagnostic Criteria**

In 2010, the [MDS PD-MCI Taskforce](#) assembled with the goals to: [1] review the literature on cognitive impairment in PD, [2] develop revised diagnostic criteria for PD-MCI (in order to differentiate these patients from those of with normal cognition or dementia), and [3] draft guidelines for use of the criteria by the PD community. The taskforce defined PD-MCI as a gradual decline in cognitive ability that is not sufficient to interfere significantly with functional independence, although subtle difficulties with day to day functioning may be present. The specific diagnostic criteria for PD-MCI are based on a patient's impaired performance on a test of global cognitive abilities or impairment on neuropsychological tests of specific cognitive domains (i.e., attention, memory, language, etc.). Likewise, a diagnosis of PD-MCI can include impairment on a single cognitive domain or impairment on two or more domains. Patients who meet criteria for PD-MCI are thought to be at greater risk of progressing to dementia.

Jennifer Goldman, MD of Rush University Medical Center led the discussion on the proposed PD-MCI diagnostic criteria. At the conclusion of the discussion, it was noted that the criteria are suitable for current drug development and clinical practice, as the guidelines provide a uniform method by which to characterize and diagnose MCI in PD. It was noted, however, that additional research needs to be conducted to further study the proposed criteria (through pooled data analysis of MCI cohorts and/or a prospective study) and optimize the criteria for real world use.

## **The Role of Specificity in Diagnosis of PD-MCI**

While the PD-MCI criteria were developed specifically for PD patients, the criteria were largely derived from the MCI criteria developed as a precursor to AD. In fact, many of the specific criteria for PD-MCI are the same as those for AD-MCI. Given these similarities it would be possible to make a diagnosis of PD-MCI in patients whose cognitive impairment is actually due to AD pathology. In fact, many PD patients have mixed pathologies, including PD pathology, AD pathology, and vascular pathology, and cognitive impairment could be attributed to effects of any of these or to an interaction between multiple pathologies. This brings up the question of specificity when making a diagnosis. Must the cognitive impairment in PD be demonstrated to be attributable to PD pathology in order to make a diagnosis of PD-MCI?

The concept of specificity is much more straightforward in the context of AD-MCI where the underlying cause of cognitive impairment is clearly defined by A-beta and tau pathology and a number of biomarkers have been developed to aid in the diagnosis. In the context of PD the underlying cause of cognitive impairment has not been clearly defined and the contributions of both PD and non-PD pathologies are not well understood. Despite this, the majority of cognitively impaired patients who eventually progress to dementia do not meet criteria for AD and many do not ever progress to dementia. Thus, PD-MCI is at this point a descriptor of symptomatology without a link to the underlying pathophysiology and the main criterion is cognitive impairment in a PD patient. The FDA indicated that they would be willing to consider an indication of PD-MCI without reference to the underlying cause of impairment.

## The Current State of Cognitive Measures for PD-MCI

Standardized measurement of PD-MCI in clinical research continues to be an unmet need in the field. Though a number of neuropsychological scales and test batteries exist and are being utilized by researchers (see Figure 2), there is a lack of consensus on which measures are most appropriate for the PD-MCI patient population. Cognitive measures are expected to be able to differentiate between individuals at different stages of cognitive impairment, detect treatment effects over short periods of time (symptomatic therapy studies), and detect changes in cognitive deficits over extended durations (disease modification studies). Dan Weintraub, MD of the University of Pennsylvania and Jaime

### **Figure 2. Common Cognitive Scales in PD-MCI Research**

- Parkinson's Disease Cognitive Rating Scale (PD-CRS)
- Montreal Cognitive Assessment (MoCA)
- Scales for Outcomes in PD Cognition (SCOPA-COG)
- Mini Mental State Examination (MMSE)
- Mattis Dementia Rating Scale (MDRS)

Kulisevsky, MD of Sant Pau Hospital led the discussion on outcome measures for PD-MCI. It was concluded that additional research is needed in a PD-MCI population with comparisons done across centers and investigators before the field can recommend a currently available scale or the development of a new composite scale (as seen with the CDR-Sum of Boxes in the AD field).

## Role of Functional Outcome Measures in Clinical Development

Recent [draft FDA guidance on cognitive impairment in AD](#), suggests that AD research sponsors can receive accelerated drug approval with a single cognitive endpoint in clinical trials paired with longer term assessments of functional decline in a post-approval setting. This is supported by evidence that suggests the underlying anatomical and pathophysiologic changes in AD begin years before the presence of clinical symptoms, making it difficult to demonstrate "clinical meaningfulness" in a trial for disease modification. By contrast, in the PD field, PD-MCI patients experience very subtle functional deficits on complex tasks (i.e. planning schedules, balancing checkbooks, and multitasking) – deficits which should be able to be measured in a clinical trial setting as proof of efficacy. The FDA indicated that drug approvals for an indication of PD-MCI will require a co-primary measure (a cognitive outcome measure and a functional measure).

## Defining the Path Forward: Symptomatic vs. Disease Modification

The pursuit of disease modifying therapies for CNS diseases, including PD, is the Holy Grail for drug developers but the regulatory requirements for FDA approval and the expense and complexities of the clinical trials represent very high hurdles. Given the challenges in pursuing a disease modifying approach, symptomatic therapies represent a valid path forward for drug development in PD-MCI. Symptomatic trials could be shorter than disease modifying trials with the assumption that if a treatment effectively treats the cognitive symptoms such an effect should be evident in a relatively short period of time, on the order of days or weeks. In addition, symptomatic approaches could potentially benefit a larger patient population as they may be beneficial even as the disease continues to progress. Disease modifying therapies may only be effective if administered early in the disease process, perhaps even before symptoms are manifest. Disease modifying therapies will also require longer trials in order to be able to measure beneficial effects and biomarkers will likely be critical both for patient selection, identifying those patients who are most likely to benefit, and as objective and hopefully sensitive measures of change over time. MJFF recently launched a Cognition Biomarkers program aimed at developing biomarkers that could be used in both symptomatic and disease modifying trials.

Following the meeting, MJFF and the workshop participants have a vested interest in filling in some of the research gaps around PD-MCI diagnosis and outcome measures. The strong showing of regulatory experts (16 members of the FDA) demonstrated strong support on their part for addressing cognitive impairment in PD along with a willingness to have open dialogue around next steps for research. MJFF is currently working to identify both short term and long term strategy for therapeutic development in PD-MCI.

**Key Regulatory Highlights:**

- The FDA is willing to provide a therapeutic indication for mild cognitive impairment in PD.
- For regulatory consideration, it may be appropriate to pursue an indication of PD-MCI without reference to the underlying cause of impairment.
- Drug approvals for an indication of PD-MCI will likely require a co-primary measure (a cognitive outcome measure and a functional measure).
- For trials that will take place in the short-term, existing cognitive scales are adequate. FDA recommends sponsor select the scale most appropriate for their clinical trial, understanding that the scale does not have to be specific for PD nor does it need to demonstrate response to treatment.
- For trials that will take place in the long term, the PD field could develop an optimal scale. The most appropriate options include a composite scale (as seen with the CDR-SOB in the AD field) or combining multiple scales into one primary outcome measure (ex: Global Statistical Approach).
- In the absence of biomarkers, sensitive cognitive and functional instruments are essential as outcome measures for both disease modifying and symptomatic trials