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Conference Proceedings

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Measuring Cognition in Clinical Trials in Parkinson's Disease, Dementia with Lewy Bodies, and Related Disorders

Roundtable Proceedings and Roadmap for Research

Cognitive changes are among the most worrisome symptoms related to the clinical syndromes associated with Parkinson's disease (PD); dementia with Lewy bodies (DLB); and related disorders on the PD/DLB spectrum, such as rapid eye movement (REM) sleep behavior disorder (RBD).[1] Treatments that address the cognitive changes associated with these clinical syndromes remain an area of high unmet need because of these changes' significant impact on daily function and quality of life. While the cognitive changes experienced by individuals with PD *who develop* mild cognitive impairment (MCI) share some clinical characteristics with patients who have undiagnosed or prodromal DLB,[2] these changes are distinct from those experienced by patients with MCI attributable to other types of dementias, such as Alzheimer's disease (AD). For example, patients with early clinical DLB are less likely to experience memory loss than patients with AD.[3] Cognitive assessments developed for AD thus might not be fully adaptable to the distinct clinical profiles of the PD/DLB spectrum. Despite a multitude of clinical outcome assessments (COAs) of cognition, there is no clear clinical development or regulatory path for novel therapies that address mild cognitive dysfunction in disorders on the PD/DLB spectrum.[4]

To spur the adaptation of existing cognition-focused measures and the development of new ones to underlie clinical trial endpoints in PD, DLB, and related disorders, The Michael J. Fox Foundation for Parkinson's Research (MJFF), Shake It Up Australia Foundation, Parkinson's UK, Parkinson Canada, Lewy Body Dementia Association, Cure Parkinson's, and the Critical Path for Parkinson's

KEY TAKEAWAYS

- Growing evidence supports reframing Parkinson's disease (PD) and dementia with Lewy bodies (DLB) as a single, biologically defined disease, called *neuronal α-synuclein disease* (NSD). Moving forward, patient populations included in clinical trials in PD and DLB may therefore increasingly be defined based on their biological features rather than their clinical presentation. This will influence the development and selection of clinical outcome assessments.
- Clinical trials that address cognitive impairment are challenging to design because competing factors influence whether a clinical outcome assessment is appropriate for use (i.e., fit for purpose). Researchers must strike a balance between defining patient populations broadly enough to encompass a wide range of individuals and ensuring that the patients within that population are homogeneous enough to detect meaningful changes in outcomes over the relatively short duration of a clinical trial. The patient population being studied must drive researchers' decisions about which clinical outcome assessment is most appropriate.
- Consensus is needed on which existing cognitive measures have the highest potential for use in clinical trials of treatments for PD and DLB, and in what context new measures are needed. The field lacks wide consensus regarding which existing measures are most appropriate for evaluating cognition in PD and DLB, introducing measure heterogeneity across treatment trials in these populations. New measures might also need to be developed and validated, and the field must align on the contexts in which this is effort would be warranted.
- Collaboration and data-sharing among academic, industry, and regulatory stakeholders will accelerate the development and validation of cognition measures to underlie clinical trial endpoints in PD and DLB. Next steps include comprehensive research syntheses of existing measures and their longitudinal performance, as well as harmonization and integration of existing datasets, particularly those that include biomarker data that can be used to characterize patients by biological stages of disease.

Consortium co-hosted the PD/DLB Cognition Roundtable on January 10 and 11, 2024, in Washington, D.C. The roundtable brought together representatives from academia and industry, as well as with representatives of regulatory agencies, community partners, patient advocates, and research funders, to build consensus and collaborate on the outcome assessment and trial design methods that will support the development of new treatments for initial or mild cognitive changes in disorders on the PD/DLB spectrum. The stated goals of the roundtable were as follows:

1. Align the field on addressing knowledge gaps in patient experience that will provide a critical foundation for developing regulatory acceptable endpoints for future clinical trials.
2. Assess trial design approaches in target populations, aligning disease biology and clinical course with cognitive measures.

The roundtable's ultimate goal was to identify and refine key opportunities to drive precompetitive, global, and patient-centered approaches to developing appropriate endpoints for early cognitive dysfunction in PD, DLB, and related disorders to accelerate drug development. In this document, we summarize the presentations and discussions from the roundtable and synthesize the discussions on cognitive measures and clinical trial design.

Background and Context

To set the context for the roundtable, we first describe the existing scientific and regulatory environment for cognition measure development in PD, DLB, and related disorders.

Regulatory Context for the Development of Clinical Outcome Assessments in Parkinson's Disease and Dementia with Lewy Bodies

COAs are measures that describe how a patient feels, functions, or survives.[5] In clinical trials, COAs can be the basis of an *endpoint*, which is a validated measure that can be used to assess whether an investigative treatment affects patients' symptoms in a manner that they find meaningful, including by slowing progression or maintaining current functioning. The FDA and the European Medicines Agency (EMA) both have released guidance to support the development of reliable, valid, and patient-focused COAs as the basis of endpoints in clinical trials for pharmacological treatments.[6] This guidance has important implications for developers of COAs in PD and DLB, as well as users of COAs in industry, academia, and clinical medicine.

There are four main types of COAs: patient-reported outcomes (PROs), clinician-reported outcomes (ClinROs), observer-reported outcomes (ObsROs), and performance outcomes (PerfOs) (Box 1).[7]

Within the FDA's Center for Drug Evaluation and Research (CDER), there are two formal paths for regulatory acceptance of a COA. In the first, a COA can be proposed within an individual drug development program as part of an investigational new drug (IND) submission.

When proposed as part of an IND submission, the COA is tied to a specific drug development program or therapeutic target and must be a "well-defined and reliable assessment," which the FDA considers and confirms as part of the submission.[8] Alternatively, CDER's Drug Development Tools program includes pathways for COA qualification. This process occurs outside an individual drug development program. Once qualified, COAs can be included in new IND submissions without the FDA needing to reconsider and reconfirm suitability in the absence of serious flaws, attempted application outside the qualified context of use, or new and conflicting scientific evidence.[9] Qualification is not required for a COA to be successfully used in clinical trials and drug development to support regulatory decisionmaking (and,

BOX 1

Main Types of Clinical Outcome Assessments

- *PROs* are based on reports from the patient about the status of the patient's health condition without amendment or interpretation by anyone else. PROs can be measured by self-report or interview. PROs can capture symptoms, unobservable concepts known only to the patient, and the patient's perspective on their own function or activities. In the context of PD and DLB, these could include self-reported measures of (1) cognitive decline over time and (2) cognitive functional abilities.
- *ClinROs* are based on reports that come from a trained health care professional after observation of a patient's health condition. ClinROs often involve clinical judgment or interpretation of observable signs, behaviors, or other manifestations of a disease or condition. ClinROs cannot directly assess symptoms known only to the patient. In the context of PD and DLB, ClinROs could include a clinician's assessment of cognitive decline over time and cognitive functional abilities that use information from an interview with the patient or a knowledgeable informant or their own observations.
- *ObsROs* are based on reports of observable signs, events, or behaviors that are related to the patient's health condition by someone other than the patient or a health professional without judgment or interpretation. Generally, ObsROs are reported by someone who observes the patient in daily life. In the context of PD and DLB, ObsROs could include measures of cognitive decline over time and cognitive functional abilities that are reported by a knowledgeable informant, such as a family member or close friend.
- *PerfOs* are based on standardized tasks actively undertaken by a patient according to a set of instructions. They may be administered by a trained individual or completed by the patient independently. In the context of PD and DLB, PerfOs would be performance-based tests of cognitive ability or cognitive function that are completed by the patient.

indeed, a relatively small number of measures have achieved full qualification). Nevertheless, the process of qualification can be useful for understanding the evidence needed for successful acceptance of fit-for-purpose COAs in all applications. EMA's process generally aligns with the FDA's regulatory roadmap for COA acceptability within the context of clinical trials, and it has analogous but separate processes for COA acceptance and qualification.[10]

State of the Field: Understanding the Disease or Condition

Recent advances in science have improved understanding of the pathophysiology underlying PD and DLB, providing evidence that these diseases are both characterized by misfolding and accumulation of α-synuclein proteins in the brain (see Box 2 for definitions of key terms). This discovery has prompted the development of a unified diagnostic and disease staging system for PD and DLB (the Neuronal α-Synuclein Disease Integrated Staging System

BOX 2

Key Terms

Amyloid and tau pathology: There is evidence of aggregated α-amyloid and tau proteins in the brain. This constitutes biological evidence of Alzheimer's disease but may be present in individuals with other diagnoses.

Dementia with Lewy bodies: This is a clinically defined syndrome that is characterized by cognitive changes preceding or absent motor changes, with underlying α-synuclein pathology.

Early: *Early* in this context is a description of biological evidence of disease. It is often used in the clinical context to describe the period following diagnosis of Parkinson's disease and dementia with Lewy bodies. *Early* is often used interchangeably with *mild* but may not be the same. There is no consensus operational definition of early, which is problematic for the use of *early* in clinical trial design. *Early* may also refer to the prodromal (pre-diagnosis) stages of Parkinson's disease and dementia with Lewy bodies.

Mild: *Mild* is a clinical description that describes the severity of symptoms. It is often used to describe mild cognitive or functional impairment. *Mild* is often used interchangeably with *early* but may not be the same. Definitions of mild have been operationalized in both diagnostic and staging criteria in neuronal α-synuclein disease and related disorders.

Neuronal *α*-synuclein disease: This is a new concept that reflects the shared underlying biology shared by Parkinson's disease and dementia with Lewy bodies. It is defined by the presence of neuronal α-synuclein and dopaminergic dysfunction. Neuronal α-synuclein disease can be diagnosed based on biomarker evidence, independent of clinical signs and symptoms.

Neuronal *α*-synuclein disease Integrated Staging System: This is a new framework for understanding biological progression and clinical severity of neuronal α-synuclein disease. The system breaks down disease stages based on the presence of neuronal α-synuclein and dopaminergic neuronal dysfunction, the severity of clinical signs and symptoms, and the level of the patient's functional impairment.

Parkinson's disease: This is a clinicopathologically defined syndrome that is characterized by motor changes preceding or, absent cognitive changes, motor changes with underlying α-synuclein pathology.

Synuclein pathology: This is shorthand for the biological evidence of neuronal α-synuclein disease. In this report, we use it to indicate evidence of misfolded and aggregated predominantly neuronal α-synuclein proteins in the brain, sometimes called "Lewy bodies." In other contexts, synuclein pathology might include α-synuclein and γ-synuclein, but not in the context of this report.

Synucleinopathies: This is shorthand, in this context, for α-synucleinopathies: a group of neurodegenerative diseases marked by histopathological evidence of pathological aggregates of misfolded α-synuclein.

[NSD-ISS]) that takes into account the presence of α-synuclein pathology and dopaminergic dysfunction, the severity of clinical signs and symptoms, and the degree of functional impairment. There is also increasing recognition that cognitive impairment is strongly related to declines in patient quality of life and functioning, not only in DLB but in PD as well. Qualitative research exploring patient experiences of disease among those diagnosed with PD has demonstrated that cognitive impairment is a top concern, but it receives relatively little clinical attention compared with the motor symptoms of PD. These findings have motivated efforts to develop treatments that are effective for managing the cognitive symptoms that emerge in PD and DLB. However, existing measures of cognition may not be appropriate for use in clinical trials in PD and DLB, which has impeded the success of therapeutic developments. Thus, it is necessary for the field to align on how to appropriately measure cognitive changes in PD and DLB to facilitate regulatory acceptance of selected cognitive measures for use in clinical trials that evaluate treatment effectiveness for cognition. In this section, we include (1) a summary of the unified diagnostic and disease-staging system for PD and DLB, (2) a review of the patterns of cognitive impairment commonly observed in PD and DLB, and (3) an overview of the cognitive measures that have been used in previous research to characterize cognitive impairment in these diseases.

Emergence of Neuronal α-Synuclein Disease

The pathophysiological similarities of PD and DLB have led to calls for unification of the two clinical syndromes,[11] and new biomarker tools are enabling biologic definition of disease—neuronal *α*-synuclein disease (NSD)—that opens new pathways for new treatments that address synuclein pathology and therefore clinical trial designs and selection of target populations that are based on biomarker-defined disease rather than clinical features alone.[12] At the time of this writing, the shift to unifying the diagnosis of PD and DLB on the basis of their shared underlying pathology is being applied only in the context of research and has not yet become part of diagnostic criteria or routine clinical care. However, as evidence supporting this framework grows and biomarker assays become more accessible for use for clinical and diagnostic purposes, this unified classification is likely to be applied in clinical contexts in the future.

NSD encompasses both PD and DLB associated with underlying synuclein pathology (Figure 1). Other clinical terms used in the literature to describe levels of cognitive impairment in patients with PD or DLB include

- Parkinson's disease–mild cognitive impairment (PD-MCI)
- dementia with Lewy bodies mild cognitive impairment (DLB-MCI)
- Parkinson's disease dementia (PDD).

Patients with these clinical diagnoses also might match the biological definition of having NSD. It should also be noted that synuclein pathology might not be the only contributing—or even the primary—cause of cognitive impairment in an individual. A significant portion of PD and DLB patients have co-occurring biomarker evidence of AD pathology or comorbid vascular disease that also could have impacts on cognitive function.

Existing Diagnostic Criteria

Diagnostic criteria for MCI in PD and DLB are highly related but distinct.[13] We present the summaries of the existing diagnostic criteria for these related conditions, including PD-MCI, PDD, and DLB-MCI, in Box 3.

Cognitive Domains Affected in Parkinson's Disease and Dementia with Lewy Bodies

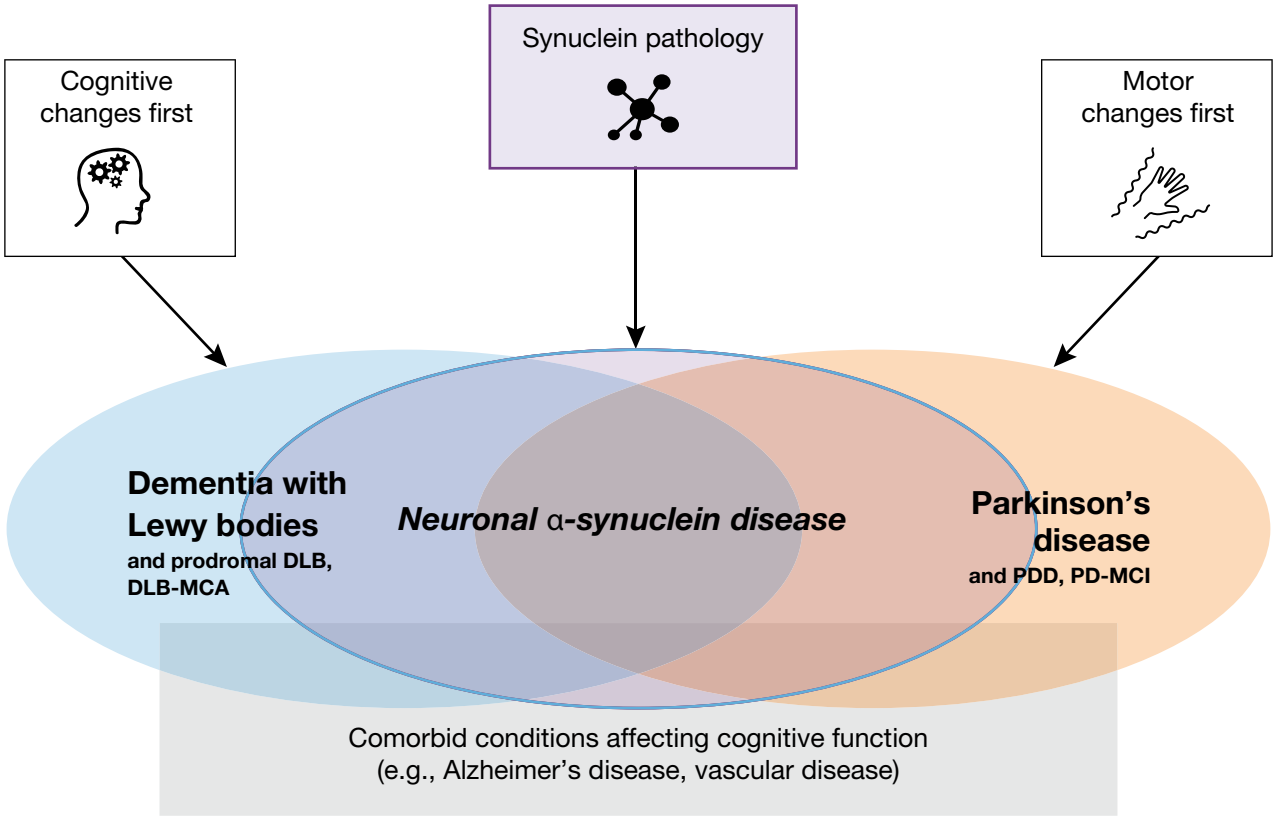
Cognitive impairment is common in PD: 40 percent of patients meet the criteria for a diagnosis of MCI,[14] and dementia is the essential criterion for a diagnosis of DLB. Multiple overlapping domains of cognition have been shown to be affected in both conditions, including executive functioning, memory, attention, visuospatial abilities, and language (Box 4).[15]

