

Clinical Endpoints Review (CER):

Devices to Manage Tremor in Parkinson's Disease and Essential Tremor



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CER Objectives

- 1) To identify the most common clinical endpoints among patients who use medical devices for the management/treatment of medication-refractory Parkinson's disease (PD) and essential tremor (ET), focusing on tremor/motor aspects.
- 2) To identify the instruments/tools commonly used to assess those endpoints and clarify clinically meaningful differences for each instrument/tool where possible.

Topic Overview: Parkinson's Disease (PD)

- Progressive loss of dopaminergic (and other) brainstem neurons → impaired motor function
- Key clinical signs: slowness of movement, muscle rigidity, and tremor (worse during rest)
- Nonmotor symptoms: mood disorders, cognitive decline, sleep disturbance, etc.
- Pharmaceutical treatment: levodopa and other dopaminergic drugs
 - Stimulation of dopamine receptors in the brain
 - Long-term use → to motor complications
 - Thus, nonpharmacologic treatments (devices) have been developed

Topic Overview: Essential Tremor (ET)

- Progressive disorder
- Motor symptoms:
 - **Tremor** (occurring during **voluntary movement**, in contrast to PD)
 - Much more likely than PD to affect head and neck
 - Mild ataxia (impaired coordination and balance)
- Nonmotor symptoms:
 - Mild cognitive impairment
 - Anxiety

Topic Overview: Nonpharmacologic Treatment

- Goal of nonpharmacologic treatment
 - Reduce motor complications (PD only) and/or
 - Provide an option for treatment-resistant tremor
- Examples of nonpharmacologic treatment
 - Deep brain stimulation (DBS)
 - Repetitive transcranial magnetic stimulation (rTMS)
 - Magnetic resonance-guided focused ultrasound (MRgFUS)
 - Subthalamotomy
 - Robot-assisted gait training
 - Wearable stimulators and sensors

CER Methods: Literature Selection

- Searched published literature (Embase and PubMed databases) January 2018-August 2023 and gray literature
- Inclusion/exclusion criteria: Table 1 in full CER
- Collected systematic reviews (Appendix Tables B1a and B1b in full CER)
 - Of any device (including wearable and other external technologies)
 - For treatment of tremor associated with PD or ET
- Also collected professional guidance documents (Appendix Table B1c in full CER)
 - Consensus statements regarding clinical endpoints for studies of any PD/ET treatment
 - Practice guidelines on management of PD/ET

CER Methods: Identification of Important Clinical Endpoints

- From systematic reviews
 - All clinical endpoints reported for each review's included studies
 - “Prioritization” of endpoints meeting a certain threshold of citation volume
- From professional guidance documents
 - Clinical endpoints emphasized either through implication or by explicit recommendation
 - Focus on endpoints most implied/recommended by ≥ 2 of 5 selected documents

External Expert Review of CER

- Intended to supplement the completed CER with clinical perspective
- 3 subject matter experts in academia
 - 1 neurosurgeon
 - 2 neurologists

Summary of CER Findings and Expert Review

See details in Tables A1, A2, B, C and D in the Word document
“PD-ET_CER Summary&Subcommittee ReviewQuestions”
(distributed prior to the March 10 premeeting)

Summary of Findings (PD): Prioritized Endpoints & Instruments [and additional expert review recommendations]

Clinician-Assessed Health Outcomes

Clinical endpoints	Instruments
Global change in motor symptom severity	UPDRS/MD-UPDRS Part III*
Gait function, postural instability, balance, falls	FOG-Q* and TUG Test Relevant items from MDS-UPDRS Part III and MDS-UPDRS Part II
Motor complications	UPDRS/MDS-UPDRS Part IV
Reduction in dyskinesia	Relevant items from MDS-UPDRS Part IV
Cognitive function	Stroop test* MoCA* instead of or in addition to Stroop Relevant subscale from MDS_UPDRS Part I
Motor-related ADL	UPDRS Part II or MDS-UPDRS Part II*
Nonmotor symptoms	MDS-UPDRS Part II*, MDS-NMSS
Speech function and swallowing	Relevant items from MDS-UPDRS Part II and MDS-NMS Speech Intelligibility Test
Abbreviations: ADL, activities of daily living; FOG-Q, Freezing of Gait Questionnaire; MDS, Movement Disorders Society; MoCA, Montreal Cognitive Assessment; NMSS, Non-Motor Symptom Scale; UPDRS, United Parkinson’s Disease Rating Scale; TUG, Time Up and Go	

*MCIDs were identified. See Table C in the CER Summary or Appendix Table C1 in the full CER.

