CLINICAL ENDPOINTS REVIEW REPORT
Devices to Manage Tremor in Parkinson's Disease and Essential Tremor
Expert Reviewer Feedback

The following responses to review questions were received from three external subject matter experts who reviewed the completed Clinical Endpoints Review (CER) report.

1. Do you believe that the search strategies used in the CER are likely to have captured the appropriate literature? (See the "Identifying the Literature" section, starting at the bottom of page 2 of the full CER).

   Yes, seems appropriate and comprehensive
   Yes, I believe that the search strategies were appropriate and comprehensive for the purpose of this report.
   Yes, the search strategies on pages 2 and 3 are comprehensive and would capture the breadth of literature involved

2. Are the most important domains and clinical endpoints for studies of PD and ET therapies reflected in the CER findings? (See Tables A1 and B in this document). Yes
   Are important domains or clinical endpoints missing, and are omissions likely due to deficiencies in the literature search strategy or omissions in the available body of clinical research literature? Please suggest additions and/or deletions to each domain with commentary as appropriate:

   The most important domains and clinical endpoints for PD and ET therapies are included.

   a. Surrogate markers, i.e., indirect assessments using biomarkers, physiologic measures, or imaging and intended to predict or act as a proxy for a target outcome of interest.

      There are some emerging surrogate biomarkers for PD (physiology and imaging based ones) but their utility in assessing clinical outcome is still correlative and undetermined.
      No. Indirect/surrogate assessments for target outcomes of interests are of great interest in the field and believed to be important to advance research. However, accurate and reliable surrogate markers do not yet exist for these disorders and outcomes.
      No surrogate markers available for tremor control

   b. Clinician-assessed health outcomes

      Would add sleep and reduction in dyskinesia (UPDRS Part IV) as important outcomes
      The most important clinician-assessed health outcomes for PD/ET are captured, including motor severity, gait/balance, cognitive function and quality of life for PD, and tremor severity in ET. In addition, for PD, I would add evaluation of speech/swallowing function, and globally, evaluation of effects of therapy on non-motor symptoms (NMS). Omission of specific evaluation

of NMS is likely a function of the available body of clinical research literature, and not due to deficits in the search.

TETRAS and hand tremor score in UPDRS are the best ones to use. CRST and FTM-TRS are less commonly used clinically.

c. Patient-reported outcomes

Nothing to add

The most important patient-reported outcome for PD/ET is captured, which is quality of life, and in ET specifically, tremor-related quality of life/ADLs.

Related to point b. with respect to PD, I would also add evaluation of NMS, which is typically done through a combination of clinician-assessed and patient-reported outcomes. UPDRS-II includes evaluations of NMS, but there are other tools, for example, the MDS-NMS scale.

As above, FTM-TRS is not commonly used clinically. Would be important to add MDS-UPDRS 2.10.

d. Safety (Your opinion on the appropriateness of assigning motor complications to this domain would be appreciated. Motor complications have been assigned to the safety domain because of the potential for tremor-controlled devices to beneficially reduce the motor complications that accompany pharmaceutical treatment.)

Motor complications would be more appropriate part of clinician-assessed outcome, as effective therapy (medication/ DBS) would ideally reduce motor complications as assessed by UPDRS Part IV. Other safety outcomes: Falls/imbalance/ataxia: which can be complications of DBS for either ET or PD.

Motor complications could be listed under safety, but I believe they are better suited listed under global severity of motor symptoms. The potential benefit from devices in motor symptoms includes benefit in in tremor but also in motor complications, including dyskinesia and motor fluctuations (on/off), which reflects motor severity of disease. Motor complications in general reflect disease severity.

The safety domain I believe should have a focus on the safety of the devices themselves, i.e. their potential of causing harm (for example, dysarthria or ataxia following HiFU, or risk of intracranial hemorrhage or infection following DBS surgery), discomfort from their implementation (for example, skin issues, or discomfort from wrists and other non-invasive wearables for tremor).

In terms of specific outcomes regarding safety, this would include report of adverse events and serious adverse events for each of the devices/interventions.

The evaluation of the included patient-, but especially clinician-reported outcomes, is an indirect evaluation of safety of devices for PD and to a lesser extent, ET. From that point of view, it may hence not be surprising that specific safety endpoints did not make the prioritized list. For example, an important safety concern from invasive devices such as HiFU and DBS is

worsening cognition and mood. Cognition is included in the prioritized list, although mood did not make the prioritized threshold.
The type and relative importance of safety outcomes is device-specific. For example, evaluation of speech/swallowing difficulties, mood (including suicidality), and cognition, is important when considering DBS and HiFU and subthalamotomies, but of much less importance when considering robot-assisted gait-training or wearables/sensors.
I would define safety as the impact of gait and speech specifically (as these are known to worsen after device-aided therapy and there is often a tradeoff between tremor control and axial symptoms). Reduction in motor complications (i.e. fluctuations) is more appropriately considered an efficacy outcome, can be assessed as a clinician-assessed outcome via MDS-UPDRS part 4.

e. Other (Respond here if you wish to recommend any important clinical endpoints that do not fit one of the preceding domains.) *None. None. n/a*

3. Patient- and technology-specific clinical endpoints

   a. Is there any difference in the clinical endpoints that should be measured in subpopulations of patients with PD or ET versus general adult populations with those diseases? Examples of subpopulations include older (age ≥ 65 years) versus younger adults, more versus less severe disease, women versus men, and patients with versus without high levels of comorbidity?