Advancements in Disease Staging

Disease frameworks in PD and DLB are increasingly incorporating biologically based definitions of disease.[16] The NSD-ISS integrates the biological

FIGURE 1

Relationship Between Neuronal α-Synuclein Disease, Parkinson's Disease, and Dementia with Lewy Bodies



NOTE: NSD is defined by the misfolding and aggregation of α-synuclein proteins in the brain (also known as *synuclein pathology*). Synuclein pathology may be clinically imperceptible or subtle at the earliest stages, and then different signs and symptoms may emerge. Patients who experience predominantly cognitive changes first may be diagnosed with DLB, while those who experience predominantly motor changes first may be diagnosed with PD. As the disease advances, patients with each of these diagnoses may begin to experience a spectrum of similar symptoms. Most patients with DLB and PD have a spectrum of other nonmotor and noncognitive symptoms, including sleep impairment, depression, anxiety, and autonomic dysfunction. Patients with NSD may have comorbid conditions, such as Alzheimer's disease and vascular disease, that may also separately contribute to cognitive or motor impairments as well. Patients diagnosed with PD or DLB may or may not have synuclein pathology.

evidence of synuclein pathology and dopaminergic dysfunction, the severity of clinical signs and symptoms, and the degree of functional impairment to describe disease progression in patients on the PD/DLB spectrum. This framework was enabled by recent (since 2018) advancements in α-synuclein seed amplification assays,[17] which, for the first time, made it possible to observe synuclein pathology in living individuals. This framework is catalyzing new regulatory paths for drug development. The NSD-ISS operationalizes stage of disease with respect to evidence of pathological neuronal α-synuclein and dopaminergic neuronal dysfunction, as well as the degree of functional impairment caused by clinical signs and symptoms. The domains for functional impairment include *cognitive, nonmotor,* and *motor*: stages of functional impairment are not present (stages 0–2), slight (stage 3), mild (stage 4), moderate (stage 5), or severe (stage 6). There are ongoing efforts to clarify the operational definitions of functional impairment. The field continues to develop and align the NSD-ISS to guide selection of biomarker-defined populations in the design of clinical trials. However, the existing active clinical trial pipeline still needs to rely on existing tools to define populations and patient experiences using the clinical—rather than biological—definitions of disease.

BOX 3

Summary of Diagnostic Criteria for Parkinson's Disease–MCI, Parkinson's Disease Dementia, Dementia with Lewy Bodies–MCI, and Dementia with Lewy Bodies

Parkinson's Disease–Mild Cognitive Impairment[a]	Parkinson's Disease Dementia[b]
• Diagnosis of PD, per UK PD Brain Bank criteria • Gradual decline, in the context of PD, in cognitive ability, reported either by the patient or informant or observed by a clinician • Documented cognitive deficits on either formal neuropsychological testing or a scale of global cognitive abilities • Cognitive difficulties not sufficient to interfere significantly with functional independence, although subtle difficulties on complex functional tasks may be present	• Diagnosis of PD per UK PD Brain Bank criteria • A dementia syndrome with insidious onset and slow progression, developing within the context of established PD, and including – impairment in two or more cognitive domains – decline from premorbid functioning – deficits severe enough to impair daily life, independent from impairment attributable to motor or autonomic symptoms
Dementia with Lewy Bodies–Mild Cognitive Impairment[c]	**Dementia with Lewy Bodies[d]**
• Concern expressed by the patient, informant, or clinician regarding cognitive decline • Objective evidence of impairment in one or more cognitive domains (see Box 4 for a summary of the domains). The cognitive impairment may be evident in any domain, but it is more likely to be observed in attention, executive functioning, visuospatial processes, or some combination thereof. • Preserved or minimally affected performance of previously attained independence in functional abilities • *Probable* diagnosis: Two or more core clinical features of DLB are present with or without proposed biomarkers, or one core clinical feature is present with one or more proposed biomarkers • *Possible* diagnosis: One or more core clinical feature of DLB is present and there are no proposed biomarkers or there are no core clinical features with one or more proposed biomarkers	• *Dementia*, defined as a progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational functions or with usual daily activities • Prominent or persistent memory impairment may not necessarily occur in this diagnosis but is usually evident with progression • Deficits on tests of attention, executive function, and visuospatial ability may be especially prominent and occur shortly after diagnosis • *Probable* diagnosis: Two or more core clinical features of DLB are present with or without proposed biomarkers *or* one core clinical feature is present with one or more proposed biomarkers • *Possible* diagnosis: One or more core clinical feature of DLB is present and there are no proposed biomarkers or there are no core clinical features with one or more proposed biomarkers

[a] Litvan et al., "Diagnostic Criteria for Mild Cognitive Impairment in Parkinson's Disease."

[b] Emre et al., "Clinical Diagnostic Criteria for Dementia Associated with Parkinson's Disease."

[c] McKeith et al., "Research Criteria for the Diagnosis of Prodromal Dementia with Lewy Bodies."

[d] McKeith et al., "Diagnosis and Management of Dementia with Lewy Bodies."

Existing Understanding of Patient Experiences in Parkinson's Disease: The Consensus Conceptual Model for Parkinson's Disease

Understanding the symptoms that are most detrimental to patient quality of life in PD, including cognitive changes, has been an important focus for research, but the field is reaching saturation. At the 2022 PD Endpoints Roundtable, participants agreed that significant progress had been made toward understanding patient experiences of early PD through qualitative research.[18] Jennifer Mammen and Jamie Adams have led an effort to create a consensus conceptual model of meaningful symptoms and impacts of patients within three years of their clinical PD diagnosis.[19] Synthesizing and building on several existing conceptual models,[20] this effort has identified more than 300 symptoms and grouped them within domain (including a cognitive domain), category, concept, and experience (motor, nonmotor, or both) using a comprehensive assessment of the literature in the field as of this writing in mid-2024. The consensus conceptual model will provide a common language for describing symptoms and impacts of new treatments for PD. Additional qualitative research might be needed to further explore patient experiences of less well-documented symptoms and to better understand patient versus families' perceptions of symptom burden.

BOX 4

Definitions of Cognitive Domains and Effects of PD and DLB on Cognition

Executive functioning: Executive functioning encompasses (1) higher-order cognitive processes that support reasoning and problem-solving, (2) behaving in a goal-directed and future-oriented manner, and (3) adapting to dynamically changing environments. It includes such functions as *cognitive flexibility*, *response inhibition*, *meta-cognition*, *manipulation of information* in working memory, and *emotion regulation*. Individuals with PD and DLB exhibit difficulties in a variety of executive functions.[a]

Memory: This broadly refers to the capacity to encode new information and later retrieve and use it. Subdomains include *working memory* (the ability to hold information over brief time periods), *episodic memory* and *semantic memory* (*episodic* refers to memories of events and personal experiences, whereas *semantic* refers to recollection of general knowledge), and *procedural memory* (memory related to cognitive and motor habits or skills). PD and DLB are associated with deficits in visuospatial and verbal working memory.[b] Impaired episodic memory and semantic memory are less common in early PD and DLB compared with AD, but these deficits often emerge as the diseases progress. Procedural memory is highly dependent on the basal ganglia, which is the primary region of the brain affected by the neurodegenerative processes in PD; indeed, evidence suggests that PD is associated with disruption of procedural learning and memory. Although DLB may also affect the basal ganglia,[c] which contributes to parkinsonism and other motor impairments, it remains unclear whether procedural memory is impaired in DLB.[d]

Attention: Attention is divided into *selective attention* (the ability to process important information while ignoring other stimuli) and *sustained attention* (the ability to maintain focus on information for an extended period). Attentional deficits are a core cognitive feature of both PD and DLB and have been linked to fall risk in PD.[e]

Visuospatial abilities: Visuospatial functioning involves automatic perceptual and attentional processes (e.g., movement perception and orientation) and more-complex and effortful processes, such as visuospatial working memory and mental rotation. Visuospatial processes permit decisionmaking based on visual sensory input and are critical for successful navigation through one's environment.[f] Deficits in visuospatial cognition are common in PD, worsen as the disease progresses, and are not fully attributable to visual deficits or motor impairments arising from striatal neurodegeneration.[g] Visuospatial deficits are also common in DLB.[h]

Language: Language skills include the ability to (1) comprehend and produce language, (2) access semantic memory (e.g., recall and verbalize the name of an object), and (3) respond to instructions. Difficulties with language production are common in PD and are attributable to both cognitive and motor deficits.[i] DLB has been associated with language dysfunction, including reduced speech fluency.[j]

[a] Harvey, "Domains of Cognition and Their Assessment"; Kudlicka, Clare, and Hindle, "Executive Functions in Parkinson's Disease."

[b] Ramos and Machado, "A Comprehensive Meta-Analysis on Short-Term and Working Memory Dysfunction in Parkinson's Disease"; Calderon et al., "Perception, Attention, and Working Memory Are Disproportionately Impaired in Dementia with Lewy Bodies Compared with Alzheimer's Disease."

[c] Botzung et al., "Pay Attention to the Basal Ganglia"; Tsuboi, Uchikado, and Dickson, "Neuropathology of Parkinson's Disease Dementia and Dementia with Lewy Bodies with Reference to Striatal Pathology"; Huber et al., "Metabolic Correlates of Dopaminergic Loss in Dementia with Lewy Bodies."

[d] Roy et al., "Interaction of Memory Systems During Acquisition of Tool Knowledge and Skills in Parkinson's Disease"; Foerde and Shohamy, "The Role of the Basal Ganglia in Learning and Memory."

[e] Yarnall, Rochester, and Burn, "The Interplay of Cholinergic Function, Attention, and Falls in Parkinson's Disease."

[f] Kravitz et al., "A New Neural Framework for Visuospatial Processing."

[g] Levin et al., "Visuospatial Impairment in Parkinson's Disease"; Cronin-Golomb and Braun, "Visuospatial Dysfunction and Problem Solving in Parkinson's Disease."

[h] Johnson, Morris, and Galvin, "Verbal and Visuospatial Deficits in Dementia with Lewy Bodies."

[i] Smith and Caplan, "Communication Impairment in Parkinson's Disease."

[j] Ash et al., "Impairments of Speech Fluency in Lewy Body Spectrum Disorder."

Existing Understanding of Patient Experiences in Dementia with Lewy Bodies

Research focused on characterizing cognitive impairment in DLB has been primarily focused on neuropsychological tests. However, there is growing interest in conducting qualitative research to better understand the patient experience of cognitive decline in DLB to align with patient-focused drug development. Given that patient experiences in DLB differ from PD, it will be important to gain a better understanding of how the cognitive symptoms of DLB are experienced by patients and their families. A 2020 systematic review of research on mild cognitive impairment in DLB identified four relevant studies that examined the specific cognitive deficits that occur in DLB.[21] This systematic review highlighted impaired executive, attentional, and visuospatial function in patients with DLB,[22] although results for memory function were mixed. Another study of key features of DLB compared with AD included auditory and visual hallucinations;[23] misinterpretation of real visual stimuli (illusions); and delusions, particularly delusional misidentifications.[24]

Summary of the State of the Field for Selecting and Developing Clinical Outcome Assessments for Cognition

Cognitive Measures

Numerous measures have been developed for understanding the cognitive impacts of dementia and MCI across a range of neurodegenerative diseases. Some measures have been designed for and primarily targeted the cognitive impacts of PD; others have been developed for AD, or dementia and MCI generally, and applied in other disease populations. Although these instruments might be appropriate for diagnosis, screening, and detecting long-term decline, whether they are appropriate for use in trials of disease-modifying therapies that target cognitive domains in the earliest stages of PD and DLB is unclear.

Existing cognitive measures that have been used to characterize cognitive deficits in PD and DLB are shown in Table 1. Many of these measures have been historically administered on paper, although they can also be recorded directly into electronic health records system notes or structured data fields. Increasingly, cognitive assessments are being designed to be completed by patients independently, without a trained administrator, on computers or mobile devices using web-based or cloud-based platforms.

There is more evidence for the use of most of these assessments in PD. Some of these assessments (shown in bold in Tables 1 and 2) are recommended by the 2022 National Institute of Neurological Disorders and Stroke (NINDS) PD v2.0 Common Data Elements Cognitive Subgroup.[25] The Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog)[26] was the primary outcome measure used in the clinical trial for the only FDA-approved drug for PDD, rivastigmine.[27] However, it is important to note that patients with PDD exhibit superior performance on the majority of ADAS-Cog subscales compared with patients with AD, and the profile of impairments differs significantly,[28] suggesting that this measure might not be optimal for detecting cognitive deficits in PD, particularly at lower levels of impairment.

Compared with PD, research focused on the development of cognitive measures that capture the specific patterns of cognitive impairment that differentiate DLB from other forms of dementia is sparse. There is a lack of consensus regarding which assessments are appropriate for use in clinical trials of therapeutics for the treatment of DLB.[29] Rodriguez-Porcel and colleagues conducted a systematic review of the existing literature to determine which outcome measures have been most widely used in clinical trials that were focused on DLB or specifically assessed domains of cognition that are differentially affected in DLB compared with AD.[30] The few scales (described in the following sections) that have been used in DLB research were designed for and validated in other dementia populations, including PDD, and they were applied to the study of cognitive functioning in DLB. There remains a pressing need to validate existing cognitive measures for use in DLB (e.g., for diagnostic purposes, tracking changes over the course of disease, evaluating treatment benefits) and to explore the development of novel measures of DLB-stage-specific outcomes.

TABLE 1

Summary of Existing Cognitive Measures Relevant to PD and DLB

		Cognition Domains Assessed						Administration Details		Validation Evidence*		
Measure	COA Type	Global	Memory	Executive Function	Attention	Visuospatial	Language	Format	Time	PD	PDD	DLB
Screening Instruments												
The Mini-Mental State Examination (MMSE)[a]	PerfO	X	X		X	X	X	11-item assessment administered by a trained professional	10 minutes	X	X	X
Montreal Cognitive Assessment (MoCA)[b]	PerfO	X	X	X	X	X	X	12-item assessment administered by a trained professional	10–15 minutes	X	X	X
Mattis Dementia Rating Scale (MDRS)[c]	PerfO	X	X	X	X	X	X	24-item assessment administered by a trained professional	30 minutes	X	X	X
Addenbrooke's Cognitive Examination-III (ACE-III)[d]	PerfO	X	X		X	X	X	19-item assessment administered by a trained professional	15–20 minutes	X	X	X
Cambridge Cognitive Assessment-Revised (CAMCOG-R)[e]	PerfO	X	X	X	X	X	X	25-item assessment administered by a trained professional	25 minutes	X		
Neuropsychological Batteries												
Preclinical Alzheimer Cognitive Composite (PACC)[f]	PerfO	X	X	X				4-task neuropsychological test administered by a trained professional	30 minutes			
Scales for Outcomes in Parkinson's Disease-Cognition (SCOPA-Cog)[g]	PerfO		X	X	X	X		10-task neuropsychological test administered by a trained professional	10–15 minutes	X	X	X
Parkinson's Disease Cognitive Rating Scale (PD-CRS)[h]	PerfO		X	X	X	X	X	9-task neuropsychological test administered by a trained professional	20 minutes	X	X	
ADAS-Cog[i]	PerfO		X			X	X	11-task neuropsychological test administered by a trained professional	30 minutes	X	X	X
Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)[j]	PerfO		X		X	X	X	12-task neuropsychological test administered by a trained professional	20–30 min	X	X	
Cognitive Functional Composite (CFC)[k]—Cognitive Measures	PerfO	X	X	X	X	X	X	7-task neuropsychological test administered by a trained professional	20–25 minutes			

Table 1—Continued

Measure	COA Type	Cognition Domains Assessed: Global	Memory	Executive Function	Attention	Visuospatial	Language	Administration Details: Format	Time	Validation Evidence*: PD	PDD	DLB
Cambridge Neuropsychological Test Automated Battery (CANTAB)[l]	PerfO		X	X	X	X		Customizable computerized self-administered testing battery	Variable	X		
Cognitive Drug Research computerized assessment system[m]	PerfO		X	X	X	X		Customizable computerized self-administered testing battery	20 minutes	X	X	X
Cogstate Battery[n]	PerfO		X	X	X	X		Customizable computerized self-administered testing battery	10 minutes	X		X
Lumos Labs NeuroCognitive Performance Tests (NCPT)[o]	PerfO		X	X	X	X		Customizable computerized self-administered testing battery	Variable			

NOTE: **Validation* is defined here as having been used in research to assess outcomes and shown to be sensitive to the impairments that are characteristic of that diagnosis. Assessments marked with an X for a given domain might not include tests of all subdomains within it. Bolded assessments are recommended by the NINDS PD v2.0 Common Data Elements Cognitive Subgroup. Additional details on the measures in Tables 1–3 are available in Appendix A online.

