USE CASE FOR DEVELOPING NOVEL ENDPOINTS GENERATED USING MOBILE TECHNOLOGY: PARKINSON'S DISEASE

OVERVIEW

The Unified Parkinson's Disease Rating Scale (UPDRS) and the Parkinson's disease Questionnaire (PDQ-39 and short-form PDQ-8) are commonly used measures in PD research. The UPDRS is a rating tool designed to follow the longitudinal course of PD. It comprises three sections: 1) Mentation, Behavior, and Mood; 2) Activities of Daily Living (ADL); and 3) Motor. These are evaluated by interview (ClinRO). A total score of 199 points is possible, with 199 representing total disability and 0 representing no disability.[1] The PDQ is a self-completed patient-reported outcome (PRO) designed to address aspects of functioning and well-being for those affected by PD. Substantial evidence is available to suggest that the PDQ is reliable, valid, responsive, and feasible as a tool for assessing quality of life in patients with PD.

In addition to the UPDRS and PDQ, many other cognitive scales and measures of disability and symptoms are commonly used in PD treatment and research. For this reason, the Movement Disorder Society Disability Task Force has recommended that no further work be done to develop completely new disability measures.[2] The reliability, reproducibility and minimally clinically important difference (the smallest change in an outcome that a patient would identify as important) of these measures are well known.

The entrenchment of these outcome measures presents a challenge to the development of novel endpoints for PD. However, measures captured by mobile technologies present significant unique opportunities, including a more complete picture of disease burden and better assessment of the impact of a new therapy on symptoms. Specifically, continuous measurement by mobile technology such as an accelerometer may capture more detail about fluctuations in functionality, responses to medication, and important information associated with symptoms that are task-triggered (such as symptoms exacerbated by stress, or episodic disturbances that are difficult to observe in clinic evaluations). The ability to capture passively generated, objective data may mitigate concerns about reporting bias and the challenges of using PROs in a patient population that may be experiencing cognitive decline; it may also reduce the burden of trial participation on patients, their caregivers and clinicians. Finally, mobile technologies offer the possibility of objectively assessing outcomes poorly described in contexts outside of the traditional clinic visit. Such outcomes include tremor, risk of falling, freezing of gait, and even the possible development of an objective description and measure of 'off' time.

SPECIFIC AIMS

This use case explores the possibility of developing accelerometer-derived endpoints for use in clinical studies of Parkinson's disease (PD). Specifically, it is meant to help determine what work is required to develop these endpoints and to evaluate what their utility may be.

STAKEHOLDERS AND INTERESTS

Stakeholders and their interests are listed below:

Patients with Parkinson's Disease

Patients are primarily interested in the promise of objective measures, potentially recorded continuously over the course of a day, that better describe a more complete picture of disease burden, particularly on activities of daily living, and provide improved data capture in patients struggling with cognitive impairment.

Industry

Industry representatives are interested in how trial feasibility may be improved in terms of size, time, and expense. Not only interested in using novel endpoints for labeling claims, but also to improve attrition rates and/or predictability rates from phase II to phase III[†] and postmarket surveillance. Early identification of pharmacological activity would also represent an advance, supporting the identification of appropriate doses and selection of a frontrunner compound from a panel of candidate drugs.

Regulators

Regulators emphasized that in the present state of development of mobile technologies and the objective data they generate, no single mobile outcome assessment is sufficient on its own. In general, use of a single mobile-technology-derived novel performance outcome assessment should be used with various other outcome measures to support a claim.

Technology manufacturers

As new stakeholders in PD research, technology manufacturers are interested in better understanding the needs of PD patients and researchers in order that they can better meet them. Similarly, technology manufacturers are interested in earlier engagement in the process of novel endpoint development and greater clarity regarding the process.

Consortia

Disease research consortia are interested in better defining the process of novel endpoint development in order to underscore the need for earlier cross-organization collaboration and data sharing.

ASSUMPTIONS

The accelerometer selected to generate the data is well tolerated by patients and produces data that are reliable, valid, and sensitive.

SCOPE

Work on these use cases is focused on the treatment benefit these outcomes can demonstrate at present. The use case outcomes are to characterize clinically relevant aspects of the disease amenable to treatment and permit objective assessment of treatment effect rather than disease prevention. In other words, in studies for which these endpoints will be used, the participants will have been diagnosed with the stated disease.

[†]Note: many phase III PD trials have failed, but it remains unclear whether this is due to lack of drug efficacy or insufficiently sensitive endpoints. This trend has been observed in other neurological diseases, including Alzheimer's disease.

The development of data standards[3] is out of scope for this use case, as is the impact of use case outcomes on patient survival.

OUTCOMES

Success Outcome(s)

The primary success outcome is the development of a novel endpoint that, either alone or as part of a "basket" of endpoints, improves upon the objectivity and responsiveness of existing gold standard PD endpoints.

