Clinical Endpoints Review

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

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Project Title

Clinical outcomes for devices to address management/treatment of medication-refractory Parkinson’s Disease (PD) and Essential Tremor (ET)

Objective

This report aims to identify the most commonly used clinical endpoints for clinical studies of medical devices for the management/treatment of medication-refractory PD and ET, focusing on tremor and motor symptoms. In this report, the term *clinical endpoint* refers to any variable used to directly or indirectly measure target outcomes. Target outcomes have to do with “how patients feel, function, or survive” (Best 2016; Ciani et al., 2017). For each of the most frequently used endpoints, this report also identifies methods and validated instruments used to measure that endpoint, any available definitions of minimal clinically important differences (MCIDs), and follow-up intervals.

Overview

PD is one of the most prevalent neurodegenerative brain diseases diagnosed in the world (Dorsey et al., 2018). From 1990 to 2015, the number of individuals with PD increased 118% globally to 6.2 million and is estimated to reach 13 million cases by 2040 (Dorsey et al., 2018). PD incidence increases with age and is higher among males (Willis et al., 2022). In North America, in 2012, the age-adjusted incidence of PD ranged from 108 to 212 per 100,000 person-years among persons ages 65 and older and from 47 to 77 per 100,000 person-years among persons aged 45 (Willis et al., 2022). The incidence of PD was higher in males (162 to 277 per 100,000 person-years) than females (66 to 161 females per 100,000 person-years) in North America among persons aged 65 years and older in 2012 (Willis et al., 2022). The natural disease course for PD is slow. It is characterized by progressive loss of dopaminergic and other brainstem neurons, resulting in malfunction of the cerebral neuronal systems responsible for motor function (Kouli et al., 2018). While the etiology of PD is currently unknown, the clinical signs are slowness of movement, muscle rigidity, and rest tremor, among other features (Kouli et al., 2018). Management involves mitigating these effects by administering medication to stimulate dopamine receptors in the brain. One of the most prescribed dopaminergic drugs is levodopa. However, long-term use of these dopaminergic drugs can lead to motor complications, such as wearing off phenomenon and dyskinesia (Connolly et al., 2014). When motor complications interfere with an individual’s quality of life (QoL) despite optimized pharmacologic management, devices such as those using deep brain stimulation (DBS) are suitable treatment options (Kalia et al., 2013). Individuals with PD and a tremor resistant to levodopa may also benefit from DBS (Kalia et al., 2013). Nonpharmaceutical treatments for PD have evolved from ablative procedures within various brain regions to implantation of electrodes into specific targets of the basal ganglia (Fujikawa et al., 2022). Several randomized clinical studies have demonstrated the effectiveness and safety of DBS surgery for controlling PD motor symptoms, especially when targeting key brain regions such as the (STN) and the globus pallidus internus (GPi). DBS surgery also allows for variable programmability and is reversible, making it a preferred option over ablative procedures.

ET is another neurological condition characterized by tremors, one of the most prevalent movement disorders worldwide (Song et al., 2021). In 2020, the overall prevalence of ET in the general population globally was 0.32% (95% CI = 0.12-0.91). Like PD, the prevalence of ET increases with age, reaching 2.87% (95% CI = 1.07-7.49) among individuals aged 80 years and older (Song et al., 2021). Like PD, ET is more prevalent in males (0.36%, 95% CI = 0.14-1.03) compared to females (0.28%, 95% CI = 0.11-0.79) (Song et al., 2021). However, PD and ET are two distinct neurological conditions having different clinical features, ages of onset, motor and non-motor symptoms, and treatment effects (Reich et al., 2020). Although PD and ET are both characterized by involuntary rhythmic shaking movements, PD patients often experience tremors that worsen when the affected body part is at rest and subside or lessen when the affected body part is in use (Reich et al., 2020). PD tremors are often asymmetric, affecting one side much more than the other, and rarely affect the head and neck (Reich et al., 2020). Additionally, handwriting can also become unusually small (micrographia) among PD patients (Reich et al., 2020). In contrast, tremors associated with ET typically present as action tremors, which are more prominent during voluntary movements (Reich et al., 2020). ET tremors worsen when using the affected body part and subside or lessen when the body part is at rest (Reich et al., 2020). ET tremors usually occur on both sides of the body, but one side might be slightly more affected and often affect the head and neck (Reich et al., 2020). Handwriting in ET can be difficult and shaky due to tremors, but it does not become unusually small (Reich et al., 2020). The mean age of onset of PD is usually around 70 years, whereas ET symptoms typically appear between 10 -19 years of age or 50-59 years of age (Reich et al., 2020). PD has a positive family history in around 15% of cases, whereas ET has a much higher rate at 60% (Reich et al., 2020). PD also involves other motor symptoms, such as slowed movements, stiffness, and changes in walking and balance, whereas ET is mainly limited to tremor (Kwon et al., 2016). Traditionally, ET was considered a monosymptomatic disease characterized exclusively by action tremor. However, this concept has been challenged with the reporting of additional motor and nonmotor features such as mild ataxia, mild cognitive impairment, and anxiety (Kwon et al., 2016). Occasionally, patients with a long history of ET may develop PD and meet the criteria for both diseases (Thenganatt et al., 2012).