[a] Arevalo-Rodriguez et al., "Mini-Mental State Examination (MMSE) for the Detection of Alzheimer's Disease and Other Dementias in People with Mild Cognitive Impairment (MCI)."

[b] Nasreddin et al., "The Montreal Cognitive Assessment, MoCA."

[c] Mattis, Jurica, and Leitten, *Dementia Rating Scale.*

[d] Sousa, Mattos Figueiredo, and Dozzi Brucki, "Addenbrooke's Cognitive Examination III."

[e] Roth et al., "CAMDEX."

[f] Donohue et al., "The Preclinical Alzheimer Cognitive Composite."

[g] Marinus et al., "Assessment of Cognition in Parkinson's Disease."

[h] Pagonabarraga et al., "Parkinson's Disease-Cognitive Rating Scale."

[i] Rosen, Mohs, and Davis, "A New Rating Scale for Alzheimer's Disease."

[j] Randolph et al., "The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)."

[k] Jutten et al., "The Cognitive-Functional Composite Is Sensitive to Clinical Progression in Early Dementia."

[l] Fray, Robbins, and Sahakian, "Neuropsychiatric Applications of CANTAB."

[m] Wesnes, "The Value of Assessing Cognitive Function in Drug Development"; Parrot and Wesnes, "Promethazine, Scopolamine and Cinnarizine."

[n] Maruff et al., "Validity of the Cogstate Brief Battery."

[o] Morrison et al., "Reliability and Validity of the NeuroCognitive Performance Test"; Human Cognition Project, "Tools for Research Collaborators."

Measures of Functional Impairment Due to Impaired Cognition

Many measures that have been used to assess the impact of cognitive impairment in previous research are measures of functional impairment (Table 2). Rather than assessing specific domains of cognition, these measures assess the impacts of cognitive impairments on the activities of daily living. These measures are therefore valuable for indexing the degree to which deficits in cognition are related to declines in functioning, which is necessary for establishing the relevance of an outcome to patients. However, because these measures do not directly assess domains of cognition, they lack the specificity needed to understand how different patterns or degrees of impairment relate to functional outcomes. Furthermore, it is challenging to design these measures in a way that makes it possible to isolate declines in functioning that are attributable to cognitive impairment from declines that are attributable to motor or sen-

TABLE 2

Summary of Existing Functional Capacity and Activities of Daily Living Measures Relevant to Parkinson's Disease and Dementia with Lewy Bodies

Measure	COA Type	Administration Details		Validation Evidence*		
		Format	Time	PD	PDD	DLB
Parkinson's Disease Cognitive Functional Rating Scale (PD-CFRS)[a]	PRO	12-item self-report questionnaire	5 minutes	X	X	
Penn Parkinson's Daily Activities Questionnaire–15 (PDAQ-15)[b]	PRO and ObsRO	15-item questionnaire completed by patient and informant	5–10 minutes	X	X	
Everyday Cognition Battery (ECB)[c]	PerfO	4 tests completed by patient in a group setting led by a trained administrator	60 minutes	X		
University of California San Diego Performance-Based Skills Assessment (UPSA)[d]	PerfO	Task-based measure of performance rated by a trained observer	30 minutes	X	X	
Direct Assessment of Functional Status (DAFS)[e]	PerfO	Task-based measure of performance rated by a trained observer	30–35 minutes	X	X	
Virtual Reality Functional Capacity Assessment Tool (VRFCAT)[f]	PerfO	Task-based measure of performance via computerized virtual reality simulation	30 minutes	X		
Alzheimer's Disease Cooperative Study—Activities of Daily Living (ADCS-ADL)[g]	ClinRO and ObsRO	Clinician-rated structured interview of severity with an informant	15–30 minutes	X	X	X
Cognitive-Functional Composite (CFC)—Instrumental Activities of Daily Living (IADL) Questionnaire[h]	ObsRO	30-item questionnaire completed by an informant	10–15 minutes			

NOTE: **Validation* is defined here as having been used in research to assess outcomes and shown to be sensitive to the impairments that are characteristic of that diagnosis. Assessments marked with an X for a given domain might not include tests of all subdomains within it. Bolded assessments are recommended by the NINDS PD v2.0 Common Data Elements Cognitive Subgroup. Additional details on the measures in Tables 1–3 are available in Appendix A online.

[a] Kulisevsky et al., "Measuring Functional Impact of Cognitive Impairment."

[b] Brennan et al., "The Penn Parkinson's Daily Activities Questionnaire-15."

[c] Allaire and Marsiske, "Everyday Cognition."

[d] Patterson et al., "UCSD Performance-Based Skills Assessment."

[e] Loewenstein et al., "A New Scale for the Assessment of Functional Status in Alzheimer's Disease and Related Disorders."

[f] Atkins et al., "Assessment of Age-Related Differences in Functional Capacity Using the Virtual Reality Functional Capacity Assessment Tool (VRFCAT)"; Ruse et al., "Virtual Reality Functional Capacity Assessment in Schizophrenia."

[g] Galasko et al., "An Inventory to Assess Activities of Daily Living for Clinical Trials in Alzheimer's Disease."

[h] Jutten et al., "The Cognitive-Functional Composite Is Sensitive to Clinical Progression in Early Dementia."

sory impairments. Therefore, these types of measures may not be appropriate for use as standalone COAs in treatment trials focused on cognitive outcomes.

Composite Measures (Hybrid Cognition-Function Measures)

Some measures include domains of cognition and other domains, such as functioning in daily life, which would then be combined into a single score as a *composite* measure (Table 3). A composite measure for cognition can be thought of in two ways. The

TABLE 3

Summary of Existing Composite Measures Relevant to Parkinson's Disease and Dementia with Lewy Bodies

		Administration Details		Validation Evidence*		
Measure	**COA Type**	**Format**	**Time**	**PD**	**PDD**	**DLB**
The Unified Parkinson's Disease Rating Scale (MDS-UPDRS)[a]	ClinRO and PRO	4-part clinical assessment with interview and observational components	30 minutes	X	X	
Clinical Dementia Rating Scale Sum of Boxes[b]	ClinRO	Clinician-rated structured interview of severity with patient and informant	30 minutes	X	X	X
Clinical Global Impression (CGI)[c]	ClinRO	Clinician-rated interview of overall severity	Variable	X	X	X

NOTE: **Validation* is defined here as having been used in research to assess outcomes and shown to be sensitive to the impairments that are characteristic of that diagnosis. Assessments marked with an X for a given domain might not include tests of all subdomains within it. Bolded assessments are recommended by the NINDS PD v2.0 Common Data Elements Cognitive Subgroup. Additional details on the measures in Tables 1–3 are available in Appendix A online.

[a] Goetz et al., "Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS)."

[b] Cedarbaum et al., "Rational for Use of the Clinical Dementia Rating Sum of Boxes as a Primary Outcome Measure for Alzheimer's Disease Clinical Trials."

[c] Busner and Targum, "The Clinical Global Impressions Scale."

[d] Skorvanek et al., "Global Scales for Cognitive Screening in Parkinson's Disease."

first is a composite score reflecting several domains of cognition that would be combined into a single indicator of overall cognitive performance across included domains (similar to many of the measures listed in Table 3, when combined into a cognitive battery). For the purposes of this roundtable, this is not what is meant by *composite measure*. The second type of composite, a hybrid cognitive-function measure, would include domains of cognition as well as other domains, such as functioning in daily life, which would then be combined into a single score.

Such hybrid cognition-function measures pose considerable challenges for measurement and regulatory acceptability because there are challenges in determining whether changes in the overall score are being driven by changes in cognition, functioning, or both. Cognition, symptoms, and function are highly intertwined; cognitive impairment in patients with PD and DLB also might alter these patients' awareness of other symptoms and their ability to report their own cognitive symptoms.[31] However, combining these concepts in a single measurement makes it difficult to interpret changes in a score. To be fit for purpose, COAs need to demonstrate change that is directly due to the benefit of a treatment; in composite measures, what domain is being affected is often unclear. Nonetheless, hybrid cognitive-function measures are commonly used as COAs in PD and DLB screening, diagnosis, assessment, and clinical trials.

Summary

Recent Advancements

Significant advancements have been made in conceptualizing cognition and cognitive decline in PD and DLB. A consensus conceptual model for recently diagnosed PD, which is in the late stages of development at the time of this writing, has provided additional insight regarding which aspects of cognitive decline in PD are most concerning to patients. There is a growing appreciation that cognitive impairment is common in PD and has a significant impact on patient quality of life and functioning. This realization has prompted the increased use of cognitive screening and diagnostic assessment in clinical management of PD. Furthermore, PD and DLB are increasingly being conceptualized together under a unifying biologic definition of NSD, and an integrated staging system has been proposed. In the future, the field will continue to shift toward implementing COAs for biologically defined populations as opposed to clinically defined populations, which

will ideally accelerate the development of effective disease-modifying treatments.

Lack of Consensus

The field lacks a gold standard of measurement to assess cognitive abilities and functional outcomes in clinical trials in PD and DLB. As noted previously, some existing measures were designed to capture cognitive impairment that is more characteristic of AD and may therefore not adequately measure the unique patterns of deficits that emerge in PD and DLB, which more commonly include poor performance in attention, executive functioning, and visuospatial domains. Because of the lack of consensus regarding which measure is most appropriate for evaluating cognitive outcomes in PD and DLB, there is significant heterogeneity in the selection of cognitive measures across treatment trials in these populations, making it difficult to compare performance and reliability of the measures across trials and treatment modalities. This lack of consensus also forces every sponsor that is developing treatments targeting cognition in PD and DLB to generate and submit evidence supporting the use of a particular outcome as part of individual IND submissions, which can lead to duplicative efforts. Thus, there is an urgent need for consensus on which concepts of interest should be measured and an agreed plan for measurement selection, modification, or development.

Roundtable Proceedings

In this section, we summarize the proceedings of the PD/DLB Cognition Measures Roundtable, which was held in Washington, D.C., on January 10 and 11, 2024. The agenda was created by the event's co-hosts: MJFF, Shake It Up Foundation, Parkinson's UK, Parkinson Canada, Lewy Body Dementia Association, Cure Parkinson's, and the Critical Path Institute Critical Path for Parkinson's Consortium, with input from academic and industry advisers. Appendix B (available online) lists participants in and presenters at the roundtable. The goals of the convening were to reach alignment across various stakeholder groups regarding how to facilitate the development of COAs that meet regulatory guidelines for use in future clinical trials and to assess trial design approaches in target populations, aligning disease biology and clinical course with measures of cognition.

Day 1: Challenges and Opportunities in Cognitive Outcomes Assessment and Development

Opening Remarks and Session Introduction

TANYA SIMUNI, NORTHWESTERN UNIVERSITY FEINBERG SCHOOL OF MEDICINE

Meeting chair Tanya Simuni began the meeting by highlighting that while the field of PD and DLB faces many challenges, there has been significant progress since the last roundtable meeting in November 2022.[32] She stated the goals of the meeting: (1) assembling a collaborative, multi-stakeholder team that spans the PD and DLB communities to work toward resolving remaining challenges, (2) developing a common vocabulary, (3) aligning on objectives, and (4) focusing on therapeutic development for MCI across the PD/DLB spectrum. She noted that the ultimate aim of the session is to help stakeholders align their efforts with the regulatory roadmap, keeping in mind that patients and their families need solutions now. She provided a high-level agenda for the meeting, which included reviewing the state of the field regarding trial designs for MCI, discussing how learnings derived from similar efforts in other diseases can be applied to PD and DLB, reviewing the state of the field with regard to cognitive measure development, and aligning on deliverables.

Cognition in Lewy Body Disorders: Progress and Unmet Needs

DANIEL WEINTRAUB, UNIVERSITY OF PENNSYLVANIA

Daniel Weintraub summarized recent progress in understanding and diagnosing cognitive impairment in the context of PD and DLB and outlined challenges for clinical trials. He noted that the existing treatment options for PDD and DLB are limited; there is only one FDA-approved medication that has been repurposed from AD—rivastigmine, which has showed modest gains for cognitive outcomes. However, he also emphasized there are many trials in progress that offer hope for the future. He reviewed evidence demonstrating that cognitive complaints

are among patients' top five most bothersome problems and such complaints are related to poorer functional outcomes. He highlighted that the recent development of diagnostic criteria for PDD, PD-MCI, DLB, and DLB-MCI, which incorporate proposed biomarkers, is an important step toward improving diagnostic accuracy and will aid in early detection of cognitive changes to slow progression.

Weintraub concluded by discussing ongoing challenges with defining cognitive endpoints and evaluating the efficacy of treatments. First, he indicated that therapeutic development is complicated by the fact that the neuropathology of PD and DLB is complex and heterogeneous, and there is significant comorbid AD pathology in many patients. Additional challenges that he highlighted included a lack of consensus on appropriate cognitive outcomes and measures, the impact of psychiatric and medical comorbidities on cognition, the confounding of cognitive and motor impairment on cognitive tests with motor components, poor concordance between patients and informants in symptom reporting, short-term fluctuations in cognitive performance, and the need to balance clinical enrichment with generalizability.

Applying Patient-Focused Drug Development to Cognitive Measure Development

CHERYL COON, CRITICAL PATH INSTITUTE

Cheryl Coon reviewed the Patient-Focused Drug Development Framework (PFDD) for developing fit-for-purpose cognitive assessment measures in the context of therapeutic drug development for PD and DLB. She noted that many existing cognitive measures do not meet regulatory requirements for outcome measurement in clinical trials, in part because rigorous patient experience data regarding the relevance of existing outcomes measures are lacking. To address this issue, FDA has created a guidance series to outline methodologies, standards, and technologies for collecting patient experience data and developing fit-for-purpose COAs for drug development. The series includes guidance on best practices for qualitative research, survey methodology, and mixed-methods studies, as well as considerations for people who cannot self-report. The series also defines COA, concept of interest (COI), and concept of use, and provides a conceptual framework for measure development and acceptance. Incorporating COAs into endpoints for regulatory decisionmaking was also addressed, focusing on ensuring that the observed treatment effect is meaningful to patients. However, she noted that some PerfO assessment tasks may appear abstract and need additional support to link changes in scores to what is meaningful in patients' lives.

What Patient-Focused Drug Development Means to People Affected by Parkinson's Disease and Dementia with Lewy Bodies

FRED GOLDSTEIN, RICK GRANT, ANGELA TAYLOR

David Dexter of Parkinson's UK moderated a discussion with a panel of three patient advocates who have lived experience of PD or DLB. Panelists noted that the cognitive changes associated with PD and DLB are very bothersome, unexpected, and frightening. Impaired cognition negatively affects daily life and diminishes the patient's ability to engage in personally meaningful activities. Panelists with a family member affected by PD or DLB additionally highlighted the common challenges associated with short-term fluctuations in cognition, particularly earlier in the disease course. One panelist described the concept of "showtime," whereby performance on cognitive measures appeared normal in the clinic but then deteriorated later in the day. She noted that this

Many existing cognitive measures do not meet regulatory requirements for outcome measurement in clinical trials, in part because rigorous patient experience data are lacking.

aspect of the disease makes it challenging to capture the true level of impairment, which has implications for clinical trials with cognitive endpoints. Panelists additionally emphasized the need for performance-based measures and informant reporting of symptoms because patient insight may be diminished, especially as the disease progresses.

Introduction to Case Studies on Measure Selection and Trial Design Considerations

TANYA SIMUNI, NORTHWESTERN UNIVERSITY FEINBERG SCHOOL OF MEDICINE

Tanya Simuni introduced case studies describing various approaches to selecting cognitive measures in the context of therapeutic trials in PD and DLB. She noted that it is beneficial to learn from approaches that have already been used so that the process of establishing fit for purpose for measures of cognition can be accelerated. She encouraged the audience to focus on the processes that were undertaken to select and implement cognitive outcome measures in each case study rather than on whether the therapeutic agent under study demonstrated efficacy.

