## Summary Statement

## Parkinson’s disease CDE Subgroup: Other Non-motor

This summary is the companion document to the NINDS Parkinson’s disease CDE Working Group – Other Non-motor Table (see **Table 1: NINDS CDE Workgroup – Other Non-motor).**

1. **Assessing “Other” Non-motor Features in Parkinson’s Disease**

The topic, “Other” Non-motor Features of Parkinson’s Disease (PD), covers a broad array of clinical phenomena that in some cases have only relatively recently been recognized as being components of PD. These non-motor features often have not been extensively studied and appropriate scales and other methods of evaluating these features have not been fully developed. Therefore, in completing our assignment the subcommittee has frequently found it necessary to resort to recommending scales that have not been designed or validated for PD. In some instances, appropriate scales are simply nonexistent. In other instances, scales are not appropriate and procedures have been recommended instead.

The absence of appropriate screening scales has been most glaringly evident, forcing the subcommittee to frequently recommend single questions extracted from other scales as the most viable screening measure. We realize that the validity of an established scale does not transfer to individual questions if they are presented in a free-standing fashion and that these items (which Dr. Martinez Martin christens “mini-scales”) should ideally be validated before they are used.

In designating separate instruments for each of the various “other” non-motor features identified, the subcommittee has not pursued another possible pathway in which at least some of the non-motor features could be addressed in a combined fashion. The SCOPA-AUT and SCOPA-SLEEP scales would be examples of this. The MDS-UPDRS also addresses many of the “other” non-motor features, though often with just a single question.

The sheer number of “other” non-motor features identified by the subcommittee poses some practical problems for actual patient assessment. Even if for screening purposes assessment was limited to a single question, it would require 17 questions (or brief procedures) to address each of the “other” non-motor features we have identified. Thus, it may not be feasible to address each of the “other” non-motor features in every situation.

The scales and instruments identified by our subcommittee are not designed to assess or even address the fluctuations – including non-motor features - that are so often a part of PD, particularly in individuals receiving dopaminergic therapy. This problem certainly is not unique to “other” non-motor features.

1. **Categories of “Other” Non-motor Features**
2. **Autonomic Dysfunction**
3. **Gastrointestinal**

Virtually all levels of the GI tract may be affected in PD. Excess saliva, dysphagia, gastroparesis, reduced bowel movement frequency, and defecatory dysfunction all may occur. Although some aspects of GI dysfunction are addressed within scales such as the MDS-UPDRS and the SCOPA-AUT, a single scale dedicated to the assessment of all aspects of GI dysfunction in PD does not currently exist. Assessing three aspects of GI dysfunction (excess saliva, dysphagia, and constipation) was undertaken by the subcommittee. For screening purposes, we have recommended extraction of single items from the MDS-UPDRS, realizing that this is not an ideal approach from a validation standpoint. With regard to measurement instruments for these three aspects of GI dysfunction, no scales have been fully validated specifically for PD, but scales have been selected that have been validated in other settings. For studies specifically focused on these individual aspects of GI dysfunction, diagnostic instruments have been identified, such as the Videofluoroscopic Swallowing Study (Modified Barium Swallow Study), the Colon Transit Time Study, Defecography, and several methods of measuring saliva production. These studies typically require specialized equipment and collaboration with other specialists.

1. **Urinary**

Urinary dysfunction in PD may be characterized by overactive, underactive or obstructive features, but overactivity is the most frequent abnormality and the subcommittee elected to focus on this aspect of PD urinary dysfunction. As with GI dysfunction, some aspects of urinary dysfunction are addressed within the MDS-UPDRS and the SCOPA-AUT but no scale specifically addressing bladder dysfunction in PD exists. For screening purposes, the subcommittee once again elected to recommend a single item from the MDS-UPDRS. As a measurement instrument we have selected the International Prostate Symptom Scale (IPSS) and the International Consultation on Incontinence Questionnaire-Overactive Bladder Module (ICIQ-OAB) as the scales of choice, although neither has been validated specifically in the setting of PD. It should be noted that the IPSS has been validated in males and in females. For studies specifically focused on urinary dysfunction, the generally accepted diagnostic instrument would be formal urodynamic testing, which would require special equipment and collaboration with a urologist.

1. **Sexual**

Sexual dysfunction has not been studied extensively in PD. No scales have been validated specifically for use in PD. Once again, the subcommittee has chosen to extract single questions from other scales for a portion of the screening function. Since sexual dysfunction has been more extensively studied in men, screening items for both erectile dysfunction and for non-gender based sexual dysfunction have been listed. For men, both the Sexual Health Inventory for Men (SHIM) and individual items from the SCOPA-AUT have been selected, but for women (or for both sexes) items have been lifted from a larger scale (NMS-QUEST); alternatively, a single item from the NMSS may be used. For measurement instruments, one scale has been chosen for men (the International Index of Erectile Function) and one for women (the Brief Index of Sexual Functioning for Women). Neither is directed specifically at PD patients. No specific diagnostic instrument was identified by the subcommittee, although standard diagnostic criteria for male erectile dysfunction and female sexual dysfunction have been formulated through expert consensus panels.