Both symptoms of PD and ET can develop over decades, and due to the progressive nature of the disease, there is considerable emotional, social, and physical impact (Kouli et al., 2018). These impacts include compromised physical function and QoL, social isolation, and increased caregiver burden (Kouli et al., 2018). Clearly defined outcomes, especially among PD patients, are essential to help reduce unwanted variations in healthcare delivery and increase the overall quality of care (de Roos et al., 2017). Efforts to identify outcomes that are meaningful to patients and caregivers have led to the establishment of various national assessment programs, such as the National Parkinson Foundation's outcomes project. However, PD outcomes remain inconsistently defined, collected, and reported worldwide. In addition, several devices are currently in development to treat PD and ET symptoms, and coverage decisions on these devices have yet to be made.

Methods

Identifying the Literature

Searches were conducted in multiple databases and evidence-based sources to comprehensively capture prioritized outcome domains, outcome measures, and measurement instruments related to the evaluation of devices used to manage PD/ET. Systematic searches using the terms detailed in **Appendix A** were conducted in Embase and PubMed on August 28th, 2023, to retrieve relevant systematic reviews (SRs), consensus statements, and clinical practice guidelines (CPGs). A supplemental search was also conducted in the Cochrane Library to retrieve relevant SRs. Eligibility criteria are listed below in **Table 1**. Two reviewers screened all articles at the title and abstract levels. Full texts for articles possibly meeting the inclusion criteria were obtained for a full review.

Table 1: Eligibility Criteria for PubMed/Embase Screening

PICOTS	Inclusion Criteria	Exclusion Criteria
Population	Adults (≥18 years) being treated/managed for medication-refractory PD or ET with a medical device	• Pediatric patient population • Patients who are being treated for an indication other than medication-refractory PD and/or ET
Intervention	Medical device used to manage/treat tremors and/or other motor symptoms from PD and/or ET (e.g., implanted DBS, wearable stimulators, ultrasound ablators, caloric vestibular stimulators) Note: Devices not used primarily for tremors and/or other motor symptoms but also intended to impact these symptoms are permissible.	• Drug, biologic, behavioral, or other non-medical device intervention • Device that is not intended to impact tremors and/or other motor symptoms as the primary or secondary focus • Device used to diagnose early PD symptoms
Comparators	• Other medical device, sham control, or non-medical device intervention (e.g., drug, biologic) • No comparator	NA
Outcomes	All efficacy and safety outcome measures	• Does not discuss or report outcome measures used to evaluate devices for management/treatment of PD/ET • No outcomes related to tremors or motor symptoms were measured
Timing	• Published on or after January 1, 2018 • Minimum study duration of 6 months for devices that require surgery or result in permanent anatomical changes (i.e., ultrasound ablation) • Wearable stimulators and other similarly noninvasive devices with <6 months of follow-up will be included	Published prior to January 1, 2018
Setting	US and Outside of the US	NA
Article type	• SRs of devices to manage tremor in PD/ET • Guidance documents regarding clinical endpoints for studies of any treatment for PD/ET • CPGs for the treatment of PD/ET • RCT, nonrandomized controlled trial*, or single-arm study of devices to manage tremor in PD/ET • N≥30 for intervention groups in research studies Note: In the absence of interventional studies, observational studies with large sample sizes and long follow-up durations will be considered.	• Case report or case series • Cross-sectional study • Case-control study • N<30 for intervention groups in research studies
Publications	• English-language publication • Peer-reviewed publication	• Non-English language publication • Commentary, opinion, editorial, or narrative review • Abstract or conference proceeding • Study protocol • Cost-effective analysis or modeling study • Pre-clinical or laboratory study

Abbreviations: CPG: clinical practice guideline; DBS: deep brain stimulation; ET: Essential Tremor; NA: Not applicable; PD: Parkinson's Disease; SR: systematic review; RCT: randomized controlled trial; US: United States

*Two of the selected SRs used the term *nonrandomized* to describe studies eligible for inclusion in that review. In one review, *nonrandomized was* not defined. In the other review, *nonrandomized* referred to any study design, whether controlled or not, other than an RCT.