Case Study 1: Trial Design Example for Symptomatic Treatment of Mild Cognitive Impairment in Parkinson's Disease (TAK-071)

ARTHUR SIMEN, TAKEDA PHARMACEUTICALS

Arthur Simen presented findings from a randomized controlled trial of TAK-071, a novel cholinergic therapeutic agent that has been shown to improve cognition in animal models while minimizing cholinergic side effects. To evaluate whether benefits observed in animal models of PD translate to human subjects, Simen and colleagues conducted a randomized controlled trial of TAK-071 among individuals with PD and cognitive impairment—mainly in the mild range—using those patients' MoCA scores. Simen stated that while the primary endpoint was gait variability, they also evaluated cognition using a composite of validated measures. He noted that relating drug effects on cognition to changes in functioning is necessary to convince payors to cover the drug, but that doing so is challenging because patients may not be aware that they are experiencing cognitive impairment or understand how it affects their functioning. He stated that this impedes efforts to establish links between cognitive improvements from treatment and functional improvements, and he recommended obtaining input from informants. He further commented that regulatory endpoints for PDD and PD-MCI are not well established, and endpoint measures used in AD and past PDD drug trials, such as ADAS-COG, might not be appropriate. Audience members noted that the field does not have to re-invent processes and approaches and can borrow from existing approaches and theories in other cognitive disorders, such as AD. Those in the audience also emphasized the need to determine how to measure the functional impact of impaired cognition in a way that is meaningful to patients. This perspective was echoed by FDA representatives.

Case Study 2: Trial Design Example for Symptomatic Treatment of Dementia with Lewy Bodies and Parkinson's Disease Dementia (Mevidalen)

KEVIN BIGLAN, ELI LILLY

Kevin Biglan presented findings from a randomized controlled trial of Mevidalen (LY3154207), a positive allosteric modulator that modifies the shape of dopaminergic D1 to increase responsiveness to dopamine, potentially targeting both cognitive and motor symptoms. He described the sample as generalized and likely heterogeneous in terms of pathology. Cognitive functioning was evaluated using the cognitive dementia rating scale computerized assessment system, ADAS-COG, ADCS-Clinical Global Impression of Change (CGIC), MDS-UPDS, and PD-CRS; ADAS-COG was chosen as one of the primary outcome measures because of its previous use in clinical trials of rivastigmine. Biglan indicated that the clinical dementia rating scale has characteristics that made it particularly valuable in the context of Eli Lilly's clinical trial, including being resistant to learning effects, being sensitive to the types of impairments common in DLB and PDD, and showing rapid responsiveness to intervention, which was important for the short time period of the trial. However, the clinical dementia rating scale showed a marked ceiling effect, so it was not possible to demonstrate benefit. He speculated that this may be because participants exhibited relatively little cognitive impairment and noted that this is important to consider when

enrolling participants in demanding and expensive trials. He also emphasized that it is difficult to measure meaningful functional change in such short-duration studies. He indicated that when selecting cognitive measures for clinical trial endpoints, it is important to consider whether to measure disease-specific cognitive domains, mechanism-specific cognitive domains, or global cognition. Audience members highlighted the potential benefit of using adaptive tests that are scaled to individual performance for overcoming ceiling and floor effects.

Case Study 3: Trial Design Example for Slowing Cognitive Decline in Parkinson's Disease (Prasinezumab)

KATHRIN BROCKMANN, UNIVERSITY OF TUBINGEN

Kathrin Brockmann presented study design considerations for a randomized controlled trial of prasinezumab among individuals with GBA-associated PD, a genetically driven form of the disease. She argued that those with GBA-associated PD comprise one of the most efficient populations in which to test disease-modifying compounds. First, these patients exhibit rapid progression of disease, meaning that the impact of a therapeutic agent on symptom progression and underlying pathology can be evaluated in a short time. Furthermore, the underlying pathology of GBA-associated PD is homogenous, characterized primarily by α-synuclein accumulation, allowing for the isolation of effects driven by α-synuclein pathology. She also noted that treating GBA-associated PD in the period during which motor symptoms are evident—but pronounced cognitive impairment is not—provides an opportunity to evaluate whether a therapeutic agent can delay or prevent cognitive decline. She stated that the clinical trial that her team conducted focused on the latter question. When selecting cognitive outcome measures, she indicated that they rejected the MoCA because it was not developed to be used as an endpoint in a clinical trial but rather was developed as screening instrument for global cognitive performance. Consequently, the team decided to integrate a comprehensive neuropsychological test battery. However, the team encountered several challenges with deriving a compositive score from their comprehensive assessment battery, including that Z-scores were not available for all tests for all countries and all languages represented in their multi-center trial, and it was unknown which of the assessments in their battery were most sensitive to detecting change in cognitive performance in GBA-associated PD. To address these issues, the team adapted the approach used to develop the PACC by generating a composite score that included the cognitive assessments that show the highest rate of decline. To identify which measures to include, the team reviewed data from sporadic PD participants without GBA mutation to generate a list of candidate assessments and then performed detailed analysis of the assessments selected for inclusion in the composite using the Parkinson's Progression Markers Initiative's (PPMI's) Original Cohort, which included 46 participants with GBA-associated PD. This yielded the PD Cognitive Composite Score (PDCCS). She noted that her team is assessing outcomes from an informant perspective to evaluate the meaningfulness of change in PDCCS scores and is attempting to differentiate between outcomes primarily driven by cognitive impairment versus motor impairment.

Synthesis of Critical Gaps and Opportunities to Advance Clinical Trials

KATHRIN BROCKMANN, UNIVERSITY OF TUBINGEN; KEVIN BIGLAN, ELI LILLY; ARTHUR SIMEN, TAKEDA PHARMACEUTICALS; GENNARO PAGANO, ROCHE PHARMACEUTICALS

Tanya Simuni moderated a panel discussion during which speakers presented case studies that highlighted challenges in cognitive measure selection and trial design. Several themes from the panel discussion emerged. First, panelists and audience members identified priorities for aligning on critical cognitive measures in PD and DLB. Panelists discussed using patient experience to guide decisions on which outcomes to measure and target therapeutically and the goal of achieving consensus on measures. They discussed achieving consensus on (1) selecting measures to identify people at risk for conversion from MCI to dementia and (2) selecting and developing measures that are based on underlying biological mechanisms of disease. The panelists also discussed including relevant stakeholders in patient selection for clinical trials.

Second, panelists agreed that biologically defined measurement and population selection is preferable

to clinically defined selection because it is more specific. Panelists also discussed the importance of biologically based staging to identify individuals earlier in the disease course to determine whether therapeutics prevent or delay conversion to more-severe disease. The panelists additionally emphasized that biomarkers used to define groups must be feasible to collect in a clinical trial context.

Third, panelists discussed the challenges of enrollment, especially when targeting individuals with cognitive impairment. Potential solutions that emerged include screening large populations, sharing data globally, talking to patients honestly about prognosis to enhance motivation to participate in research trials and undergo difficult or time-consuming assessments (e.g., lumbar punctures, long cognitive batteries), promoting the importance of screening to clinicians who may not have expertise in cognitive neurology, and considering less restrictive recruitment criteria. Patient advocates noted that sharing data with trial participants is motivating and may help retain such participants. Panelists and audience members also discussed the challenges associated with cognition and movement disorder clinics being siloed from one another and the need to provide better education across specialties to increase awareness of the full symptom spectrum in PD and DLB.

Patient advocates noted that sharing data with trial participants is motivating and may help retain such participants.

Lessons from the Development of Measures for Alzheimer's Disease and the Regulatory Acceptance Process

SONYA EREMENCO, CRITICAL PATH INSTITUTE

Sonya Eremenco provided an overview of the processes undertaken by the PRO Consortium's Cognition Working Group at the Critical Path Institute to develop and secure regulatory acceptance of COAs in AD to facilitate therapeutic product development. She highlighted the efforts of the PRO Consortium's Cognition Working Group, whose primary focus has been on MCI in AD. The initial goal was to develop a measure of MCI in AD because existing measures lacked sensitivity in MCI deficits or were developed without input from patients regarding which impairments are most important or impactful to them. She described the process of developing a PRO measure that focuses on interpersonal functioning and IADLs, and the barriers that the team encountered when seeking regulatory qualification from the FDA. She noted that the FDA expressed concern that patients with MCI and AD may lack insight into their cognitive impairment and may therefore not have the capacity to accurately report on their own outcomes. This prompted a shift to a PerfO assessment instead of PRO measure development. Of the 11 PerfO measures under consideration, a panel decided to focus on qualification of the UCSD Performance-Based Skills Assessment (UPSA). However, the evidence generated was not from biologically defined populations with AD and did not include patient perspectives. FDA requested qualitative data about whether the outcomes measured by the UPSA would be meaningful to patients. By this time, biologically defined diagnosis confirmation was necessary for any studies being used to support FDA qualification of a measure in AD. The UPSA had also become outdated, and all these challenges led the Cognition Working Group to drop pursuit of qualification for UPSA–Three Dimensions (3D). The group refocused its efforts on the VRFCAT, an immersive gamification of IADLs, such as meal planning, shopping, transportation, and handling money. Given these challenges and the need to reorient their approach on multiple occasions, she shared several recommendations for future efforts to develop and obtain regulatory acceptance for cognitive measures in PD.

These included seeking early alignment with regulatory agencies to ensure that there is agreement with pursuing qualification for a given measure; gathering input from regulatory agencies throughout the measure-development process, particularly regarding key decision points; and taking into consideration what measures are most appropriate for the given population and the context of use for which approval is being sought.

Insights from the Preclinical Alzheimer Cognitive Composite (PACC) Measure for Alzheimer's Disease Prevention

MICHAEL DONOHUE, UNIVERSITY OF SOUTHERN CALIFORNIA

Michael Donohue provided a review of the process that he and colleagues undertook to optimize the PACC cognitive composite measure in AD using data from existing studies, such as Alzheimer's Disease Neuroimaging Initiative. He noted that the PACC was ideal for this process because it comprises cognitive assessments that are widely administered in AD studies, making it possible to evaluate the sensitivity, validity, and consistency of the measure over different cohorts and at different stages of disease progression and to correlate it with a variety of biomarkers. He acknowledged that there were inconsistencies across studies in the component cognitive assessments that were available, as well as in the collection of biomarkers, although he noted that they matched measures across studies to the extent possible. He indicated that they undertook the process of attempting to optimize the PACC to improve its sensitivity to cognitive changes in AD, which would increase statistical power and thus reduce the number of participants needed to detect a treatment effect in clinical trials. Several optimization approaches were implemented to improve PACC's statistical power. However, he noted that none of the approaches yielded substantive improvements in statistical power. Furthermore, he stated that optimization may reduce the face validity of measures, which could impede regulatory acceptance, and that it is difficult to make decisions about which outcomes a measure like the PACC should be optimized to detect given the existing understanding of the disease. He concluded that statistical optimization approaches should be regarded with skepticism.

Insights from Developing a Cognitive Composite for Measuring Change in Progressive Supranuclear Palsy

TIEN DAM, NEUMORA THERAPEUTICS

Tien Dam shared insights gathered during the process she and her colleagues undertook to develop a cognitive composite measure sensitive to change in progressive supranuclear palsy (PSP), an atypical parkinsonism that is rapidly progressive. PSP is characterized by significant executive functioning impairments that are more pronounced than those in AD and PD. Historically, the RBANS has been used to evaluate cognitive performance in PSP and has been shown to differentiate PSP from other diagnoses, especially in the visuospatial construction domain. However, there was concern that motor symptoms of PSP may interfere with performance in a way that is not dependent on cognitive functioning, and RBANS scores therefore may not be sensitive to change in cognitive functioning but rather reflect ocular motor impairments, bradykinesia, or dysarthria in PSP. The goal was to adapt RBANS for PSP, and the PSP composite was developed to measure three factors that would not be confounded with motor deficits in PSP. The PSP composite was found to perform better than RBANS and is more sensitive to cognitive impairments in PSP, requiring fewer participants in a trial focused on cognitive functioning. She noted that this work demonstrates the potential benefit of modifying existing measures to improve fit for purpose and sensitivity, rather than undertaking the substantial effort to develop and validate a new measure.

Learnings from a Consensus Conceptual Model for Early Parkinson's Disease and Opportunities to Advance Novel Measure Development

JENNIFER MAMMEN, UNIVERSITY OF MASSACHUSETTS DARTMOUTH (IN ABSENTIA), PRESENTED BY MICHELLE CAMPBELL (OUTSIDE HER ROLE AT THE FDA) ON BEHALF OF JENNIFER MAMMEN

Jennifer Mammen prepared a presentation describing the effort that she and colleagues undertook to develop a consensus conceptual model of meaningful

symptoms and impacts in early PD (0–3 years since diagnosis) that was informed by patient input, which was conducted in response to a call to action arising from the November 2022 roundtable meeting. The consensus model aims to align with the FDA PFDD guidance, guide research focused on endpoint evaluation and measure development, and be adaptable to accommodate emerging data and viewpoints. A systematic literature review was conducted to determine the most meaningful symptoms of and impacts to people with early PD. This process yielded more than 300 concepts drawn from 89 studies, which Mammen and colleagues then mapped onto ten symptom domains and two impact domains, guided by input from multiple stakeholder groups (e.g., patients, clinical experts, FDA). Patients were enthusiastic about the overall conceptual model and the domains that were included, although they requested translation into more patient-friendly terminology. There are some critical limitations, including the model's non-alignment with the concurrently emergent NSD-ISS; difficulty uniting inconsistent use of terms in the literature; and inadequate data, particularly in the cognitive domain. The next steps are to harmonize the definition of terms, solicit community review, publish findings, and explore patient-facing resources to help patients communicate with others, including providers, about their lived experience.

Stakeholder Reflections on Case Studies and Roundtable Discussion Focused on Key Opportunities to Advance Parkinson's Disease and Dementia with Lewy Body Fields

Tanya Simuni moderated a discussion among attendees regarding the Day 1 presentations. The discussion covered various topics related to the development of COAs for PD and DLB. Attendees emphasized the need to balance leveraging what has been done with treatment of other diseases with ensuring that the application in PD and DLB is appropriate. The group discussed the use of composite measures that incorporate multiple symptom domains. FDA representatives cautioned that composites can be challenging because all components of a composite must be relevant and also warned that that interpreting changes in composite measures can be challenging.

Attendees also discussed the limitations of optimizing measures using existing data possibly being even greater in PD and DLB because sample sizes are smaller than in studies of AD. The discussion additionally covered the challenges of developing COAs for cognitive impairment, especially when subtle cognitive changes may affect function. Attendees highlighted the need for operational definitions of biologically based staging in early DLB or PD and additional research exploring the boundaries between disease stages is needed. The importance of understanding what symptoms prompt patients to see their doctors in the first place was also discussed. Determining how to prioritize measures was reviewed; attendees noted the need to consider not only whether an outcome is likely to be sensitive to intervention but also whether it is important to patients, characteristics which do not always align. The need for better training and co-training of providers in movement and cognition was highlighted, particularly given that patients with PD and DLB may present very differently and at different stages in the disease course. There was related debate about whether an integrated staging system was appropriate and whether it might be preferable to develop COAs separately for PD and DLB to ensure they meet fit-for-purpose and context-of-use requirements. Finally, the discussion touched on the evaluation of functional impairment using such measures as the CGIC and VRFCAT and mapping functional impairment onto underlying pathophysiologic characteristics.

At the end of the first day, participants reflected on the day's discussions; the group was especially interested in hearing from U.S. government representatives in attendance. FDA representatives emphasized (1) the importance of engaging with the agency early on questions related to the use of cognitive batteries and composites to underlie endpoints and (2) the need for input from patients about clinical meaningfulness. The roles of PerfO, PRO, and ObsRO measures and the need for a combination of all of these measures were also discussed. Continuous measurement—or, at least, more-dense repeated measures—could be very useful, and attendees noted that combining data across datasets and increasing data-sharing could prevent duplicative efforts. A representative from that National Institute on Aging (NIA) emphasized the

need for input on how to speed up the development of therapeutics and indicated that the institute is now requiring a data-sharing plan from all funded investigators. She noted that NIA additionally is interested in funding research focused on biomarker development and validation, as well as research exploring how to use real-world data that are more readily available for analysis (e.g., electronic health records data) to aid in classification and outcomes assessment. Participants also highlighted the need for multimodal biomarker assessment, communication with patients about cognitive symptoms in PD, and dual training of clinicians in movement and cognition.