Success outcomes are not limited to the successful development of a novel endpoint that may be used to support regulatory applications. Success is also defined as the development of a novel endpoint that improves the efficiency of the drug development process (for example: dose selection, attrition rates, and/or predictability of successful transition from phase II to phase III clinical studies).

Failure Outcome(s)

Development of a novel PD endpoint will be considered a failure if it cannot improve upon the information and utility of existing gold standard PD endpoints.

CONCEPT OF INTEREST

Non-purposeful movement of upper limb.

CONTEXT OF USE CONSIDERATIONS

The hypothetical endpoint of number of episodes and total duration of bothersome tremor should be used only in patients diagnosed with PD who score at least 1 on Part 3 of the UPDRS and report experiencing bothersome tremor. Measurement of the outcome may occur anywhere, but patients should wear accelerometers on both wrists[*] for continuous data capture.

DESCRIPTION OF A PROPOSED NOVEL ENDPOINT

Number of episodes and total duration of bothersome tremor.

MAIN SUCCESS PATHWAY FOR DEVELOPMENT OF ENDPOINT

Step 1. Defining Tremor Characteristics with Meaningful Impact on Patient Function

Conduct observational studies to characterize duration, severity, and impact of bothersome tremor during activities of daily living that capture both accelerometer data and contemporaneous PRO data. Also consider accelerometer technologies with functionality that allows direct patient input (for example, pushing a button on the technology) when bothersome tremor occurs.

Note that:

- ▶ A range of accelerometer values would be expected to define bothersome tremor

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[*]Note: placing accelerometers on patients' wrists was a decision made by the team in the context of a use case. In reality, studies to assess the different locations for technology placement would be conducted to improve measurement accuracy and inform optimal body placement.

- It may be possible to define different types of bothersome tremor or different subpopulations of patients who experience bothersome tremor in different ways

Such observational studies would also provide additional critical information regarding the following:

- Patient compliance with and tolerance of technologies
- Identifying appropriately sensitive accelerometer technologies required to maximize signal: noise ratio in measurement of bothersome tremor
- Data properties (in order to properly design and size subsequent clinical studies)

Step 2. Conducting Validation Studies to Confirm Reliability and Relevance of Bothersome Tremor as an Outcome Assessment for PD

The new endpoint should be compared with the gold standard in a controlled environment.

Step 3. Setting Standards Allowing Unification and Comparison across/between Related Measures

This step includes both hardware and software. One challenge that may emerge is the need to overcome efforts to protect intellectual property (IP), including:

- Black box restrictions to accessing raw data (technology manufacturers)
- Protection of algorithms generated to identify bothersome tremor as IP (industry)

Setting standards requires precompetitive data sharing and the integration of robust clinical data sets. See Stephenson et al. for a roadmap to achieve such collaboration in PD[4] and Weninger et al for principles of data sharing that may also be useful to PD research.[5]

Step 4. Defining Meaningful Change in Number and Duration of Bothersome Tremor Episodes (Endpoint)

One approach may be to use accelerometers to measure the duration of bothersome tremor in a *de novo* group of PD patients who begin treatment with Levodopa (shown to be an effective short-medium term treatment for PD). Some people's tremor will improve, others will not—this information can be used to determine the meaningful change to patients.

Step 5. Ecological Validation of the Endpoint

Approaches to ecological validation may include incorporating the following into early-phase and additional observational studies:

- Examination of correlation of novel endpoint with traditional measures (note: the novel endpoint would be expected to be more sensitive and objective, especially if it is so disruptive that it is measuring something completely different than traditional measures.)
- Inclusion of a PRO diary would increase understanding regarding meaningfulness of the measure to the patient and potentially support validation efforts in nontraditional research environment
- Soliciting patient input on data captured during a specific "training period" may facilitate opportunities for personalization of the measure

Context of use should also be challenged and explored.

Exceptions

One possible exception was noted: when tremor is present only in the patient's non-dominant side. Some discussants noted that this may be addressed by 1) the use of accelerometers on

both wrists in all patients and 2) taking a patient-centered approach to defining "bothersome tremor." However, no conclusions were reached.

ISSUES

Work on this use case was predicated on the assignment of a specific mobile technology, an accelerometer, for data capture to generate a novel endpoint. The use case team identified this as a significant issue, agreeing that the identification and development of novel endpoints should be driven primarily by patient insight.

The endpoint "number of episodes and total duration of bothersome tremor" that the use case team identified and developed as an endpoint for PD research was not intended to be used in isolation. Rather, it was intended to be used as part of a basket of outcome assessments to paint a more complete picture of the burden of PD and leverage the benefits of using an objective, novel measure generated by passive data collection during activities of daily living. Other suitable complementary endpoints to include in this basket of measures were not discussed in detail.

Measuring tremor is important to PD patients and may address an unmet need. However, trials would need to include other outcome measures including other concepts of interest applicable to all PD patients, as approximately 30% of people with PD do not experience tremor. The use case team identified this as a critical consideration when developing the basket of endpoints to include with "number of episodes and total duration of bothersome tremor."