Additional gray literature searches were conducted on August 29, 2023, for relevant material regarding expert recommendations and consensus statements. Supplemental searches were also performed to ensure a thorough search of literature. Searches were conducted separately for PD and ET using the terms "Parkinson's disease" or "essential tremor" and "device" or "implant" in each of the supplemental sources. To ascertain whether research on PD or ET core outcomes was available, searches were executed in the Core Outcome Measures in Effectiveness Trials (COMET) Initiative, International Consortium for Health Outcomes Measurement (ICHOM), Health Technology Assessment International (HTAi), and Patient-Centered Outcomes Research Institute (PCORI) databases. Supplementary scans were also completed within the following sources: Food and Drug Administration (FDA) repository, US Department of Health & Human Services National Institutes of Health (NIH) repository, US Department of Health and Human Services Community Health Applied Research Network (HHS CHARN), Trip Medical Database, and various professional societies and working groups. Professional societies included the American Academy of Neurology, International Parkinson and Movement Disorder Society, Parkinson's Foundation, National VA Parkinson's Disease Consortium, American Parkinson Disease Association, and International Essential Tremor Foundation. Working groups were comprised of the Joint Guidelines Committee of the American Association of Neurological Surgeons (AANS) and, the Congress of Neurological Surgeons (CNS), European Academy of Neurology, and the European section of the Movement Disorder Society on the treatment of PD – invasive therapies. Targeted searches were also conducted to capture reliability, validity, and clinically meaningful differences (i.e., minimal clinically significant differences (MCID), minimal important differences (MID), and minimum detectable difference (MDD) where possible for instruments that were used to assess/measure the prioritized outcomes. Details of these scans are documented in **Appendix A, Table A1**.

Data Abstraction and Data Management

Data on clinical endpoints, associated measurement instruments with their specifications, and timing of administration were abstracted from the SRs identified in PubMed and Embase. Where clinical endpoint descriptions were similar, they were combined (*e.g.*, gait function, postural instability, and balance were grouped into one clinical endpoint descriptor), and citation volume was calculated(**Appendix B, Table B2**). Data on relevant clinical endpoints and whether they were categorized as primary versus secondary, as well as additional instruments and time points not captured in the initial abstraction, were recorded.

Where available, extracted data included study design, clinical focus (PD, ET, or both), types of studies included in SRs, age group of study patients (adult, $\geq$18 years), sample size, device used by intervention group, control treatment, primary clinical endpoints listed, and secondary clinical endpoints listed (**Appendix B, Table B1**). The information regarding the instruments used to assess/measure them was also extracted for each primary and secondary endpoint. While inclusion criteria for eligible SRs specified an age range for enrollment, not all articles provided details on the age ranges of actual patients enrolled.

Data Analysis

Data were harmonized to create a prioritized list of clinical endpoints and instruments commonly used to measure those endpoints. A clinical endpoint was considered prioritized if it was cited by ≥40% of the studies included in the SR publications that discussed that endpoint. Citation volumes for instruments used to assess the clinical endpoints were also calculated similarly, again using 40% as the prioritization cutoff.

Details for prioritized instruments can be found in **Appendix C, Table C1**, capturing additional information obtained through targeted literature searches on reliability, validity, and minimal clinically meaningful differences (MCIDs) where possible. This information was only retrieved if it pertained to PD or ET for the clinical endpoint of interest. Every attempt was made to find validation and minimal difference studies conducted in the US or other English-speaking countries where PD or ET patients received surgical or other device therapies, particularly for patient-reported outcomes. Furthermore, instrument-specific characteristics that could influence decision making were captured (*i.e.,* feasibility, recall period, reporter, dimensions assessed, intent of development, and access).

Results

Literature

Using the search terms specified in **Appendix A, Table A1**, 4,117 records were retrieved via PubMed/Embase and exported to EndNote. The EndNote library was deduplicated using a modified Bramer method (Bramer et al., 2016), and 951 duplicate references were identified and removed. After deduplication, 3,166 records were screened at the title/abstract level and 118 SRs and CPGs/consensus statements were included for full-text screening. SRs were selected for this Clinical Endpoint Review because they offer a comprehensive method for selecting and reviewing relevant literature and synthesizing results from multiple primary studies on clinical endpoints. Moreover, SRs emphasize the methodological approach of all potentially relevant articles and use explicit, reproducible criteria in selecting articles for review. Interventional studies were ultimately excluded due to the adequate size and content of the evidence base comprised of SRs, consensus statements, and CPGs. After full-text articles for these records were obtained and screened, 35 papers met the eligibility criteria for this review. Out of the 83 full-text articles that were excluded, 65% were SRs in which over 80% of the included studies were published before 2018, 14% did not include the outcomes of interest, 13% did not cover the intervention of interest or were unrelated to the topic, and 7% did not pertain to the population of interest.