Day 2: Measure Development Case Studies and Implications for Trial Design

Case Study 1: Insights into the Development of Computerized Cognitive Test Batteries and Performance in Clinical Trials for Parkinson's Disease and Dementia with Lewy Bodies

CHRIS EDGAR, COGSTATE

Chris Edgar presented on efforts to develop computerized cognitive test batteries. He reviewed the use of digital task performance as a COA and emphasized the need to use the same approaches to validation as for all COAs. Edgar also advocated for the use of PerfOs, arguing that these types of measures circumvent issues related to insight among patients who have difficulty self-reporting their symptoms because of disease-related impairment. He noted that PerfOs are useful for assessing outcomes that are not well-understood by patients, such as disentangling effects driven by memory impairments versus attentional impairments. He indicated that PerfOs are also affected to a lesser degree than self-report by co-occurring psychiatric symptoms, such as depressed mood. Edgar discussed the importance of a disease-specific battery approach and outlined how his team approached implementing the PFDD framework to select and validate outcome measures. He emphasized the need to gather qualitative and quantitative data to demonstrate that the measure is valid in the context in which it is intended to be used and to ensure that it assesses an outcome that is meaningful to patients. He addressed the concept of minimum clinically important difference, including how to define it in the context of a clinical trial. He recommended defining this difference by linking scores to another meaningful outcome, such as patient, family member, or clinician report of functioning, and complementing this with distribution-based indicators of change. He also discussed whether and how to communicate with participants about their performance. FDA representatives commented that the approach to measure development and validation adopted by Edgar and colleagues aligned well with their guidance.

Case Study 2: Creation and Performance of a Cognitive Summary Score in De Novo Parkinson's Disease

DANIEL WEINTRAUB, UNIVERSITY OF PENNSYLVANIA

Daniel Weintraub provided an overview of the approach he and colleagues took to develop and validate a cognitive summary score in PD to determine whether a summary score demonstrated superior sensitivity compared with the component test scores. He argued that cognitive summary scores combine the richness of a full cognitive assessment battery with the simplicity of a single score and may facilitate the identification of novel biomarkers if they demonstrate better sensitivity relative to individual tests. He indicated that their approach to calculat-

PerfOs can circumvent issues related to insight among patients who have difficulty self-reporting their symptoms because of disease-related impairment.

ing the summary score was to standardize all tests to Z-scores using both published norms and internal norms derived from regression modeling that accounted for demographic factors. He described the process of defining a "super healthy" control group to differentiate individuals who might potentially be mischaracterized as cognitively healthy but who may have subclinical disease, noting that the inclusion of these individuals might reduce the sensitivity of an outcome measure. Results indicated that the summary score performed better than the individual tests in differentiating between individuals with PD and healthy controls, with the exception of the symbol-digit modalities test (SDMT), although he advised against using the SDMT as a single outcome given that it measures only one cognitive domain affected in PD. Reflecting on this process, he shared several recommendations, including implementing rigorous training procedures for test administrators to ensure consistent and valid data collection, performing regular data checks to permit the early resolution of issues and deriving internal norms rather than relying on published norms. He indicated that the team is now exploring the utility of the summary score among individuals with prodromal PD, examining performance of the summary score over time, comparing the summary score with MoCA scores, applying the score across the proposed disease staging system, and exploring biological correlates.

Case Study 3: A Composite Scale for Rapid Eye Movement Sleep Behavior Disorder

BRADLEY BOEVE, MAYO CLINIC

Bradley Boeve presented on efforts to develop a composite measure of symptoms common in RBD. Boeve noted that individuals with RBD experience an 8-percent conversion rate to PD, DLB, or multiple system atrophy per year, with 40–50 percent of those individuals developing PD, 40–50 percent developing DLB, and 2–5 percent developing multiple system atrophy, making this an important population to target in studies that are focused on understanding mechanisms underlying disease progression in PD and DLB. Boeve provided details of the North American Prodromal Synucleinopathy (NAPS) 2 study, in which he and colleagues are conducting longitudinal testing among individuals with RBD to evaluate predictors of conversion to PD and DLB to inform the development of disease-modifying treatments. He described the processes he and colleagues undertook to develop the Prodromal Synucleinopathy Rating Scale (PSRS), a seven-domain assessment that can be used to rate cognitive, sleep, behavioral and psychiatric, motor, sensory, and autonomic function, as well as functional capacity changes. He noted that the PSRS has potential applications for clinical trials to determine sensitivity to change with treatment and evaluate treatment effects. He stated that his team also uses a neuropsychological battery to aid in the diagnosis of MCI and dementia, and he noted that only 40 percent of patients are straightforward to characterize diagnostically. The discussion highlighted the complexity of synucleinopathies and the need for biomarker collection in RBD cohorts. The diagnostic challenges associated with cognitive fluctuations were also discussed.

Case Study 4: A Composite Domain Rating Scale for Dementia with Lewy Bodies

JOHN-PAUL TAYLOR, NEWCASTLE UNIVERSITY

John-Paul Taylor presented about the processes that he and colleagues are undertaking to develop a composite cognitive measure for use in clinical trials in DLB. He noted that because DLB is marked by significant fluctuations in cognition, it is particularly challenging to develop cognitive measures that meet regulatory criteria for fit for purpose in clinical trials. The newly developed DLB Domain Rating Scale was designed to assess multiple domains of functioning in DLB: Conceptual development was grounded in a literature review and expert stakeholder engagement. He noted that he and his team are still defining what they will measure and how (e.g., symptom severity, symptom frequency) and are soliciting input from expert and patient stakeholders to inform their decisions. The measure is intended to allow for measuring and tracking progression from the prodromal stage through full dementia and is not intended to be used as a diagnostic measure. The discussion highlighted the need for a measure that can accommodate patient heterogeneity and be applicable to both DLB and PDD.

Case Study 5: Leveraging WATCH-PD Qualitative Data to Identify a Fit-for-Purpose Patient Reported Outcome Measure for Early Parkinson's Disease

DAVE CELLA, NORTHWESTERN UNIVERSITY

Dave Cella provided an overview of the processes that he and colleagues undertook to leverage qualitative data from the Wearable Assessment in the Clinic and at Home in PD (WATCH-PD) study in patients with recently diagnosed PD to inform the development of a novel PRO measure. He noted that all measures with regulatory approval for use as a basis for cognitive endpoints have been validated in PD; limited research has focused on recently diagnosed PD. To date, the team has conducted a review of three qualitative studies to document the prevalence and importance of motor and nonmotor symptoms for patients, retained a list of symptoms that were documented in at least two of three reviewed studies, and obtained stakeholder input on the list of retained items. Cella stated that they are working on finalizing a codebook, conducting a secondary analysis of WATCH-PD symptom maps to inform selection of items, and generating a pool of potential items to include from existing HealthMeasures item banks. He reviewed the measurement formats being considered and the benefits and drawbacks of each. Discussion emphasized the differences in patient experience of symptoms in recently diagnosed PD compared with later periods and how that could impede measure development. Cella further highlighted the benefits of leveraging existing data to construct novel measures, including the potential to accelerate measure acceptance and treatment development.

Stakeholder Reflections on Case Studies of Measures in Development Toward Application in Clinical Trials

RICHARD CAMICIOLI, UNIVERSITY OF ALBERTA; SONYA EREMENCO, CRITICAL PATH INSTITUTE; GENNARO PAGANO, ROCHE PHARMACEUTICALS

Rebecca Fuller of CHDI moderated a panel discussion regarding key takeaways from the case study presentations. The discussion focused on the next steps for developing cognitive measures to underlie endpoints in recently diagnosed PD. The group emphasized the need for a measure that is meaningful to patients, is responsive to treatment, and tracks disease progression, while measuring symptoms that are mechanistically linked to the biological pathway being modified by the pharmaceutical treatment. Limitations of existing biomarkers for tracking disease progression were reviewed, as were the implications of this for cognitive measure development. The group also highlighted the importance of measuring reliable change in symptoms that translates into clinically meaningful change and reflects biology, including psychiatric symptoms that affect function and are distressing to patients. The group discussed the need for longitudinal assessments of measurement characteristics over time and the measurement of function. The group also discussed the potential usefulness of a remote ObsRO checklist or screener for symptoms in recently diagnosed PD or DLB, but they noted that not all patients may have a close family member or friend, so it might be challeng-

The group emphasized the need for a measure that is meaningful to patients, is responsive to treatment, and tracks disease progression, while measuring symptoms that are mechanistically linked to the biological pathway being modified by the pharmaceutical treatment.

ing to identify an appropriate observer. The group discussed the potential use of observer reports and the importance of providing detailed explanations of symptoms and operationalization of severity levels to increase the accuracy of reporting by observers.

Roundtable Discussion: Synthesizing and Elevating Additional Themes Across Case Studies with a Focus on Clinimetrics and Regulatory Learning to Identify Future Directions in the Field

To synthesize efforts to advance the field, Cheryl Coon and Tanya Simuni facilitated further discussion of the insights from each presentation. The discussion emphasized the importance of gathering additional qualitative data where needed, including soliciting input from experts who can translate cognitive concepts into lay language and talk with patients about these concepts. Participants noted that qualitative data are particularly sparse in DLB research. The group also discussed the need to measure multiple domains to determine the efficacy of disease-modifying treatments and the relevant symptoms for symptom-focused treatments. The group highlighted the importance of data-sharing and collaboration between individuals with complementary expertise. The group also discussed the need to consider all four types of COAs (PRO, ClinO, ObsO, PerfO) and measures derived from digital devices. Using data presented on the SDMT, participants concluded that this test should not be used alone but included in a battery of tests. The group discussed the need to incorporate newly developed measures into trials and observational studies and leverage data already being collected. Overall, the group emphasized the need to identify COIs, determine which measures exist that are relevant to those concepts, and evaluate the validity of identified measures for use as COAs in recently diagnosed PD and DLB.

Participant and Family Experience in Clinical Trials

FRED GOLDSTEIN, RICK GRANT, ANGELA TAYLOR

Helen Matthews of Cure Parkinson's moderated a panel discussion focused on patient and family experiences when participating in clinical trials. Panelists shared their experiences with neuropsychological tests and emphasized the need for better communication about the purpose of these tests. The group discussed the feasibility of using applications in clinical trials and the importance of keeping patients engaged through feedback and monetary rewards. The group also highlighted the potential for data in clinical trials to be skewed because of recruitment bias and the need for regular assessment and biomarker data collection. Panelists emphasized the importance of incorporating caregiver needs and improving the health literacy of patients and caregivers. The group also discussed the importance of data-sharing and creating data and biobanks. Finally, the group discussed the meaning of clinically meaningful change and the need to communicate with patients that stabilization can be a positive outcome in a progressive disease.

Roundtable Discussion: Contextualizing Measure Development Within Trial Design for Early Stages of Cognitive Dysfunction, Focusing on Population Selection, Co-Pathologies, and How the Field Can Continue Advancing Drug Development While Developing Improved Measures

Kathleen Poston and Tien Dam facilitated a roundtable discussion on advancing measurement approaches and treatment development. The discussion focused on patient selection and the importance of aligning on biology rather than splitting diagnoses. The group discussed the challenges of using the same measures in phenotypically different groups and the need for a consensus approach to analysis. The group emphasized the importance of data-sharing and the need for a consensus paper describing the qualitative and quantitative characteristics of the strongest contenders for fit-for-purpose cognitive measures. The group also discussed the need for more exploratory work on the MCI phase of disease and the importance of aligning on outcomes that could be used while additional research and development progresses on more-sensitive measures.

Reflections: Synthesis of Critical Gaps in Regulatory Science and Opportunities to Advance Research Toward Improved Clinical Trial Design

Tanya Simuni moderated a discussion that outlined research gaps to be prioritized and addressed in the near term. The discussion focused on the need for more-sensitive measures to detect changes in early disease, the importance of research in diverse populations, and the need for computerized testing and better assessment of function in clinical trials. The group emphasized the need for a consensus paper on the strongest contenders for cognitive measures to underlie clinical trial endpoints, as informed by fit-for-purpose criteria that support measure selection, modification, and development. The group agreed that data-sharing, harmonization, and analysis will be critical for efficiently moving these efforts forward. The group also discussed the need to improve education and awareness of these diseases and the potential for a trial design paper describing an approach to a trial that focuses on cognitive measures in the biologically defined NSD population that spans phenotypes. Action items included collecting qualitative data, reviewing existing measures to identify which of them may be fit-for-purpose, improving education and awareness, and addressing barriers to data-sharing, harmonization, and analysis.

Key Themes

The roundtable presentations and discussions coalesced around a few themes related to general directions of the field, challenges related to defining populations and recruiting for clinical trials, and challenges related to measuring cognition in clinical trials. There was consensus about the direction of the field, including needs for more-concerted measure-development efforts in recently diagnosed PD and DLB. The field needs to generate additional data to better characterize measure fit-for-purpose for clinical trials, including the appropriateness of measures for various populations and how well they measure expected effects of treatment. Participants acknowledged that multiple types of COAs may provide useful and complementary information on cognitive outcomes and that learning from other disease areas may help accelerate efforts. Themes also emerged around challenges for patient recruitment and population definition in clinical trials, including defining *early* versus *mild* cognitive impairment, and opportunities to address these challenges through the use of emerging tools, including biomarkers to assess co-pathologies, the NSD-ISS, and innovative recruitment approaches. Themes related to challenges for measuring cognition included the importance of disentangling cognitive and motor impairments, including meaningful functional outcomes as an endpoint, defining meaningful symptom change, accounting for cognitive fluctuations, benefits and drawbacks of composite measures, and important learning, ceiling, and floor effects of existing measures.

Consensus for Moving Forward

Participants agreed that COAs for cognition are urgently needed in NSD and that there are numerous efforts that can move forward in parallel.

The field needs to generate additional data to better characterize measure fit-for-purpose for clinical trials, including the appropriateness of measures for various populations and how well they measure expected effects of treatment.

More Concerted Measure-Development Efforts for Mild Cognitive Impairment in Parkinson's Disease and Dementia with Lewy Bodies Are Needed

As efforts to develop and validate cognitive measures in PD and DLB move forward, it may not be necessary to develop novel measures. Rather, it is likely that adapting and refining existing measures to be fit for purpose, especially by filling gaps demonstrating meaningfulness to patients or optimizing fit for purpose in the target populations, is possible and desirable. There are no COAs measuring cognition that are fully aligned with FDA guidance to support endpoints for mild cognitive changes in PD. While some measures may be validated for use in PD generally, the features of the disease that predominate at progressive levels of impairment and disability may differ, as do patient and caregiver perceptions of which symptoms are most impactful. Participants discussed leveraging data from existing studies (e.g., WATCH-PD, PPMI) to identify fit-for-purpose COAs, including the potential to avoid duplicative efforts and arrive at a measure suitable for regulatory approval more quickly. In DLB, additional research, including qualitative research, may be needed to identify which symptoms are most problematic and distressing for patients and their caregivers, which would aid in determining which domains to prioritize in measure-development efforts. It can be difficult to accurately classify participants as healthy versus impaired when conducting research focused on mild cognitive changes. This difficulty can lead to incorrect classification for measure performance. In addition, given that there is significant symptom heterogeneity among patients with PD and DLB, even among those with similar degrees of cognitive impairment, it will be challenging to develop a cognitive measure that will perform well across such heterogeneous patients. Incorporation of other affected domains into a measure, as was done with RBD, may help to overcome this challenge.

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Collecting Multiple COAs Is Beneficial Because They Provide Useful and Complementary Information

Different kinds of COA measurement types provide useful and complementary information, and collection of multiple types of COAs may be beneficial if there is a clear plan for how they will be used to interpret outcomes. FDA representatives emphasized that the field should not aim to come to consensus on a single or even a limited number of measures. Instead, the field should pursue many paths in parallel to expand the toolbox of measures that could be selected based on being fit for purpose. PRO measures are beneficial for gathering information about patient experience and are relatively easy to administer in the context of a clinical trial. However, the FDA has expressed concern about the validity of PRO measures at progressive levels of cognitive impairment, where patient insight about their experience may itself be impaired. It remains unclear when patient insight is considered too limited to rely on self-reports. Recently diagnosed patients may not conceptualize the difficulties they are experiencing as being related to their diagnosis and may therefore underreport them, particularly cognitive changes, given that these are underrecognized in PD. Informant reports may help to overcome these challenges and complement patient reports. ObsRO measures are often sensitive to treatment effects, but respon-

dents may require guidance on how to rate outcomes appropriately. ClinRO measures may be useful, but they may overestimate cognitive performance because of what some called "showtime"—better than usual performance in the presence of an evaluating observer; PerfO assessments may also be vulnerable to this effect. Highlighted benefits of PerfO assessments include the ability to capture aspects of functioning that patients may not have awareness of or language to describe as well as standardized administration across time and across individuals. However, the domains captured by PerfO assessments do not always have a clear link to meaningful outcomes; are vulnerable to learning, floor, and ceiling effects; and often require substantial training to administer. Time-to-event measures, such as the amount of time to no longer being able to work because of cognitive impairment, may be more statistically powerful and meaningful than continuous measures.