The use case team agreed that the development, and particularly qualification, of any novel endpoint for PD trials could not reasonably be expected to occur without collaboration. Additional detail on how this may occur is provided in both the *Main Success Pathway* and *Additional Notes* sections. However, the recommendations for creating an amalgamated dataset will only be implemented if the culture around IP is addressed; specifically, redefining IP as the execution of the algorithm underpinning the novel endpoint, not the algorithm itself.

TO DO

The pathway to developing the novel endpoints for PD need not be followed as a linear process. Patients with PD could be immediately engaged to drive and direct efforts to identify potential novel endpoints. Similarly, technology manufacturers should be included in these conversations without delay in order to better understand technological requirements. Efforts to establish collaborative syndicates should be prioritized in order to create a culture of precompetitive cooperation and identify the logistical and technical frameworks required to build an amalgamated dataset.

Thinking more specifically about the development of "number of episodes and total duration of bothersome tremor" as an endpoint for PD, clarity is required regarding the additional endpoints that would be included in the basket of endpoints.

CONCLUSION

The field of PD is well positioned to develop a novel endpoint that, either alone or as part of a basket of endpoints, improves upon existing gold standard PD endpoints. "Number of episodes and total duration of bothersome tremor" is an example of a measure that could address unmet need for the assessment of an aspect of PD and realize the benefits of passive, continuous

objective data capture in this population. The development of such a novel endpoint may also increase the likelihood of an investigational PD therapy for motor symptoms being able to progress to phase III clinical studies.

REFERENCES

1. Massachusetts General Hospital website. Hoehn and Yahr Staging of Parkinson's Disease, Unified Parkinson Disease Rating Scale (UPDRS), and Schwab and England Activities of Daily Living. Available at: http://neurosurgery.mgh.harvard.edu/Functional/pdstages.htm. Accessed March 23, 2017.

2. Shulman LM, Armstrong M, Ellis T, et al. Disability rating scales in Parkinson's disease: Critique and recommendations. *Mov Disord.* 2016; 31(10):1455-65. doi: 10.1002/mds.26649. PMID: 27193358

3. Compton C. Data standards: What are they and who needs them? NIH Data Standards Forum. October 19, 2012. Available at: https://c-path.org/wp-content/uploads/2013/09/Data-Standards-What-Are-They-and-Who-Needs-Them.pdf. Accessed March 21, 2017.

4. Stephenson D, Hu MT, Romero K, et al. Precompetitive data sharing as a catalyst to address unmet needs in Parkinson's disease. *J Parkinsons Dis.* 2015;5(3):581-94. doi: 10.3233/JPD-150570. PMID: 26406139 PMCID: PMC4887129

5. Weninger S, Carrillo MC, Dunn B, et al. Collaboration for Alzheimer's Prevention: Principles to guide data and sample sharing in preclinical Alzheimer's disease trials. *Alzheimers Dement.* 2016;12(5):631-2. doi: 10.1016/j.jalz.2016.04.001. PMID: 27157073 PMCID: PMC5111162

ADDITIONAL NOTES

► One concept of interest that the team did not develop but noted as being of particular interest was accelerometer-derived characteristics of gait (this would include the ability to capture episodes of freezing, near falls and falls, etc.). There was consensus on the unique value that developing a machine-learning outcome assessment may be able to provide PD research.
   • This could also be extended to machine derived characteristics of episodes of more general physical activity

► Other COIs considered but not pursued included:
   • Arm swing with ambulation
     Possible outcome assessments that could be captured using an accelerometer include:
        ▪ Arm swing magnitude
        ▪ Arm swing asymmetry
   • Quantity of activity
     Possible outcome assessments that could be captured using an accelerometer include:
        ▪ Activity frequency
        ▪ Duration of walking
        ▪ Intensity of activity

► Other symptoms proposed during brainstorming but not pursued included:
   • Mood
   • Constipation
   • Loss of smell
   • Slowness
   • Sleep
   • Stiffness
   • Drooling
   • Pain
   • Falls
   • Hospitalization
   • Orthostatic hypertension
   • Off state

- ▶ Additional suggestions for reducing friction in the novel endpoint development process were also proposed:
  - To promote collaboration:
    - Start and drive conversations with data
    - Standardize consent forms and data use agreements
    - Develop a standardized ontology for meta-data
    - Earmark resources
  - Seek FDA input early
  - The FDA is open to considering novel endpoints
  - Publishing
    - Including algorithms, protocol and level of detail required to actually replicate the study and generate further data

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- ▶ *This Use Case was developed at a CTTI-hosted multi-stakeholder expert meeting in September 2016 as a part of the MCT Novel Endpoints Project. (Updates incorporated on February 24, 2017.) Three additional Use Cases were created for trials involving:*
  - *Heart Failure*
  - *Diabetes*
  - *Duchenne's muscular dystrophy*