Four CPGs and one consensus statement (five professional guidance documents) on the treatment of motor symptoms in PD were identified from PubMed, Embase, and gray literature searches. Each publication was either drafted or endorsed by professional societies or organizations. Two statements were drafted by the International Parkinson and Movement Disorder Society (IPMDS) (Fox et al., 2018; Odin et al., 2018), and one each by the Congress of Neurological Surgeons (CNS) and American Society for Stereotactic and Functional Neurosurgery (ASSFN) (Rughani et al., 2018), the European Academy of

Neurology (EAN) and European section of the Movement Disorder Society (MDS) (Deuschl et al., 2022), and Scientific Department of Movement Disorders of the Brazilian Academy of Neurology (BAN) (Saba et al., 2022). Two statements focused on invasive therapies, primarily DBS (Rughani et al., 2018; Deuschl et al., 2022). Another focused on continuous assessment (referred to as *objective measurement*) of motor symptoms by means of wearable devices (Odin et al., 2018). Two considered a mix of therapies (Fox et al., 2018; Saba et al., 2022). No useful guidance documents related to ET were identified.

Data Synthesis

Clinical Endpoints: Published Systematic Reviews of Clinical Studies

Clinical endpoint and instrument data were abstracted from 30 SRs retrieved from PubMed and Embase, of which 23 SRs focused on PD and seven on ET. None of the included SRs assessed both PD and ET. SRs specifically assessing PD included non-randomized trials (n=11), randomized controlled trials (RCT) (n=8), observational studies (n=2), and a combination of interventional and observational studies (n=2). Databases searched by these SRs were PubMed (78%), Embase (60%), Cochrane Database of Systematic Reviews (56%), Web of Science (34%), Medline (20%), PEDro (13%), SCOPUS (13%), Cochrane Library-Cochrane Central Register of Controlled Trials (4%), ClinicalTrials.gov (4%), BioMed Central (4%), and CENTRAL (4%). Study funding was identified in 39% of reports. The devices assessed in the reviews were DBS (60%), robot-assisted gait training (8%), repetitive transcranial magnetic stimulation (rTMS; 8%), wearable devices/sensors (8%), subthalamotomy (4%), magnetic resonance-guided focused ultrasound (MRgFUS; 4%), and a combination of multiple devices (8%). The number of studies included in each review ranged from 2 to 184. The total number of patients enrolled ranged from 67 to 1,929. The mean age of included patients ranged from 54 to 76.6 years old.

Among SRs assessing ET, the included study type was nonrandomized trial (n=3), RCT (n=2), and observational studies (n=2). The databases searched were PubMed (100%), Embase (42%), Google Scholar (28%), Cochrane Central Register of Controlled Trials (28%), Cochrane Database of Systematic Reviews (28%), Medline (14%), Cochrane Movement Disorders Group Trials Register (14%), and SCOPUS (14%). Study funding was identified in 14% of reports. The technologies assessed in the reviews were MRgFUS, DBS, Gamma knife thalamotomy, transcranial direct current stimulation (tDCS), robot-assisted gait training, spinal cord stimulation and the Cala system (a wearable device). Most studies included in the selected reviews investigated MRgFUS or DBS devices. The number of studies included in each review ranged from 8 to 45. The number of patients enrolled ranged from 395 to 1,679. The mean age of included patients ranged from 56.6 to 78 years old.

Given that it was not possible to extract individual study-level data from each included SR and the number of studies included in each review ranged from 2 to 184, a resulting limitation is the possibility that some primary studies were counted more than once during prioritization.

Out of the 19 identified clinical endpoints for treatment/management of PD in the included literature, five spanning two domains were classified as prioritized (see **Table 2**). The five prioritized clinical endpoints focused on reducing symptom severity and improving disease-related activities of daily life (ADL) or disease-specific QoL; the endpoints were usually designated primary. Both clinical endpoints identified for the treatment/management of ET in the included literature were classified as prioritized based on the selected SRs (**see Table 2**) and were like the prioritized endpoints for Parkinson’s Disease.

Appendix B, Table B2 summarizes the citation volume of all 21 clinical endpoints and their respective instruments; **Appendix C, Table C1** presents instrument details.

Table 2: Prioritized Clinical Endpoints and Instruments for PD and ET

Domain	Clinical endpoints (citation volume)*	Instruments (citation volume)†
PARKINSON'S DISEASE		
Clinician-Assessed Health Outcomes	Global change in motor symptom severity (65%)	UPDRS III (97.8%)
	Gait function, postural instability, and balance (40%)	FOG-Q (60.3%) and TUG (60.3%)
	Cognitive function (42%)	Stroop test (85.7%)
	ADL (48%)	UPDRS II (47.5%)
Patient-Reported Outcomes	PD-related QoL (53%)	PDQ-39 (43.6%)
ESSENTIAL TREMOR		
Clinician-Assessed Health Outcomes	Reduction in tremor (89%)	FTM-TRS (66.1), Hand Tremor score (30.8), CRST (15.7), and TETRAS (2.3%)‡
Patient-Reported Outcomes	Tremor-related QoL OR tremor-related ADL (44%)	QUEST (42.2%) and FTM-TRS Part C (24.4%)