1. **Thermoregulatory**

Thermoregulatory dysfunction has not been extensively studied in PD. Once again, individual items from more comprehensive scales have been chosen by the subcommittee as screening instruments. For a measurement instrument, eight items addressing sudomotor function, drawn from the 73-item Composite Autonomic Symptom Scale (COMPASS), have been recommended since no scale specifically addressing thermoregulatory dysfunction in PD exists. For studies specifically addressing thermoregulatory dysfunction, diagnostic instruments such as the Quantitative Sudomotor Axon Reflex Test (QSART) and the Thermoregulatory Sweat Test (TST) may be utilized, although abnormalities in these tests are not specific for PD.

1. **Cardiovascular**

Orthostatic hypotension is the most widely recognized cardiovascular abnormality of PD. For screening purposes, three questions drawn from the SCOPA-AUT have been selected, with two items from the NMS-s or one item from the NMS-Q as alternates. Actual orthostatic blood pressure and pulse measurement, however, seems most appropriate as a measurement instrument and formal tilt table testing should be considered the diagnostic instrument. Although not directly assessing the issue of orthostatic hypotension, MIBG scanning as a measure of cardiac sympathetic denervation in PD might also be considered as a diagnostic instrument.

1. **Respiratory**

Respiratory abnormalities have not been extensively studied in PD, although respiratory dysfunction is one of the most common causes for death in PD patients. No PD-specific scales have been developed. Some studies have noted a restrictive pattern of dysfunction (presumably due to chest wall rigidity) to be the predominant respiratory abnormality of PD, while others document an upper airway obstructive pattern. Spirometric studies, rather than subjective scales, appear to be the most appropriate method to assess respiratory function in PD. With this in mind, either the Maximum Voluntary Ventilation (MVV) or the Forced Expiratory Volume in the first second (FEV1) can be used as a screening instrument and also as a measurement instrument. For studies specifically addressing respiratory function in PD, full pulmonary function testing is the diagnostic measure of choice.

1. **Sleep Dysfunction**
2. **Sleep Onset and Sleep Maintenance Insomnia**

Although sleep onset and sleep maintenance insomnia may be experienced independently, available scales typically do not differentiate between the two. Therefore, their assessment has been combined in this document. For both screening and rating instruments, the subcommittee has chosen the SCOPA-sleep nighttime subscale if sleep is the primary outcome being studied. If it is not, a single item from the UPDRS may be employed for screening. The SCOPA-sleep scale, like the other SCOPA scales, was developed specifically for use in PD. The scale in its entirety has been validated, although only a portion of the full scale is being recommended to assess sleep onset and maintenance insomnia. Diagnostic Criteria for Insomnia Disorder have been formulated by the American Academy of Sleep Medicine and the ultimate diagnostic instrument for assessing insomnia would be the polysomnogram.

1. **Excessive Daytime Sleepiness**

The Epworth Sleepiness Scale (ESS) is recommended by the subcommittee as a screening, measurement and diagnostic instrument for excessive daytime sleepiness. The SCOPA-sleep daytime subscale is considered by the subcommittee to be a very good alternate choice (especially if combined with the SCOPA-sleep nighttime subscale to evaluate both nighttime insomnia and daytime somnolence). If excessive daytime sleepiness is not the primary outcome being studied, a single item from the UPDRS may be employed for screening. The ESS is the most widely used subjective scale of daytime somnolence and has been used extensively in PD studies with good validation. In studies requiring an objective measure of daytime somnolence, the Multiple Sleep Latency Test serves as the recommended diagnostic instrument.

1. **Sleep Apnea**

The presence of sleep apnea in PD has not been extensively studied or systematically evaluated. No PD-specific scales exist. The subcommittee recommends the Berlin Questionnaire, a generically validated scale, as a screening instrument. No adequate subjective scale exists for use as either a measurement or diagnostic instrument. Polysomnography is the accepted objective diagnostic instrument.

1. **REM Sleep Behavior Disorder**

No screening questionnaire has been specifically validated for PD patients. Of the scales available for the general assessment of RBD, the subcommittee has chosen the 10-item RBD Screening Questionnaire (Stiasny-Kolster) as the preferred instrument. Several single question screens have also been used with regard to RBD, but have not been validated. No subjective rating instrument for RBD exists. Polysomnography is the accepted objective diagnostic instrument.