      No additional outcomes as previous ones are very comprehensive.
      First, for PD, I think the biggest difference or emphasis in terms of clinical endpoints pertains to the older patient population with PD (age ≥ 65 years), and in those with longer disease duration (>5-7 years). Most important clinical endpoints in these two subpopulations include gait/balance/falls, and cognition/mood (including evaluation of psychosis). These endpoints are more important in this subtype that in younger individuals, who are less at risk. Those are however already included in the prioritized list. For those with longer disease duration, motor complications should be higher in the priority list.
      For ET, a difference in clinical endpoints pertains also to the subpopulation of older individuals. For this subpopulation, evaluation of ataxia and gait/balance/falls should be measured.
      Cognitive outcomes (MoCA, etc) should likely be weighted more in older adults than younger.

   b. Is there any difference in important clinical endpoints, particularly safety endpoints, according to type of technology? Examples: invasive versus noninvasive.

      Stimulation-induced side effects (dysarthria, imbalance, contracts, mood dysregulation).

Yes, I believe the importance of safety outcomes is technology-specific. Broadly, that means invasive vs non-invasive technologies, but also with subtleties within each category.
For DBS, important clinical endpoints include, regarding safety: the risk of hemorrhage, infections, need for additional surgery, risk for worsening gait/balance, effects on mood and cognition, effects of speech/swallowing; and in terms of effectiveness/motor outcomes, effects on motor severity, motor fluctuations and medication reduction.
For ablations, including subthalamotomies and HiFU (MRgFUS), in terms of safety, they will share with DBS risk for worsening gait/balance (including causing ataxia), effects on mood and cognition, effects of speech/swallowing, but risk of hemorrhage/infection is nearly exclusive of DBS, and not an issue in ablations. Same shared effectiveness/motor outcomes as DBS.
An important aspect of invasive technologies with higher risks is the issue of magnitude of benefit, with greater and more lasting benefits expected from more invasive technologies.
Specific for rTMS is the potential for causing (or worsening) seizures.
The endpoints themselves should remain the same, however for an invasive procedure I would want to see a higher degree of benefit and/or lower safety risk, compared to a non-invasive procedure.

4. Measurement instruments

    a. Consider the instruments and measurement methods listed in Tables A1 and B in this document. Are these appropriate for studies investigating devices to manage PD- and ET-related tremor? Are there others that should be considered?

        Would recommend MoCA [Montreal Cognitive Assessment] instead of Stroop test for cognitive assessment
        For global change in motor symptoms in PD, I would include the subscale from the MDS-UPDRS (Part IV), which evaluates motor complications of therapy, including fluctuations, dyskinesia and off-dystonia.
        For gait function, postural instability and balance, I would include Part III of the MDS-UPDRS as specific items regarding gait/posture, freezing and postural instability, as well as the pertinent questions regarding gait/balance/freezing from Part II.
        For cognition, I would include the Montreal Cognitive Assessment (MoCA), and the subscale from the MDS-UPDRS (Part I).
        For cognitive outcomes for PD, would suggest MoCA in addition to Stroop. Stroop only looks at executive function, but MoCA has a more comprehensive set of assessments, and is also commonly used clinically.

    b. Consider any additional endpoints you identified in response to question #2. What instruments or methods would you recommend for measuring these endpoints?

        UPDRS Part IV for dyskinesia, MoCA as part of cognitive function

I would include Part II of the MDS-UPDRS, as well as the MDS-NMS scale for evaluation of speech/swallow and other non-motor symptoms.
As above, would add MoCA as an option for cognitive endpoint.

5. MCIDs

   a. Do you know of any published definitions of MCID, other than those referenced in Appendix Table C1 of the full CER, for the clinical endpoints that are in that table?
   No.
   No. The ones listed are the ones known in the field.
   Not aware of any other MCID definitions

   b. Can you offer MCID definitions for any clinical endpoints you identified in response to Question #2?
   I believe there are published MCID for MDS-UPDRS Part II. The MDS-NMS scale is a newer scale and I am not aware of MCID definitions for the scale.
   MCID for MOCA = 1 point (https://doi.org/10.1016/j.cccb.2024.100222)

6. Based on your clinical expertise, what is the domain-specific <u>minimum duration of follow-up</u> that should be observed in studies of devices to manage PD- and ET-related tremor? If appropriate follow-up intervals vary within domains according to various endpoints, device type, or patient characteristics, please provide that information.

   <u>Clinician-assessed health outcomes</u>:
   3 months
   Three months for wearables/sensors and robot-assisted gait trainers, six months outcomes for rTMS, one-year outcomes for DBS and ablations (subthalamotomies and MRg-FUS)
   6 months, 12 months

   <u>Patient-reported outcomes</u>:
   3 months
   Three months for wearables/sensors and robot-assisted gait trainers, six months outcomes for rTMS, one-year outcomes for DBS and ablations (subthalamotomies and MRg-FUS).
   6 months, 12 months

   <u>Clinician-assessed or patient-report safety outcomes</u>:
   1 month
   Three months for wearables/sensors and robot-assisted gait trainers, six months outcomes for rTMS, one-year outcomes for DBS and ablations (subthalamotomies and MRg-FUS).
   1 month, 3 months, 6 months

   <u>Patient adherence</u>:

3 months
Three months for wearables/sensors and robot-assisted gait trainers, six months outcomes for rTMS. Patient adherence is not an issue for DBS and ablations.
6 months, 12 months

Device durability:

12 months
Six months for wearables/sensors and robot-assisted gait trainers. Device durability is not an issue for ablations. For DBS studies, these are permanently implanted devices, durability should be at least 5 years and beyond. For the currently FDA-approved devices, this has been achieved.
12 mo, 24 mo

Other: *No reviewers offered additional information.*