Abbreviations: ADL: Activities of daily living; CRST: Clinical Rating Scale for Tremor; FOG-Q: Freezing of Gait Questionnaire; FTM-TRS: Fahn Tolosa Marin Tremor Rating Scale; MDS UPDRS: Movement Disorder Society–Sponsored Revision Unified Parkinson's Disease Rating Scale; PDQ-39: Parkinson Disease's Questionnaire-39; QoL: Quality of life; QUEST: Quality of Life Essential Tremor Questionnaire; TETRAS: Tremor Research Group Essential Tremor Rating Assessment scale; TUG test: Time Up and Go Test; UPDRS: Unified Parkinson's Disease Rating Scale

*A clinical endpoint was considered prioritized if it was cited by ≥40% of the studies included in the systematic reviews that discussed that endpoint. For example, the systematic reviews that discussed change in motor severity collectively included 278 primary studies, and 180 (64.78%) investigated change in motor severity; thus, motor severity was prioritized.

†Citation volume was calculated in a manner analogous to that used for clinical endpoint citation volume.

‡Due to high heterogeneity in the instruments used for assessing prioritized clinical endpoints, instruments for some prioritized endpoints did not reach the cut-off value of ≥40%.

Clinical Endpoints: Professional Guidance Documents

Table 3 summarizes the clinical endpoints described in the selected professional guidance documents for the management of PD. All five documents emphasized global assessment of motor symptoms, with the Unified Parkinson's Disease Rating Scale (UPDRS) as the instrument of choice. Part III of the UPDRS addresses motor symptoms. Most of the documents also referred to the measurement of various sets of specific motor symptoms; tremor was not necessarily mentioned. Other clinical endpoints in the clinician-assessed health outcomes domain mentioned by at least two documents included cognitive function, mood or behavioral disorders (impulsivity-compulsivity, depression, suicidality, and/or apathy), and disease-related ADL. Parts I or II of the UPDRS and other instruments were mentioned for these endpoints. Within the patient-reported outcomes domain, two documents recommended assessment of QoL and depression, each citing the same self-report instruments for those endpoints. Four of the documents recommended the evaluation of safety endpoints with a common emphasis on reducing motor complications. Motor complications are symptoms that occur after chronic treatment of PD. Key examples are motor fluctuations due to the wearing off of treatment effectiveness and levodopa-induced dyskinesia (Freitas et al., 2017). As noted previously, no useful professional guidance documents related to ET were identified. **Appendix B, Table B1**, provides complete details about the selected professional guidance documents and the abstracted data.

Table 3. Clinical Endpoints Derived from Professional Guidance Documents on Parkinson's Disease

Clinical Endpoints	**Fox et al., (2018) (IPMDS).** Updates to evidence-based int'l CPG, broad range of therapies	**Odin et al., (2018) (IPMDS).** Expert panel recommendations regarding how to assess use of wearable sensor devices	**Rughani et al., (2018) (CNS/ASSFN).** Evidence-based CPG on comparative effectiveness of DBS to the STN vs. GPi	**Deuschl et al., (2022) (EAN and European section of the MDS).** Evidence-based CPG on invasive therapies for advanced PD	**Saba et al., (2022) (BAN).** Evidence-based Brazilian CPG, pharmaceutical and DBS treatment of motor symptoms
Clinician-Assessed Health Outcomes					
Disease severity				Staging according to Hoehn and Yahr ("important")	
Global measures of motor symptom severity	*Discussed without reference to measurement method except for a single reference to UPDRS endpoints in a pharmaceutical treatment*	UPDRS *(cited as a scale for purposes of assessing correlation with sensor measurements)*	• UPDRS III • Reduction in dopaminergic medications	• UPDRS III ("critical") • Daily dosage of anti-PD medication (levodopa mg equivalent) ("important")	• UPDRS III
Specific aspects of motor function	*Discussed without reference to measurement method; gait and balance are mentioned*	• AIMS *(cited as a scale for purposes of assessing correlation with sensor measurements)* • Measured by sensor: Bradykinesia, tremor, dyskinesia, immobility during sleep	*Measurement methods not specified*	• Gait ("important") • Speech ("important") *No tools recommended, but UPDRS III includes gait and speech scales.*	
Beneficial effect: reduction in or delay of motor complications*	*Discussed without reference to measurement method*		*Discussed without reference to measurement method*	• According to UPDRS IV ("critical") • Motor fluctuations reported by patient diary ("critical")	*Both reduction and delay are mentioned.*
Cognitive function				UPDRS-I, MoCA, MMSE ("important")	
Mood and behavioral disorders		Risk marker for impulsivity measured by sensor (NOTE: This actually	Depression (HDRS) Suicidality (UPDRS-I)	• HDRS ("important") • Apathy ("important") (No tool recommended, but	