Applying Lessons from Treatment of Other Diseases Will Accelerate Efforts in Parkinson's Disease and Dementia with Lewy Bodies

Cognitive endpoint development in PD and DLB can be accelerated by reviewing and applying lessons learned by researchers undertaking this effort in other diagnostic groups, such as AD and PSP. In AD, challenges in obtaining regulatory acceptance for PRO measures highlighted the importance of engaging regulatory partners in key decisions early in the measure-development process. The AD field also provides a useful example of effective bridging of research in clinically defined populations to biomarker-defined populations; the fields of PD and DLB will need to do this to align with the NSD-ISS. Selecting existing measures that may already meet many of the regulatory requirements can increase efficiency because doing so reduces the time and effort needed to establish that they are fit for purpose in PD and DLB. For example, modification of the RBANS to remove tasks with motor components that would be confounded with motor symptoms of PSP was shown to improve sensitivity of the RBANS to cognitive deficits in PSP. That said, efforts to optimize the PACC for the detection of amnestic MCI have shown that statistical optimization approaches may not yield reliable improvements in sensitivity.

Challenges for Population Definition and Recruitment for Clinical Trials in Neuronal α-Synuclein Disease

Roundtable presentations, panels, and discussions touched on various challenges defining populations for clinical trials and for recruiting patients into clinical trials. A key tension exists between broadly clinically defining patient populations of interest and ensuring that patient populations are homogeneous enough in terms of disease stage, symptom severity, underlying biological features, or functional status to detect change in outcomes over the short duration of a clinical trial.

Harmonized Terminology for Distinguishing Levels of Cognitive Impairment Is Important

Harmonizing language and definitions related to levels of cognitive impairment is useful for all stakeholders, especially sponsors and regulators. Distinguishing early versus mild cognitive impairment is critical, and there is a need to develop a better understanding of when an individual transitions between disease stages. Once biomarker evidence is more readily available, *early disease* should refer to the

Distinguishing early versus mild cognitive impairment is critical, and there is a need to develop a better understanding of when an individual transitions between disease stages.

biological evidence of disease, which includes preclinical and peri-diagnostic periods of disease, while *mild disease* should refer to the manifestation of clinical signs and symptoms. Early disease and MCI are not equivalent in terms of symptom severity or level of disease progression, especially across clinical trajectories of PD and DLB, despite the term *early* often being conflated with *mild*. While the patient journey for patients diagnosed with PD and DLB differs with respect to the timeline of potential cognitive impacts, the experience of cognitive impairment (if present) is similar; more-subtle differences in cognitive performance happen earlier in the disease course. Such subtle differences increase the risk of misclassification based on clinical assessment and potentially affect the sensitivity of measures to detect differences.

Neuronal α-Synuclein Framework Opens New Possibilities for Clinical Trial Design

There are important implications for trial design and participant recruitment in the context of shifting conceptualizations of PD and DLB as NSD—one disease with a shared underlying pathology and different clinical manifestations. There is increasing enthusiasm for defining the patient population of interest based on biological features rather than clinical presentation. While most existing cohort data lacks biomarkers, future generations of biomarker tests are expected to make biomarker assessment more scalable in the near future. If such an approach were adopted, the selection of cognitive outcome measures in trials of disease-modifying treatments should be driven by the shared biological pathway being targeted rather than specific symptoms that might differ across diagnoses with shared biology. However, significantly more research is needed to advance the understanding of the underlying biology of both PD and DLB, and more research investment in DLB is necessary to achieve parity with research investment in PD. The NSD paradigm also presents some practical difficulties: for example, PD and DLB patients are seen in different clinics by completely different providers, which will require new clinician engagement and recruitment strategies.

Improve Clinical and Patient Education and Data-Sharing to Address Recruitment Challenges

Recruitment of patients into clinical trials of treatments targeting cognition is a challenge. Clinicians tend to minimize the impact of PD on cognitive functioning, focusing predominantly on the management of motor symptoms. Patients may be more motivated to participate in treatment trials focused on cognition if they have more awareness of the fact that cognitive decline is a common experience in PD and that it can significantly impair functioning. Patient advocates shared that patients may be motivated by being given access to their performance data, noting that patients want to be informed about how they are doing and what impact their participation is having. Participants also agreed that educating clinicians on both the motor and cognitive components of PD and DLB, as well as their shared underlying biology, is needed. More-widespread screening for cognitive impairment in movement disorder clinics would be beneficial for identifying individuals who may be eligible for research studies. Sharing data across trials would help achieve multiple aims, including understanding the performance of cognitive measures in clinical trials compared with observational studies, enabling disease modeling to increase regulatory confidence in specific measures, and providing information to increase sponsor confidence in measure selection for trials. Standardized language for consent forms to permit data-sharing could also be developed.

Challenges for Measurement of Cognition for Clinical Trials in Parkinson's Disease and Dementia with Lewy Bodies

Participants emphasized the need for cognition measures that could be used in PD, PDD, and DLB clinical trials. Lack of a regulatory path forward for evaluating novel treatments could result in treatment developers abandoning their programs. Sensitive, reliable, and meaningful endpoints are essential to clinical trial design for NSD, and the existing lack of evidence on these endpoints is a critical barrier that

needs to be overcome. To do so, the field will need to consider and address challenges for measurement identified in the following sections.

Fit-for-Purpose Measures Should Disentangle Cognitive and Motor Impairment

Some validated measures that are commonly used to assess cognitive functioning are confounded by motor impairments. Such measures, including time-based or speech-based tasks, may make it difficult to determine whether impaired performance is reflective of a decline in cognitive abilities or is attributable to motor symptoms of PD. The selection of measures should therefore include an evaluation of whether a cognitive measure under consideration requires intact motor performance to distinguish variation in cognitive performance. Another approach is to revise an existing neuropsychological battery to remove tests that involve significant motor components and to assess the sensitivity of the revised battery for detecting cognitive impairments and changes in cognitive functioning in the target population.

Assessments That Measure Functional Impairment Attributable to Cognitive Impairment Should Be Incorporated into Endpoints

Measurement of cognition should incorporate an assessment of functional outcomes that are directly meaningful for maintaining independence; cognition and function are so inextricably linked that they possibly should not be considered as separate domains. Measures that include tasks that closely resemble activities in daily life may have some advantages in establishing a more direct relationship between an outcome assessment and the meaningful aspects of health that are identified as important to patients. Payers may be more likely to cover treatments if cognitive benefits also yield functional benefits, which has implications for endpoint selection. Meaningful functional change can be challenging to measure in trials of short duration, making it difficult to establish an effect of treatment on function in typical treatment trials. Measures of functional impairment may not be appropriate for use in the earliest clinical stages of disease, in which symptoms have not progressed to the point of interfering with function. Furthermore, it may not be necessary to understand the cause of functional impairment (i.e., cognitive or motor) for it to be an endpoint in treatment trials.

It Is Necessary to Define What Constitutes Meaningful Symptom Change

It is important to define what constitutes meaningful symptom change in the context of a treatment trial, although it can be challenging. One way of establishing the meaningfulness of observed changes in the primary cognitive endpoint would be to correlate changes in the primary cognitive endpoint to the degree of change in functional impairment. Selection of the primary endpoint should be informed by whether it has been associated with symptoms considered meaningful to patients. Demonstrating that statistically significant change in the selected measure also reflects clinically significant symptom change for patients is important. Patients may not perceive symptom stability as a meaningful outcome, even though this could be considered evidence that a treatment slows disease progression. Setting expecta-

Some validated measures, including time-based or speech-based tasks, may make it difficult to determine whether impaired performance is reflective of a decline in cognitive abilities or is attributable to motor symptoms of PD.

tions for patients regarding what defines a *positive treatment outcome* could be beneficial.

Cognitive Fluctuations Must Be Incorporated into Trial Design

Fluctuations in cognition and alertness are characteristic of DLB and may also occur in PD at more-advanced stages of the disease. Roundtable participants, particularly patient advocates, agreed that fluctuating cognition presents a challenge for the measurement of cognitive deficits in both research and clinical contexts. Inability to predict the severity of cognitive dysfunction is a source of frustration, particularly when deficits are underestimated during clinical evaluations. Implications for research were also noted, including difficulty detecting treatment effects or tracking decline if cognition is assessed during a relatively high functioning period. Continuous or dense repeated measurement of cognition to derive an average index of performance might be useful for overcoming this issue. Developing a better understanding of the causes of cognitive fluctuations may inform the conceptualization of these diseases.

Strategies Are Needed to Account for Concomitant Disease Pathology in Clinical Trial Design

Managing concomitant pathology from such diseases as AD and vascular disease and α-synuclein pathology is an important issue in clinical trial design. Participants agreed that it is important to measure both biomarker evidence of AD and α-synuclein to determine the extent to which a given patient sample exhibits mixed pathology and estimate that pathology's impact on outcomes. Now that analyses can be stratified by the presence of biomarker evidence of AD, participants indicated that such stratification is needed given the impact on treatment efficacy; in the absence of stratification, individuals presenting with mixed pathologies should be excluded from trials. However, doing so requires large samples to preserve statistical power. Furthermore, existing methods for obtaining measures of underlying α-synuclein pathology are invasive and expensive, making it a challenge to routinely assess large numbers of individuals or to do so in trials of shorter duration. Participants agreed that more–readily accessible biomarker assays are needed. Treatment trials focused on GBA-associated PD were also highlighted as a potential solution to this issue because individuals with GBA-associated PD do not exhibit concomitant AD pathology. Finally, participants noted that treatment trials successfully moved forward in AD prior to the development of validated AD biomarkers, meaning that concomitant pathology is not an insurmountable barrier to the development of effective treatments. Increased understanding of amyloid and α-synuclein pathologies is also opening possibilities to develop and test (1) anti-amyloid therapies in people with PD and DLB with amyloid pathology, (2) anti–α-synuclein therapies for people with AD with α-synuclein pathology, and (3) precision medicine approaches using combination therapies.

Composite Cognitive Measures Have Both Benefits and Drawbacks

Composite measures may combine the richness of a comprehensive assessment battery with the simplicity of a single score and the potential to increase sensitivity to detect outcomes of interest compared with the individual components included in a composite measure. However, it can be difficult to interpret effects when using a composite measure to support an endpoint. For example, effects may be driven by changes in some components of a composite but not others, but this might not be possible to distinguish. Furthermore, if subcomponents change but in opposite directions, the overall observed effect will be null, therefore obscuring potentially meaningful change. Studies of Huntington's disease have shown an important example of issues that can emerge when scores were derived using sample means and unfixed measurement units. There was disagreement about the value of norming composite components using Z-scores: Some participants highlighted issues with interpretability and others noted the wide use of Z-scores for norming. FDA representatives noted that having multiple endpoints can be challenging statistically and that all components of a composite measure should be relevant and should change in a similar way to be considered valid for use to support an endpoint. They reminded participants that they have

issued applicable guidance on multiple endpoints.[33] Investigators should seek guidance from regulatory bodies early in measure development, especially when considering a composite measure approach.

Many Measures Have Important Learning, Ceiling, and Floor Effects

Several presenters noted that there are difficulties in detecting treatment effects in trials using existing cognition measures because of learning, ceiling, and floor effects, prompting a discussion of how to manage these issues. Characteristics of the target population should also be considered when selecting cognitive measures to assess outcomes of interest. For example, studies focused on evaluating effects among individuals with early disease or mild impairment should consider administering cognitive measures that have previously been shown to be sensitive to subtle changes in cognition. A battery that has been shown to be effective for measuring clinically meaningful change in people with mild symptoms will likely not be appropriate for measurement of change in people with severe symptoms and vice versa. Adaptive measures that are scaled to individual performance may also help to overcome these testing effects. The lack of representativeness in many clinical trials from biases toward recruiting highly educated participants might also be an important contributor to these observed effects, so diversifying clinical trials may help address them. Furthermore, the presence of ceiling or floor effects may be indicative of the inappropriate recruitment of patients who do not meet study inclusion criteria, and there was discussion of how to address this through training of test administrators. Regarding learning effects, some measures are more resistant to this than others and these therefore may be more appropriate for use in studies of shorter duration. For instance, use of measures that have validated, equivalent alternate forms can minimize practice effects.

Roadmap for Research: Next Steps for the Field

Several concrete action steps emerged. These included collecting additional qualitative data among individuals with DLB and biomarker-confirmed NSD, conducting and publishing a research synthesis of existing cognitive measures and their performances in clinical trials, publishing data-driven recommendations for cognitive measurement selection in PD and DLB research, sharing and harmonizing data across academic and industry studies, educating clinicians and patients regarding the cognitive sequalae of PD, and publishing a paper describing how to approach the study design for trials focused on biologically defined populations that span clinical phenotypes.

Conduct Additional Qualitative Research in Individuals with Dementia with Lewy Bodies and Biomarker-Confirmed Neuronal α-Synuclein Disease

Work is still needed to clarify which cognitive symptoms are most relevant to patients with DLB and biomarker-confirmed NSD. Participants highlighted the relative lack of qualitative research among individuals with a diagnosis of DLB compared with those diagnosed with PD. It was proposed that new qualitative data collection in this population should be pursued. Given the emergence of the NSD-ISS and growing emphasis on defining populations by shared underlying biology rather than clinical phenotypes,[34] it was agreed that additional qualitative work among individuals with biomarker-confirmed α-synuclein pathology is needed to determine which measures to prioritize to underly endpoints in clinical trials of therapeutics targeting α-synuclein. Jennifer Mammen and colleagues are pursuing this effort in the PPMI study, which includes biomarker assessment of participants, and they are focusing specifically on enriching their sample with individuals in the early stages of disease and individuals who have MCI.

Develop Consensus Positions Regarding Which Measures to Pursue for Use as Clinical Outcome Assessments

Ideas emerged for two consensus papers that would reduce duplicative efforts in industry and reduce

uncertainty in appropriateness of study design and measurement selection choices. While these efforts may be time-intensive, they would be undertaken in parallel to ensure that the insights gathered can be leveraged as soon as possible.

The first consensus paper would help the field coalesce on measures to be prioritized for validation. This effort would entail conducting a systematic review of existing measures, mapping those measures onto relevant conceptual domains, and determining the strength of the evidence supporting the use of each measure as a fit-for-purpose COA for assessing cognitive changes and cognitive impairment in PD and DLB. The findings from this effort could be used to develop and publish a consensus position regarding which measures should be prioritized for validation as a cognitive measure in clinical trials.

The second consensus paper would help the field understand longitudinal performance of these selected measures. Harmonizing data across longitudinal studies could be pursued, followed by an evaluation of longitudinal performance of these cognitive measures (e.g., sensitivity to progression and conversion between disease stages, correlation with biomarkers). The results from this analysis could be published as a second consensus paper detailing which measures exhibit the best performance.

Create a Data-Sharing Initiative and Repository

Progress toward developing sensitive, meaningful, and reliable measures validated for use in clinical trials for PD and DLB would be accelerated by data-sharing across studies. Integrating across diagnostic groups would also be beneficial, particularly with datasets that include biomarkers to permit subgroup analysis that is based on underlying biology. These efforts would help to alleviate recruitment challenges encountered by individual studies and would facilitate alignment on measure selection and analytic approaches. Critical Path Institute is well situated to serve as a data repository because of its extensive experience coordinating data-sharing in PD and other disease areas. The magnitude of the cost and effort associated with data harmonization raised concerns; funders will need to support this process. A related action item is developing standardized language, to be included in consent forms, that permits data-sharing. Finally, it is necessary for the field to develop a standardized set of protocols for the collection of biomarkers to enable data-sharing and harmonization across studies. It was noted that a similar effort is underway in AD research.

Improve Education and Awareness of Parkinson's Disease and Dementia with Lewy Bodies Among Patients, Clinicians, and Payers

Increased awareness among various stakeholder groups of the cognitive consequences of PD and the shared biology of PD and DLB is needed. The field should define concrete steps to work toward this goal.

Continue to Create Opportunities for Collaboration and Precompetitive Alignment

Cognitive endpoint development, validation, and regulatory acceptance may be accelerated by ongoing communication and collaboration among stakeholders from the private, public, and nonprofit sectors. Additional roundtable meetings should be convened to review progress toward existing goals, reassess priorities, and accordingly set new goals to continue advancing research toward improved treatments for PD, DLB, and related disorders.