Summary of Findings (PD): Prioritized Endpoints & Instruments

[and additional expert review recommendations] (cont)

Patient-
Reported
Outcomes

Clinical endpoints	Instruments
PD-related QoL	PDQ-39*
Sleep quality	PDSS-2*, relevant items from MDS-UPDRS I
Abbreviations: MDS, Movement Disorder Society; PD, Parkinson’s Disease; PDQ-39, Parkinson’s Disease Questionnaire-39; PDSS-2, Parkinson’s Disease Sleep Scale 2nd version; UPDRS, United Parkinson’s Disease Rating Scale	

Device-
Related Safety

Not addressed in the CER. Variable across devices.	
<u>More serious:</u> <ul style="list-style-type: none"> Worsening gait/balance Speech/swallowing difficulties Mood changes (including suicidality) Cognitive decline DBS only: intracranial hemorrhage, infection, or need for additional surgery 	<u>Less serious:</u> <p>Discomfort or skin issues from noninvasive wearables</p>

*MCIDs were identified. See Table C in the CER Summary or Appendix Table C1 in the full CER.

Summary of Findings (ET): Prioritized Endpoints & Instruments [no additional expert review recommendations]

	Clinical endpoints	Instruments
Clinician-Assessed Health Outcomes	Reduction in tremor	FTM-TRS*, Hand Tremor score, CRST, and TETRAS
Patient-Reported Outcomes	Tremor-related QoL OR tremor-related ADL	QUEST, FTM-TRS Part C
Device-Related Safety	Same as those listed for PD	

Abbreviations: ADL, activities of daily living; ET, essential tremor; CRST, Clinical Rating Scale for Tremor; FTM-TRS; Fahn Tolosa Marin Tremor Rating Scale; QoL, quality of life; QUEST, Quality of Life Essential Tremor Questionnaire; TETRAS, Tremor Research Group Essential Tremor Rating

No MCIDs were identified for the instruments identified in the CER report from studies of ET treatment.

*One reviewer cautioned that FTM-TRS is not commonly used clinically.

Professional Guidance Documents, PD

- 5 selected documents
 - International clinical practice guideline (CPG), broad range of therapies
 - Expert recommendations, assessment of wearable sensor devices
 - CPG comparing 2 DBS targets (subthalamic nucleus v. globus pallidus interna)
 - European CPG, invasive therapies for advanced PD
 - Brazilian CPG, pharmaceutical and DBS treatment of motor symptoms
- Clinical endpoints emphasized by ≥ 2 documents
 - Global measures of motor symptom severity*
 - Specific aspects of motor function**
 - Motor complications*
 - Behavioral and mood changes**
 - Motor-related ADL*
 - QoL*
 - Adverse events*

(Cognitive decline mentioned in only 1 document)

For more detail: Table B in CER Summary, Table 3 in full CER

*Deemed by a European CPG to be “critical”. **Deemed by same CPG to be “important”.

Follow-up Duration: Expert Reviewers' Recommendations

Domain	Reviewer Recommendations
Clinician-assessed health outcomes And Patient-reported outcomes	3 mos Wearables/sensors and robot-assisted gait trainers, 3 mos. rTMS, 6 mos. DBS and ablations (subthalamotomies and MRg-FUS), 1 yr 6 mos and 1 yr
Safety	1 mo Same as for Clinician-assessed and patient-reported 1, 3 and 6 mos
Device durability	1 mo Wearables/sensors and robot-assisted gait trainers, 6 mos. rTMS, No response. DBS, should last for ≥ 5 yrs. Ablations (subthalamotomies and MRg-FUS), N/A 1 yr and 2 yrs

Applicability to Medicare Beneficiaries

- No systematic reviews or professional guidance documents focused on older adults
However, mean age 54 to 77 years across the systematic reviews.
- In the systematic reviews: mix of disease severity according to the Hoehn and Yahr scale
- Insufficient information to allow assessment of applicability according to demographic characteristics

For Additional Detail

Please refer to the
“PD-ET_CER Summary&Subcommittee ReviewQuestions”
document or to the full CER,
both distributed prior to the March 10 premeeting.