Clinical Endpoints	**Fox et al., (2018) (IPMDS).** Updates to evidence-based int'l CPG, broad range of therapies	**Odin et al., (2018) (IPMDS).** Expert panel recommendations regarding how to assess use of wearable sensor devices	**Rughani et al., (2018) (CNS/ASSFN).** Evidence-based CPG on comparative effectiveness of DBS to the STN vs. GPi	**Deuschl et al., (2022) (EAN and European section of the MDS).** Evidence-based CPG on invasive therapies for advanced PD	**Saba et al., (2022) (BAN).** Evidence-based Brazilian CPG, pharmaceutical and DBS treatment of motor symptoms
		belongs in the Surrogate Marker domain.)		UPDRS III includes an apathy scale) • Ardouin-scale, QUIP, QUIP-RS, MIDI, BIS ("important")	
Composite of mood, cognitive, and behavioral effects			*Measurement methods not specified*		
ADL			UPDRS-II	UPDRS-II ("critical")	UPDRS-II
Patient-Reported Outcomes					
QoL		*Assumed to improve under continuous assessment*	PDQ-39	PDQ-39 or PDQ-8 ("critical")	
Mood and behavioral disorders			Depression (BDI)	Depression (BDI) ("important")	
Other	*Reduction in falls (mentioned in the context of pharmaceutical treatment and physical therapy)*				
Safety (clinician-assessed or patient-reported)					
Harmful effects	• "Acceptable risk with/without specialized monitoring" *(no identification of specific risks to be considered)* • Unacceptable risk		Adverse events	Serious adverse medical and surgical events ("critical")	Discontinuation of treatment (tolerability)
Other					
					• Duration of response

Clinical Endpoints	**Fox et al., (2018) (IPMDS).** Updates to evidence-based int’l CPG, broad range of therapies	**Odin et al., (2018) (IPMDS).** Expert panel recommendations regarding how to assess use of wearable sensor devices	**Rughani et al., (2018) (CNS/ASSFN).** Evidence-based CPG on comparative effectiveness of DBS to the STN vs. GPi	**Deuschl et al., (2022) (EAN and European section of the MDS).** Evidence-based CPG on invasive therapies for advanced PD	**Saba et al., (2022) (BAN).** Evidence-based Brazilian CPG, pharmaceutical and DBS treatment of motor symptoms
					• Discontinuation of treatment (lack of efficacy)

Abbreviations: ADL: Activities of Daily Living; ASSFN: American Society for Stereotactic and Functional Neurosurgery; BAN: Brazilian Academy of Neurology; BIS: Barrett Impulsivity Scale; CNS: Congress of Neurological Surgeons; CPG: clinical practice guidelines; DBS: deep brain stimulation; EAN: European Academy of Neurology; HDRS, Hamilton Depression Rating Scale; MDS: Movement Disorder Society; IPMDS: International Parkinson and Movement Disorder Society; MIDI: Minnesota Impulsivity-Compulsivity Disorders Interview; MoCA: Montreal Cognitive Assessment; MMSE: Mini-Mental State Examination; PD: Parkinson’s disease; PDQ: Parkinson’s Disease Questionnaire; QoL: quality of life; QUIP(-RS): Questions for Impulsivity-Compulsivity Disorders (-Rating Scale); STN: subthalamic nucleus

*Motor complications are symptoms that occur after chronic treatment of PD. Key examples are motor fluctuations due to the wearing off of treatment effectiveness and levodopa-induced dyskinesia (Freitas et al., 2017).

Consensus Between the Clinical Research Literature and Professional Guidance Documents

The clinical endpoints commonly emphasized in professional guidance regarding the management of PD were very similar to the prioritized list of clinical endpoints derived from the selected SRs. They predominately fell into the clinician-assessed health outcomes and patient-reported outcomes domains.

However, some endpoints mentioned by at least two guidance documents are missing from the prioritized list based on SRs. Few of the reviewed SRs addressed mood or behavioral disorders and few addressed motor complications or any other safety endpoint, yet these endpoints were emphasized by at least two of the five professional guidance documents. A European CPG document labeled depression as an “important” outcome and labeled both motor complications and serious adverse events as “critical” (Deuschl et al., 2022; see Table 3). The European CPG addressed invasive treatments, including but not limited to the technologies of interest in this report. Motor complications have been assigned to the safety domain because of the potential for tremor-controlled devices to beneficially reduce the motor complications accompanying pharmaceutical treatment.

Prioritized Instruments

The most common measurement tools are listed for each of the clinical endpoints prioritized on the basis of the selected SRs in Table 2. The Unified Parkinson’s Disease Rating Scale (UPDRS) is a key scale. Its most up-to-date version is referred to as the Movement Disorder Society UPDRS (MDR-UPDRS) (MDS 2019). The overall scale has five standalone parts that correspond to clinical endpoints in the domains of clinician-assessed health outcomes, patient-reported outcomes, and safety: Part I (nonmotor experiences of daily living), Part II (motor experiences of daily living), Part III (motor examination) and Part IV (motor complications). Although the five scales are primarily clinician-administered, some include patient-reported segments. The selected professional guidance documents also emphasized the UPDRS (see **Table 3**). The SRs and professional guidance documents showed the PDQ to be the most widely used scale for patient-reported QoL in patients with PD.