Notes

1 Palermo et al., "Early Autonomic and Cognitive Dysfunction in PD, DLB and MSA."

2 McKeith et al., "Revisiting DLB Diagnosis."

3 Sabbagh et al., "Listening Session with the US Food and Drug Administration, Lewy Body Dementia Association, and an Expert Panel."

4 Eberling et al., "Therapeutic Development Paths for Cognitive Impairment in Parkinson's Disease."

5 U.S. Food and Drug Administration (FDA) and National Institutes of Health Biomarker Working Group, *BEST (Biomarkers, EndpointS, and Other Tools) Resource.*

6 FDA, "FDA Patient-Focused Drug Development Guidance Series for Enhancing the Incorporation of the Patient's Voice in Medical Product Development and Regulatory Decision Making"; European Medicines Agency, "Qualification of Novel Methodologies for Drug Development."

7 FDA, *Patient-Reported Outcome Measures.*

8 FDA, "FDA Patient-Focused Drug Development Guidance for Enhancing the Incorporation of the Patient's Voice in Medical Product Development and Regulatory Decision Making."

9 FDA, "Clinical Outcome Assessment (COA) Qualification Program."

10 European Medicines Agency, "Qualification of Novel Methodologies for Drug Development."

11 Weintraub, "What's in a Name?"

12 Simuni et al., "A Biological Definition of Neuronal α-Synuclein Disease."

13 Weintraub, "What's in a Name?"

14 Baiano et al., "Prevalence and Clinical Aspects of Mild Cognitive Impairment in Parkinson's Disease."

15 Donaghy and McKeith, "The Clinical Characteristics of Dementia with Lewy Bodies and a Consideration of Prodromal Diagnosis."

16 Simuni et al., "A Biological Definition of Neuronal α-Synuclein Disease."

17 Grossauer et al., "α-Synuclein Seed Amplification Assays in the Diagnosis of Synucleinopathies Using Cerebrospinal Fluid."

18 O'Hanlon et al., *Clinical Outcome Assessments and Digital Health Technologies Supporting Clinical Trial Endpoints in Early Parkinson's Disease.*

19 The Michael J. Fox Foundation for Parkinson's Research, "Feedback on a Proposed Conceptual Model of Early Parkinson's Disease."

20 Staunton et al., "A Patient-Centered Conceptual Model of Symptoms and Their Impact in Early Parkinson's Disease"; Morel et al., "Patient Experience in Early-Stage Parkinson's Disease."

21 Hemminghyth et al., "The Cognitive Profile of Mild Cognitive Impairment Due to Dementia with Lewy Bodies."

22 Massa et al., "Neuroimaging Findings and Clinical Trajectories of Lewy Body Disease in Patients with MCI"; Under et al., "Clinical and Imaging Characteristics Associated with Color Vision Impairment in Lewy Body Disease"; van de Beek et al., "Prodromal Dementia with Lewy Bodies"; Yoo et al., "Dopaminergenic Depletion, β-Amyloid Burden, and Cognition in Lewy Body Disease."

23 Eversfield and Orton, "Auditory and Visual Hallucination Prevalence in Parkinson's Disease and Dementia with Lewy Bodies."

24 Shea, Ha, and Chu, "Comparisons of Clinical Symptoms in Biomarker-Confirmed Alzheimer's Disease, Dementia with Lewy Bodies, and Frontotemporal Dementia Patients in a Local Memory Clinic."

25 NINDS, "NINDS Common Data Elements."

26 Rosen, Mohs, and Davis, "A New Rating Scale for Alzheimer's Disease."

27 Emre et al., "Rivastigmine for Dementia Associated with Parkinson's Disease."

28 Bronnick et al., "Profile of Cognitive Impairment in Dementia Associated with Parkinson's Disease Compared with Alzheimer's Disease."

29 Sabbagh et al., "Listening Session with the US Food and Drug Administration, Lewy Body Dementia Association, and an Expert Panel."

30 Rodriguez-Porcel et al., "Clinical Outcome Measures in Dementia with Lewy Bodies Trials."

[31] Pennington, Duncan, and Ritchie, "Altered Awareness of Cognitive and Neuropsychiatric Symptoms in Parkinson's Disease and Dementia with Lewy Bodies."

[32] O'Hanlon et al., *Clinical Outcome Assessments and Digital Health Technologies Supporting Clinical Trial Endpoints in Early Parkinson's Disease*.

[33] FDA, *Multiple Endpoints in Clinical Trials*.

[34] Simuni et al., "A Biological Definition of Neuronal α-Synuclein Disease."

References

Allaire, Jason C., and Michael Marsiske, "Everyday Cognition: Age and Intellectual Ability Correlates," *Psychology and Aging*, Vol. 14, No. 4, December 1999.

Arevalo-Rodriguez, Ingrid, Nadja Smailagic, Marta Roqué i Figuls, Agustín Ciapponi, Erick Sanchez-Perez, Antri Giannakou, Olga L. Pedraza, Xavier Bonfill Cosp, and Sarah Cullum, "Mini-Mental State Examination (MMSE) for the Detection of Alzheimer's Disease and Other Dementias in People with Mild Cognitive Impairment (MCI)," *Cochrane Database of Systematic Reviews*, No. 3, March 5, 2015.

Ash, Sharon, Corey McMillan, Rachel G. Gross, Philip Cook, Delani Gunawardena, Brianna Morgan, Ashley Boller, Andrew Siderowf, and Murray Grossman, "Impairments of Speech Fluency in Lewy Body Spectrum Disorder," *Brain and Language*, Vol. 120, No. 3, March 2012.

Atkins, A. S., I. Stroescu, N. B. Spagnola, V.G. Davis, T. D. Patterson, M. Narasimhan, P.D. Harvey, and R. S. E. Keefe, "Assessment of Age-Related Differences in Functional Capacity Using the Virtual Reality Functional Capacity Assessment Tool (VRFCAT)," *Journal of Prevention of Alzheimer's Disease*, Vol. 2, No. 2, June 2015.

Baiano, Chiara, Paolo Barone, Luigi Trojano, and Gabriella Santangelo, "Prevalence and Clinical Aspects of Mild Cognitive Impairment in Parkinson's Disease: A Meta-Analysis," *Movement Disorders*, Vol. 35, No. 1, January 2020.

Botzung, Anne, Nathalie Philippi, Vincent Noblet, Paulo Loureiro de Sousa, and Frédéric Blanc, "Pay Attention to the Basal Ganglia: A Volumetric Study in Early Dementia with Lewy Bodies," *Alzheimer's Research and Therapy*, Vol. 11, No. 1, December 21, 2019.

Brennan, Laura, Andrew Siderowf, Jonathan D. Rubright, Jacqueline Rick, Nabila Dahodwala, John E. Duda, Howard Hurtig, Matthew Stern, Sharon X. Xie, Lior Rennert, Jason Karlawish, Judy A. Shea, John Q. Trojanowski, and Daniel Weintraub, "The Penn Parkinson's Daily Activities Questionnaire-15: Psychometric Properties of a Brief Assessment of Cognitive Instrumental Activities of Daily Living in Parkinson's Disease," *Parkinsonism and Related Disorders*, Vol. 25, April 2016.

Bronnick, Kolbjorn, Murat Emre, Roger Lane, Sibel Tekin, and Dag Aarsland, "Profile of Cognitive Impairment in Dementia Associated with Parkinson's Disease Compared with Alzheimer's Disease," *Journal of Neurology, Neurosurgery and Psychiatry*, Vol. 78, No. 10, October 2007.

Busner, Joan, and Steven D. Targum, "The Clinical Global Impressions Scale: Applying a Research Tool in Clinical Practice," *Psychiatry (Edgmont)*, Vol. 4, No. 7, July 2007.

Calderon, J., R. J. Perry, S. W. Erzinclioglu, G. E. Berrios, T. R. Dening, and J. R. Hodges, "Perception, Attention, and Working Memory Are Disproportionately Impaired in Dementia with Lewy Bodies Compared with Alzheimer's Disease," *Journal of Neurology, Neurosurgery and Psychiatry*, Vol. 70, No. 2, February 2001.

Cedarbaum, Jesse M., Mark Jaros, Chito Hernandez, Nicola Coley, Sandrine Andrieu, Michael Grundman, and Bruno Vellas, "Rationale for Use of the Clinical Dementia Rating Sum of Boxes as a Primary Outcome Measure for Alzheimer's Disease Clinical Trials," *Alzheimer's and Dementia*, Vol. 9, Supp. 1, February 2013.

Cronin-Golomb, Alice, and Ann E. Braun, "Visuospatial Dysfunction and Problem Solving in Parkinson's Disease," *Neuropsychology*, Vol. 11, No. 1, January 1997.

Donaghy, Paul C., and Ian G. McKeith, "The Clinical Characteristics of Dementia with Lewy Bodies and a Consideration of Prodromal Diagnosis," *Alzheimer's Research and Therapy*, Vol. 6, No. 4, July 21, 2014.

Donohue, Michael C., Reisa A. Sperling, David P. Salmon, Dorene M. Rentz, Rema Raman, Ronald G. Thomas, Michael Weiner, and Paul S. Aisen, "The Preclinical Alzheimer Cognitive Composite: Measuring Amyloid-Related Decline," *JAMA Neurology*, Vol. 71, No. 8, August 2014.

Eberling, Jamie, Lona Vincent, Jennifer G. Goldman, Daniel Weintraub, Jamie Kulisevsky, Connie Marras, Glenn Stebbins, and Karl Kieburtz, "Therapeutic Development Paths for Cognitive Impairment in Parkinson's Disease: Report of a Regulatory Roundtable," *Journal of Parkinson's Disease*, Vol. 4, No. 4, 2014.

Emre, Murat, Dag Aarsland, Alberto Albanese, E. Jane Byrne, Gunther Deuschl, Peter P. De Deyn, Franck Durif, Jamie Kulisevsky, Teus van Laar, Andrew Lees, Werner Poewe, Alain Robillard, Mario M. Rosa, Erik Wolters, Peter Quarg, Sibel Tekin, and Roger Lane, "Rivastigmine for Dementia Associated with Parkinson's Disease," *New England Journal of Medicine*, Vol. 351, No. 24, December 9, 2004.

Emre, Murat, Dag Aarsland, Richard Brown, David J. Burn, Charles Duyckaerts, Yoshikino Mizuno, Gerald Anthony Broe, Jeffrey Cummings, Dennis W Dickson, Serge Gauthier, et al., "Clinical Diagnostic Criteria for Dementia Associated with Parkinson's Disease," *Movement Disorders*, Vol. 22, No. 12, September 15, 2007.

European Medicines Agency, "Qualification of Novel Methodologies for Drug Development: Guidance to Applicants," revision 3, November 10, 2014.

Eversfield, Charlotte Louise, and Llwyd David Orton, "Auditory and Visual Hallucination Prevalence in Parkinson's Disease and Dementia with Lewy Bodies: A Systematic Review and Meta-Analysis," *Psychological Medicine*, Vol. 49, No. 14, October 2019.

FDA—*See* U.S. Food and Drug Administration.

Foerde, Karin, and Daphna Shohamy, "The Role of the Basal Ganglia in Learning and Memory: Insight from Parkinson's Disease," *Neurobiology of Learning and Memory*, Vol. 96, No. 4, November 2011.

Fray, Paul J., Trevor W. Robbins, and Barbara J. Sahakian, "Neuropsychiatric Applications of CANTAB," *International Journal of Geriatric Psychiatry*, Vol. 11, No. 4, 1996.

Galasko, D., D. Bennett, M. Sano, C. Ernesto, R. Thomas, M. Grundman, and S. Ferris, "An Inventory to Assess Activities of Daily Living for Clinical Trials in Alzheimer's Disease. The Alzheimer's Disease Cooperative Study," *Alzheimer Disease and Associated Disorders*, Vol. 11, Supp. 2, 1997.

Goetz, Christopher G., Barbara C. Tilley, Stephanie R. Shaftman, Glenn T. Stebbins, Stanley Fahn, Pablo Martinez-Martin, Werner Poewe, Cristina Sampaio, Matthew B. Stern, Richard Dodel, et al., "Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale Presentation and Clinimetric Testing Results," *Movement Disorders*, Vol. 23, No. 15, November 15, 2008.

Grossauer, Anna, Greta Hemicker, Florian Krismer, Marina Peball, Atbin Djamshidian, Werner Poewe, Klaus Seppi, and Beatrice Heim, "α-Synuclein Seed Amplification Assays in the Diagnosis of Synucleinopathies Using Cerebrospinal Fluid-A Systematic Review and Meta-Analysis," *Movement Disorders Clinical Practice*, Vol. 10, No. 5, May 2023.

Harvey, Philip D., "Domains of Cognition and Their Assessment," *Dialogues in Clinical Neuroscience*, Vol. 21, No. 3, September 2019.

Hemminghyth, Mathilde S., Luiza Jadwiga Chwiszczuk, Arvid Rongve, and Monica Haraldseide Breitve, "The Cognitive Profile of Mild Cognitive Impairment Due to Dementia with Lewy Bodies—An Updated Review," *Frontiers in Aging Neuroscience*, Vol. 12, 2020.

Huber, Maria, Leonie Beyer, Catharina Prix, Sonja Schönecker, Carla Palleis, Boris-Stephan Rauchmann, Silvia Morbelli, Andrea Chincarini, Rose Bruffaerts, Rik Vandenberghe, et al., "Metabolic Correlates of Dopaminergic Loss in Dementia with Lewy Bodies," *Movement Disorders*, Vol. 35, No. 4, April 2020.

Human Cognition Project, "Tools for Research Collaborators," webpage, undated. As of December 20, 2023: https://www.lumosity.com/hcp/research/tools

Johnson, David K., John C. Morris, and James E. Galvin, "Verbal and Visuospatial Deficits in Dementia with Lewy Bodies," *Neurology*, Vol. 65, No. 8, October 25, 2005.

Jutten, Roos J., John E. Harrison, A. J. Brunner, R. Vreeswijk, R. A. J. van Deelen, Frank Jan de Jong, Esther M. Opmeer, Craig W. Ritchie, André Aleman, Philip Scheltens, and Sietske A. M. Sikkes, "The Cognitive-Functional Composite Is Sensitive to Clinical Progression in Early Dementia: Longitudinal Findings from the Catch-Cog Study Cohort," *Alzheimer's and Dementia*, Vol. 6, No. 1, April 17, 2020.

Kravitz, Dwight J., Kadharbatcha S. Saleem, Chris I. Baker, and Mortimer Mishkin, "A New Neural Framework for Visuospatial Processing," *Nature Reviews Neuroscience*, Vol. 12, No. 4, April 2011.

Kudlicka, Aleksandra, Linda Clare, and John V. Hindle, "Executive Functions in Parkinson's Disease: Systematic Review and Meta-Analysis," *Movement Disorders*, Vol. 26, No. 13, November 2011.

Kulisevsky, Jaime, Ramón Fernández de Bobadilla, Javier Pagonabarraga, Saül Martínez-Horta, Antonia Campolongo, Carmen García-Sánchez, Berta Pascual-Sedano, Roser Ribosa-Nogué, and Carolina Villa-Bonomo, "Measuring Functional Impact of Cognitive Impairment: Validation of the Parkinson's Disease Cognitive Functional Rating Scale," *Parkinsonism and Related Disorders*, Vol. 19, No. 9, September 2013.

Levin, B. E., M. M. Llabre, S. Reisman, W. J. Weiner, J. Sanchez-Ramos, C. Singer, and M. C. Brown, "Visuospatial Impairment in Parkinson's Disease," *Neurology*, Vol. 41, No. 3, March 1991.

Litvan, Irene, Jennifer G. Goldman, Alexander I. Tröster, Ben A. Schmand, Daniel Weintraub, Ronald C. Petersen, Brit Mollenhauer, Charles H. Adler, Karen Marder, Caroline H. Williams-Gray, et al., "Diagnostic Criteria for Mild Cognitive Impairment in Parkinson's Disease: Movement Disorder Society Task Force Guidelines," *Movement Disorders*, Vol. 27, No. 3, March 2012.

Loewenstein, D. A., E. Amigo, R. Duara, A. Guterman, D. Hurwitz, N. Berkowitz, F. Wilkie, G. Weinberg, B. Black, B. Gittelman, et al., "A New Scale for the Assessment of Functional Status in Alzheimer's Disease and Related Disorders," *Journal of Gerontology*, Vol. 44, No. 4, July 1989.