1. **Restless Leg Syndrome**

The subcommittee has chosen the Cambridge-Hopkins Restless Legs Syndrome Questionnaire (CH-RLSq) as the screening instrument for RLS. It has some advantages over the NIH-RLS scale. However, it has not been specifically validated for PD. The International Restless Legs Syndrome Study Group (IRLSSG) has developed the IRLSSG rating scale (IRLS) as a measurement instrument for assessing severity of RLS symptoms. This scale has been used in PD studies but has not been specifically validated for PD. Formal diagnostic criteria for RLS have also been developed by the IRLSSG. No objective diagnostic instrument exists for RLS.

1. **Sensory Dysfunction**
2. **Vision Impairment**

The aspect of vision impairment in PD that has received the most attention is impairment of contrast sensitivity, which reflects retinal involvement. Although other aspects of vision (such as color vision) may also be affected in the setting of PD, the subcommittee has chosen to focus on impaired contrast sensitivity in its assessment. The Pelli-Robson chart is recommended as both a screening and a measurement instrument for impairment of contrast sensitivity. It is the oldest and most widely known of the charts that have been developed for office testing of visual contrast sensitivity. It has not been validated specifically for use in PD, but has been used extensively in ophthalmologic practices and research. More sophisticated measures for assessing visual contrast sensitivity are used in some research settings, but would not be feasible for widespread use. Optical Coherence Tomography (OCT) has recently been shown to demonstrate direct morphologic evidence of retinal involvement in PD and thus may be useful as a diagnostic instrument in studies specifically focusing on vision impairment in PD.

1. **Olfaction Impairment**

Impairment of olfaction has been extensively studied in PD and the most frequently employed testing instrument has been the 40-item University of Pennsylvania Smell Identification Test (UPSIT). Shorter modifications of this study that are more suitable as a screening instrument have been developed. In this regard, the 12-item Brief Smell Identification Test – Version B (also known as the Cross-Cultural Smell Identification Test) is particularly appealing because the odors it contains are well-known in most cultures and many of the odors it contains have been shown to be impaired in PD patients. It has been validated and found to have high sensitivity, specificity and predictive value in patients with PD. The full 40-item UPSIT, however, is more appropriate for use as a measurement instrument and a diagnostic instrument.

1. **Pain**

Pain has not been widely studied in PD and no instruments have been developed specifically for the assessment of pain in PD. Pain in PD may be multifactorial, which further complicates its assessment. The Brief Pain Inventory (BPI)-Short Form is a generic instrument that measures pain intensity and is recommended by the subcommittee as a screening instrument. It has been used extensively in the study of pain and has demonstrated validity and reliability across cultures. Although a Visual Analogue Scale has most frequently been used in PD studies as an instrument for measuring pain severity and change over time, the Numerical Rating Scale – Box 21 Scale is recommended by the subcommittee because it appears to be less error prone in an elderly population. There is no objective diagnostic instrument for diagnosing or measuring pain.

1. **Other Non-motor Dysfunction**
2. **Fatigue**

Fatigue has not been extensively studied in PD and no PD-specific fatigue scales exist. For screening purposes, we have again recommended a single question from the MDS-UPDRS. As a rating instrument, the 9-item FSS or the 13-item FACIT-F are recommended. No objective diagnostic instrument for fatigue exists.

1. **Nutritional Status**

Nutritional status is not actually a non-motor feature of PD in and of itself. However, it does tie in with gastrointestinal dysfunction and weight loss. Therefore, the subcommittee has designated the MNA as a screening instrument for nutritional status. It is a validated measure that has been used in PD. No single measurement instrument has been by the subcommittee. Formal dietary assessment serves as the diagnostic instrument.

1. **Weight Loss/Weight Change**

For this item, formal scales are not necessary (or perhaps one should say that a scale of a different type is necessary). Weight or Body Mass Index (BMI) can be utilized as the assessment tool.

Parkinson’s disease CDE Working Group – Other Non-motor Table 1

| **Type of Instrument** | **GI-Saliva** | **GI-Dysphagia** | **GI-Constipation** | **Urinary (Evatt)** | **Sexual (Fernandez)** | **Thermo-****regulatory (Fernandez)** | **Cardiovaculary (Fernandez)** | **Respiratory (Pfeiffer)** | **Sleep-Insomnia (Postuma)** | **Sleep-Excessive Daytime sleepiness (Postuma)** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site |
| Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site |
| Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site |
| Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site |

Parkinson’s disease CDE Working Group – Other Non-motor Table 2

| **Type of Instrument** | **Sleep-Sleep Apnea (Postuma)** | **Sleep-REM Sleep behavior disorder** | **Sleep-Restless Leg Syndrome (van Hilten)** | **Sensory Dysfunction-Vision Impairment (Pfeiffer)** | **Sensory Dysfunction-Olfacttion Impairment (Pfeiffer)** | **Sensory Dysfunction-Pain (van Hilten)** | **Fatigue (Evatt)** | **Nutritional Status (Evatt)** | **Weight Loss (Evatt)** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site |
| Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site |
| Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site |
| Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site | Data to be entered by site |