Common instruments for assessing reduction in tremor, tremor-related QoL and tremor-related ADL in patients with ET are identified in Table 2. The FTM-TRS and TETRAS are considered to be subject to bias from placebo effects, anxiety, or “white coat syndrome,” where patients apply extra effort that results in a performance that does not accurately reflect patients’ abilities (Lora-Millan et al., 2021). To overcome this, a metric was developed by the Tremor Research Group to merge clinical and technical quantification of tremors. This was adopted in the studies proposed by Cala Health to evaluate the performance of their tremor suppression neuromodulation device (Lora-Millan et al., 2021). However, no report of this metric being employed was noted in the SRs evaluated for this review.

Further details about the prioritized instruments appear in **Appendix Table C1.**

Minimal Clinically Important Differences and Follow-up Duration

Published MCIDs for all the prioritized measurement tools pertaining to PD (see Table 2) were identified in the literature. For the prioritized tools related to ET, no MCID definitions were identified, but minimal detectable change (MDC) definitions were identified for two of the tremor scales. MDC is a statistical term that denotes the smallest detectable change considering measurement error. Full descriptions of the prioritized measurement tools and associated validation studies are described in **Appendix Table C1**. MCID and validation information for the Beck Depression Index and Hamilton Depression Rating Scale have also been added to Appendix Table C1.

Most SRs did not summarize the duration of follow-up observed in the included studies. Those reviews that provided information on follow-up duration in studies of PD treatments reported variable lengths of duration without making the information specific to devices or clinical endpoints:

- DBS studies:
    - Up to 4 years but most patients were followed for only a year or less (Razmkon et al., 2023).
    - 4-24 months (Eghlidos et al., 2022)
    - ≥ 1 year (Hamdan et al., 2022)
    - Posttreatment to 12 months (Ramanathan et al., 2022)
    - < 24 months in some studies, ≥ 24 months in others (Lin et al., 2021)
    - ≥ 6 months (Manez-Miro et al., 2021)
    - Minimum 6 months (Geraedts et al., 2020)
- Comparisons of continuous subcutaneous apomorphine infusion, DBS, and continuous infusion of levodopa-carbidopa gel with each other or with best medical treatment: 4 days to 5 years (Nijhuis et al., 2021)
- Spinal cord studies: 1 week to 3 years (Streumer et al., 2023).
- Wearable sensor studies: Follow-up duration not reported; study duration, 1 month to 2.5 years (Bouça-Machado et al., 2023).
- Robot-assisted gait training: 4-5 weeks (Picelli et al., 2021)

Reviews of ET treatments reported this information:

- Gamma Knife thalamotomy: ≥ 1 year (Kondapavulur et al., 2023)
- DBS:
    - Average, 13 or 15 years, depending on the stimulation target (Fan et al., 2022)
    - Average for short-term follow-up, 10 or 11 months, depending on stimulation target; for long-term follow-up, 36 or 39 (Kondapavulur et al., 2022)
- MRgFUS:
    - 3 months to 5 years (Agrawal et al., 2021)
    - ≥ 3 months (Miller et al., 2022)

Applicability

The mean age of included subjects ranged from 54 to 76.6 years for PD patients and from 56.6 to 78 years for ET patients; hence, the findings of this review are relatively applicable to the US Medicare population in terms of age (65 years or older). Due to a lack of data on concurrent disability, end-stage renal disease, or other comorbidities, applicability to the US Medicare population was unable to be determined regarding these factors. Disease severity was measured differently across studies, with most studies enrolling patients suffering from both early-moderate (Hoehn and Yahr <3) and advanced (Hoehn and Yahr ≥3) PD. Disease duration was not available for all studies, so caution is warranted when applying this literature review's findings to patients in different stages of disease progression and severity. It should be noted that the assessment of applicability based on sex, race, and the number of US versus non-US studies could not be determined. Furthermore, the prioritized endpoints may not be considered important for studies of all device types. This could be because invasive and non-invasive medical devices have unique characteristics, and the devices included in this review include prototypes that have not been studied in real-world settings.

The included professional guidance statements are from different geographic regions. One each is from Europe, the US, and Brazil, while two were based on the International Parkinson and Movement Disorder Society, which limits applicability to the US population. It is also unknown whether these guidance documents are meant to apply to individuals with disability, end-stage renal disease, or other comorbidities, with limited applicability to the US Medicare population.