Marinus, J., M. Visser, N. A. Verwey, F. R. J. Verhey, H. A. M. Middelkoop, A. M. Stiggelbout, and J. J. van Hilten, "Assessment of Cognition in Parkinson's Disease," *Neurology*, Vol. 61, No. 9, November 11, 2003.

Maruff, Paul, Elizabeth Thomas, Lucette Cysique, Bruce Brew, Alex Collie, Peter Snyder, and Robert H. Pietrzak, "Validity of the Cogstate Brief Battery: Relationship to Standardized Tests and Sensitivity to Cognitive Impairment in Mild Traumatic Brain Injury, Schizophrenia, and AIDS Dementia Complex," *Archives of Clinical Neuropsychology*, Vol. 24, No. 2, March 2009.

Massa, Federico, Dario Arnaldi, Francesca De Cesari, Nicola Girtler, Andrea Brugnolo, Matteo Grazzini, Matteo Bauckneht, Riccardo Meli, Silvia Morbelli, Matteo Pardini, et al., "Neuroimaging Findings and Clinical Trajectories of Lewy Body Disease in Patients with MCI, *Neurobiology of Aging*, Vol. 76, April 2019.

Mattis, Steven, Paul J. Jurica, and Christopher L. Leitten, *Dementia Rating Scale: Professional Manual*, Psychological Assessment Resources, 1988.

McKeith, Ian G., Bradley F. Boeve, Dennis W. Dickson, Glenda Halliday, John-Paul Taylor, Daniel Weintraub, Dag Aarsland, James Galvin, Johannes Attems, Clive G. Ballard, et al., "Diagnosis and Management of Dementia with Lewy Bodies: Fourth Consensus Report of the DLB Consortium," *Neurology*, Vol. 89, No. 1, July 4, 2017.

McKeith, Ian G., Tanis J. Ferman, Alan J. Thomas, Frédéric Blanc, Bradley F. Boeve, Hiroshige Fujishiro, Kejal Kantarci, Cristina Mucio, John T. O'Brien, Ronald B. Postuma, et al., "Research Criteria for the Diagnosis of Prodromal Dementia with Lewy Bodies," *Neurology*, Vol. 94, No. 17, April 28, 2020.

McKeith, Ian, John-Paul Taylor, Alan Thomas, Paul Donaghy, and Joseph Kane, "Revisiting DLB Diagnosis: A Consideration of Prodromal DLB and of the Diagnostic Overlap with Alzheimer Disease," *Journal of Geriatric Psychiatry and Neurology*, Vol. 29, No. 5, September 2016.

The Michael J. Fox Foundation for Parkinson's Research, "Feedback on a Proposed Conceptual Model of Early Parkinson's Disease," webpage, undated. As of May 31, 2024: https://www.michaeljfox.org/EarlyPDConsensusConceptualModel

Morel, Thomas, Sophie Cleanthous, John Andrejack J, Roger A. Barker, Geraldine Blavat, William Brooks, Paul Burns, Stefan Cano, Casey Gallagher, Lesley Gosden, et al., "Patient Experience in Early-Stage Parkinson's Disease: Using a Mixed Methods Analysis to Identify Which Concepts Are Cardinal for Clinical Trial Outcome Assessment," *Neurology and Therapy*, Vol. 11, No. 3, September 2022.

Morrison, Glenn E., Christa M. Simone, Nicole F. Ng, and Joseph L. Hardy, "Reliability and Validity of the NeuroCognitive Performance Test, a Web-Based Neuropsychological Assessment," *Frontiers in Psychology*, Vol. 6, 2015.

Nasreddine, Ziad S., Natalie A. Phillips, Valérie Bédirian, Simon Charbonneau, Victor Whitehead, Isabelle Collin, Jeffrey L. Cummings, and Howard Chertkow, "The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool for Mild Cognitive Impairment," *Journal of the American Geriatrics Society*, Vol. 53, No. 4, April 2005.

National Institute of Neurological Disorders and Stroke, "NINDS Common Data Elements: Parkinson's Disease," webpage, undated. As of November 17, 2022: https://www.commondataelements.ninds.nih.gov/Parkinson%27s%20Disease

NINDS—*See* National Institute of Neurological Disorders and Stroke.

O'Hanlon, Claire E., Carrie M. Farmer, Jamie L. Ryan, and Natalie C. Ernecoff, *Clinical Outcome Assessments and Digital Health Technologies Supporting Clinical Trial Endpoints in Early Parkinson's Disease: Roundtable Proceedings and Roadmap for Research*, RAND Corporation, CF-A2550-1, 2023. As of May 8, 2024: https://www.rand.org/pubs/conf_proceedings/CFA2550-1.html

Pagonabarraga, Javier, Jaime Kulisevsky, Gisela Llebaria, Carmen García-Sánchez, Berta Pascual-Sedano, and Alexandre Gironell, "Parkinson's Disease-Cognitive Rating Scale: A New Cognitive Scale Specific for Parkinson's Disease," *Movement Disorders*, Vol. 23, No. 7, May 15, 2008.

Palermo, Giovanni, Eleonora Del Prete, Ubaldo Bonuccelli, and Roberto Ceravolo, "Early Autonomic and Cognitive Dysfunction in PD, DLB and MSA: Blurring the Boundaries Between α-Synucleinopathies," *Journal of Neurology*, Vol. 267, No. 12, 2020.

Parrott, A. C., and K. Wesnes, "Promethazine, Scopolamine and Cinnarizine: Comparative Time Course of Psychological Performance Effects," *Psychopharmacology*, Vol. 92, No. 4, 1987.

Patterson, Thomas L., Sherry Goldman, Christine L. McKibbin, Troy Hughs, and Dilip V. Jeste, "UCSD Performance-Based Skills Assessment: Development of a New Measure of Everyday Functioning for Severely Mentally Ill Adults, *Schizophrenia Bulletin*, Vol. 27, No. 2, 2001.

Pennington, Catherine, Gordon Duncan, and Craig Ritchie, "Altered Awareness of Cognitive and Neuropsychiatric Symptoms in Parkinson's Disease and Dementia with Lewy Bodies: A Systematic Review," *International Journal of Geriatric Psychiatry*, Vol. 36, No. 1, January 2021.

Ramos, Ari Alex, and Liana Machado, "A Comprehensive Meta-Analysis on Short-Term and Working Memory Dysfunction in Parkinson's Disease," *Neuropsychology Review*, Vol. 31, No. 2, June 2021.

Randolph, C., M. C. Tierney, E. Mohr, and T. N. Chase, "The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): Preliminary Clinical Validity," *Journal of Clinical and Experimental Neuropsychology*, Vol. 20, No. 3, June 1998.

Rinehardt, Eric, Kevin Duff, Michael Schoenberg, Michelle Mattingly, Kersi Bharucha, and James Scott, "Cognitive Change on the Repeatable Battery of Neuropsychological Status (RBANS) in Parkinson's Disease With and Without Bilateral Subthalamic Nucleus Deep Brain Stimulation Surgery," *Clinical Neuropsychologist*, Vol. 24, No. 8, November 2010.

Rodriguez-Porcel, Federico, Kathryn A. Wyman-Chick, Carla Abdelnour Ruiz, Jon B. Toledo, Daniel Ferreira, Prabitha Urwyler, Rimona S. Weil, Joseph Kane, Andrea Pilotto, Arvid Rongve, et al., "Clinical Outcome Measures in Dementia with Lewy Bodies Trials: Critique and Recommendations," *Translational Neurodegeneration*, Vol. 11, No. 1, May 2, 2022.

Rosen, W. G., R. C. Mohs, and K. L. Davis, "A New Rating Scale for Alzheimer's Disease," *American Journal of Psychiatry*, Vol. 141, No. 11, November 1984.

Roth, M., E. Tym, C. Q. Mountjoy, F. A. Huppert, H. Hendrie, S. Verma, and R. Goddard, "CAMDEX: A Standardised Instrument for the Diagnosis of Mental Disorder in the Elderly with Special Reference to the Early Detection of Dementia," *British Journal of Psychiatry*, Vol. 149, No. 6, December 1986.

Roy, Shumita, Norman W. Park, Eric A. Roy, and Quincy J. Almeida, "Interaction of Memory Systems During Acquisition of Tool Knowledge and Skills in Parkinson's Disease," *Neuropsychologia*, Vol. 66, January 2015.

Ruse, Stacy A., Philip D. Harvey, Vicki G. Davis, Alexandra S. Atkins, Kolleen H. Fox, and Richard S. E. Keefe, "Virtual Reality Functional Capacity Assessment in Schizophrenia: Preliminary Data Regarding Feasibility and Correlations with Cognitive and Functional Capacity Performance," *Schizophrenia Research: Cognition*, Vol. 1, No. 1, March 2014.

Sabbagh, Marwan N., Angela Taylor, Douglas Galasko, James E. Galvin, Jennifer G. Goldman, James B. Leverenz, Kathleen L. Poston, Bradley F. Boeve, David J. Irwin, and Joseph W. Quinn, "Listening Session with the US Food and Drug Administration, Lewy Body Dementia Association, and an Expert Panel," *Alzheimer's and Dementia: Translational Research and Clinical Interventions*, Vol. 9, No. 1, February 8, 2023.

Shea, Yat Fung, Joyce Ha, and Leung-Wing Chu, "Comparisons of Clinical Symptoms in Biomarker-Confirmed Alzheimer's Disease, Dementia with Lewy Bodies, and Frontotemporal Dementia Patients in a Local Memory Clinic," *Psychogeriatrics*, Vol. 15, No. 4, December 2015.

Simuni, Tanya, Lana M. Chahine, Kathleen Poston, Michael Brumm, Teresa Buracchio, Michelle Campbell, Sohini Chowdhury, Christopher Coffey, Luis Conca-Marambio, Tien Dam, et al., "A Biological Definition of Neuronal α-Synuclein Disease: Towards an Integrated Staging System for Research," *Lancet Neurology*, Vol. 23, No. 2, February 2024.

Skorvanek, Matej, Jennifer G. Goldman, Marjan JahanshahiConnie Marras, Irena Rektorova, Ben Schmand, Erik van Dujin, Christopher G. Goetz, Daniel Weintraub, Glenn T. Stebbins, and Pablo Martinez-Martin, "Global Scales for Cognitive Screening in Parkinson's Disease: Critique and Recommendations," *Movement Disorders*, Vol. 33, No. 2, February 2018.

Smith, Kara M., and David N. Caplan, "Communication Impairment in Parkinson's Disease: Impact of Motor and Cognitive Symptoms on Speech and Language," *Brain and Language*, Vol. 185, October 2018.

Sousa, Nariana Mattos Figueiredo, and Sonia Maria Dozzi Brucki, "Addenbrooke's Cognitive Examination III: Diagnostic Utility for Detecting Mild Cognitive Impairment and Dementia in Parkinson's Disease," *Arquivos de Neuro-Psiquiatria*, Vol. 81, No. 2, February 2023.

Staunton, Hannah, Kim Kelly, Louise Newton, Mathias Leddin, Raul Rodriguez-Esteban, K. Ray Chaudhuri, Daniel Weintraub, Ronald B. Postuma, and Pablo Martinez-Martin, "A Patient-Centered Conceptual Model of Symptoms and Their Impact in Early Parkinson's Disease: A Qualitative Study," *Journal of Parkinson's Disease*, Vol. 12, No. 1, 2022.

Tsuboi, Yoshio, Hirotake Uchikado, and Dennis W. Dickson, "Neuropathology of Parkinson's Disease Dementia and Dementia with Lewy Bodies with Reference to Striatal Pathology," *Parkinsonism and Related Disorders*, Vol. 13, Supp. 3, 2007.

U.S. Food and Drug Administration, *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*, industry guidance document, December 2009.

U.S. Food and Drug Administration, *Multiple Endpoints in Clinical Trials: Guidance for Industry*, U.S. Department of Health and Human Services, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, October 2022.

U.S. Food and Drug Administration, "Clinical Outcome Assessment (COA) Qualification Program," webpage, October 27, 2023. As of May 8, 2024: https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/clinical-outcome-assessment-coa-qualification-program

U.S. Food and Drug Administration, "FDA Patient-Focused Drug Development Guidance Series for Enhancing the Incorporation of the Patient's Voice in Medical Product Development and Regulatory Decision Making," webpage, February 14, 2024. As of May 8, 2024: https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical

U.S. Food and Drug Administration and National Institutes of Health Biomarker Working Group, *BEST (Biomarkers, EndpointS, and Other Tools) Resource*, U.S. Food and Drug Administration and National Institutes of Health, updated November 29, 2021.

Unger, Robert H., Patrick M. Flanigan, Mitra Khosravi, James B. Leverenz, and Babak Tousi, "Clinical and Imaging Characteristics Associated with Color Vision Impairment in Lewy Body Disease," *Journal of Alzheimer's Disease*, Vol. 72, No. 4, 2019.

van de Beek, Marleen, Inger van Steenoven, Jessica J. van der Zande, Frederik Barkhof, Charlotte E. Teunissen, Wiesje M. van der Flier, and Afina W. Lemstra, "Prodromal Dementia with Lewy Bodies: Clinical Characterization and Predictors of Progression," *Movement Disorders*, Vol. 35, No. 5, May 2020.

Weintraub, Daniel, "What's in a Name? The Time Has Come to Unify Parkinson's Disease and Dementia with Lewy Bodies," *Movement Disorders*, Vol. 38, No. 11, November 2023.

Wesnes, Keith A., "The Value of Assessing Cognitive Function in Drug Development," *Dialogues in Clinical Neuroscience*, Vol. 2, No. 3, September 2000.

Yarnall, Alison, Lynn Rochester, and David J. Burn, "The Interplay of Cholinergic Function, Attention, and Falls in Parkinson's Disease," *Movement Disorders*, Vol. 26, No. 14, December 2011.

Yoo, Han Soo, Sangwon Lee, Seok Jong Chung, Yang Hyun Lee, Phil Hyu Lee, Young H. Sohn, Seungyeoun Lee, Mijin Yun, and Byoung Seok Ye, "Dopaminergic Depletion, β-Amyloid Burden, and Cognition in Lewy Body Disease," *Annals of Neurology*, Vol. 87, No. 5, May 2020.

Abbreviations

AD	Alzheimer's disease
ADAS-Cog	Alzheimer's Disease Assessment Scale-Cognitive
CDER	Center for Drug Evaluation and Research
CGIC	Clinical Global Impression of Change
ClinRO	clinician-reported outcome
COA	clinical outcome assessment
COI	concept of interest
DLB	dementia with Lewy bodies
DLB-MCI	dementia with Lewy bodies–mild cognitive impairment
EMA	European Medicines Agency
FDA	U.S. Food and Drug Administration
IADL	instrumental activities of daily life
IND	investigational new drug
MCI	mild cognitive impairment
MDS-UPDRS	Movement Disorders Society-sponsored revision of the Unified Parkinson's Disease Rating Scale
MJFF	The Michael J. Fox Foundation for Parkinson's Research
MMSE	Mini-Mental Status Examination
MoCA	Montreal Cognitive Assessment
NIA	National Institute on Aging
NINDS	National Institute of Neurological Disorders and Stroke
NSD	neuronal α-synuclein disease
NSD-ISS	Neuronal α-Synuclein Disease Integrated Staging System
ObsRO	observer-reported outcome
PACC	preclinical Alzheimer's cognitive composite
PD	Parkinson's disease
PDCCS	Parkinson's disease cognitive composite score
PDD	Parkinson's disease dementia
PD-MCI	Parkinson's disease–mild cognitive impairment
PerfO	performance outcome
PFDD	Patient-Focused Drug Development Framework
PPMI	Parkinson's Progression Markers Initiative
PRO	patient-reported outcome
PSP	progressive supranuclear palsy
PSRS	Prodromal Synucleinopathy Rating Scale
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RBD	rapid eye movement sleep behavior disorder
UPSA	University of California San Diego Performance-Based Skills Assessment
VRFCAT	Virtual Reality Functional Capacity Assessment Tool

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About These Conference Proceedings

This document summarizes the Parkinson's Disease/Dementia with Lewy Bodies (PD/DLB) Cognition Measures Roundtable, which was held in Washington, D.C., on January 10 and 11, 2024. This event was hosted by the Critical Path for Parkinson's Consortium, Cure Parkinson's, Lewy Body Dementia Association, The Michael J. Fox Foundation for Parkinson's Research (MJFF), Parkinson Canada, Parkinson's UK, and Shake It Up Australia Foundation. This event brought together representatives from academia and industry with those from regulatory agencies, community partners, and research funders to discuss challenges in developing clinical outcome assessments for cognitive impairment in PD and DLB and identify priorities for the field and opportunities for collaboration. An annex with additional details on cognitive measures and information on roundtable participants is available online.

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