Discussion

A review of the clinical research literature for relevant clinical endpoints to consider when evaluating the effectiveness and safety of invasive and noninvasive devices to treat/manage PD and ET tremor identified a list of five prioritized clinical endpoints for PD and two prioritized endpoints for ET, along with their commonly used instruments. For both PD and ET the prioritized endpoints included reduction in motor symptoms (globally or symptom-specific), disease-relevant assessment of ADL and disease-specific QoL. Cognitive function in patients with PD was also a prioritized endpoint. All of these endpoints fell into the domains of clinician-assessed health outcomes or patient-reported outcomes. No endpoints belonging to the domains of surrogate markers or safety met the prioritization threshold. It is important to note that this is not an exhaustive list of all clinical endpoints but rather a list of the most frequently used measures in the peer-reviewed research literature. It is also noteworthy that all the endpoints prioritized based on a review of peer-reviewed clinical research were also referenced in joint guidance from the European Academy of Neurology and the European section of the MDS and deemed to be either “critical” (global reduction in motor symptoms, ADL, QoL) or “important” (reduction in specific motor symptoms, cognitive function) (Deuschl et al., 2022). Additionally, QoL and ADL have been ranked as important outcomes in a survey of patients with PD (Nijhuis et al., 2021).

Studies of different devices used similar sets of clinical endpoints. As **Appendix C, Table C2** demonstrates, each of the prioritized clinical endpoints identified in the clinical research literature was used in studies of a variety of devices. Some DBS devices had special features such as an adaptive design or remote programming, and the stimulation target(s) within the brain varied. Other stimulation-based technologies included rTMS, tDCS, MRgFUS and spinal cord stimulation. Surgical technologies included unilateral pallidotomy and subthalamotomy. Robotic exoskeletons and wearable devices were also represented. This report’s inclusion criteria were restricted to publications from the last five years to capture the most recent research; however, it is possible that more newly available devices may not have been included in the SRs retrieved. One very recent device for caloric vestibular stimulation (ThermoNeuroModulation device) was identified. However, a brief scan of the clinical studies for this device did not appear to alter the findings of this report.

There was no overlap of prioritized motor clinical endpoints between PD and ET. The prioritized motor endpoints from PD reviews were global reduction in motor symptom severity and improvement in motor symptoms related specifically to gait. In reviews of ET studies the focus was on reduction of tremor.

The prioritization process did not identify motor complications, mood and behavioral disorders, safety issues, device durability or patient acceptance/satisfaction as important clinical endpoints. In contrast, the European guidance document labeled motor complications and serious adverse events as “critical” and certain mood and behavioral disorders as “important” (Deuschl et al., 2022), and these endpoints were emphasized by some of the other guidance documents as well. The absence of motor complications (motor symptoms resulting from chronic treatment) and safety endpoints in the prioritized list is especially surprising. This may reflect the fact that SRs typically focus on specific issues, and that some of the selected reviews excluded observational studies, which are key sources of safety data. Another possible explanation is the fact that some studies investigated relatively low-risk technologies, i.e., robotic and wearable devices; however, only a minority of the studies included in the selected systematic reviews involved these noninvasive technologies. A review of primary studies rather than SRs or citation volume calculations specific to device types may have resulted in a different prioritized list of clinical endpoints. In a survey that guided the protocol for one of the selected SRs, patients with PD prioritized not only QoL, activities of daily living (ADL) and physical effects, but also complications/adverse effects (Nijhuis et al., 2021).

The prioritization of instruments within this review was based on citation volume as a reflection of general acceptability among researchers (see **Appendix B Table B2)**. Validation within the intended patient population was completed for most of the prioritized instruments (see **Appendix C Table C1)**. However, not all validation studies were conducted in the US or other English-speaking countries, which might limit their applicability to US-based studies.

The values for MCIDs seen in **Appendix C Table C1** were calculated within highly contextual bases and should be interpreted as such. MCIDs were defined in the literature as “the smallest differences in scores in the domain of interest, which patients perceive as beneficial, and which would mandate, in the absence of troublesome side effects and high costs, a change in the patient’s management” (Jaeschke et al., 1989). MCIDs can be highly variable due to differences in calculation, patient population, intervention, disease severity, time points of analysis, and study setting. Furthermore, studies to determine MCID values were generally not conducted among patients representative of the Medicare beneficiary population. Another approach to assessing the clinical significance of study findings is to consider a therapeutic target. However, a panel of PD experts has reported that no therapeutic targets have been defined for PD rating scales, such as the UPDRS, other than a “zero level”, which is rarely achieved (Odin et al., 2018).

This report provides information on the most used clinical endpoints in studies of devices to manage tremor, commonly used measurement instruments, and definitions of MCIDs according to those instruments. The information provided in the systematic reviews and professional guidance documents that served as the basis for this report’s assessments is limited. Thus, conclusions about the relative importance of clinical endpoints, particularly in the safety domain, for different types of technology were not possible. Nor can it be assumed that MCID definitions apply equally to all technologies or patient subpopulations. Lastly, appropriate follow-up intervals for specific clinical endpoints could not be evaluated.

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