DDT COA #000106 **REQUEST FOR QUALIFICATION PLAN**

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Dear Dr. Daumer,

We have completed our review of the letter of intent (LOI) submission for DDT COA #000106 received on August 29, 2018.

You have proposed to develop a digital health technology clinical outcome assessment (COA) to evaluate a change in real-world walking speed in patients with multiple sclerosis. We agree to enter this project into CDER's COA Qualification Program. The tracking number for this project has been assigned to DDT COA #000106. Please refer to DDT COA #000106 in all future communications.

Specific details related to the qualification (e.g., concept of interest, context of use) may evolve over the course of instrument development. As limited information was provided related to the concept of interest and context of use, we cannot agree to specifics until you have provided detailed materials for review and comment. We strongly encourage you to request a meeting with the qualification review team (QRT) as you develop your qualification plan.

Our response to your question included in the submission can be found below.

Question 1: What would be the most promising approach to move towards FDA acceptance of real world walking speed as Phase 3 outcome, in particular, is there an existing category of COAs we should focus on (PRO, ClinRO, ObsRO, PerfO) or should we think about a new category, e.g., a novel class of "mPRO" (mobile sensor PRO)?

FDA Response:

The FDA acknowledges that clinical outcome assessments collected in a "real-world" setting using digital health technology can provide useful complementary information to clinical outcome assessments performed in the clinic or based on patient self-report. The FDA is open to any type of COA that has been demonstrated to be fit-for-purpose for use in clinical trials to support medical product labeling. We have the following general considerations for evaluation of digital health technology drug development tools for use as an endpoint in clinical trials.

(1) Before using digital health technology tools in clinical trials, they should be shown to be reliable in measuring the parameters for which they are designed (e.g., acceleration, velocity, temperature, pressure, time). There should be a demonstration of accuracy, precision, consistency and uniformity of measurements made by the tool over time, in comparison to a reference value.

(2) To ensure the endpoints represent outcomes that are meaningful to patients, we recommend obtaining patient input early in the process to understand what concepts and aspects are the most important to measure, and what constitutes improvement. For example, patients with a disease that affects ambulation may provide input that a particular aspect of ambulation is most important and relevant compared to others (e.g., ease of walking, total distance walked, or walking speed). It is important to think about how the outcomes assessed can be translated into describing how the patients feel or function, and how this information can be clearly described in medical product labeling.

(3) In the real-world setting, there are multiple factors that impact walking speed, including weather, as well as patient factors such as fatigue and pacing. These factors may impact the ability to detect a treatment effect. Given that walking speed has been used as a performance-outcome assessment (e.g., Timed 25-Foot Walk test) in clinical trials, it would be informative to gather this information to allow comparison with actibelt®-derived measurements. You may also wish to gather information from patient-reported outcomes (e.g., fatigue) to assist in data interpretation.

(4) We also recommend gathering information during instrument development to help inform what threshold of improvement and deterioration represents a meaningful change to patients. Typically, this relies on the use of multiple sources of data (e.g., anchor-based methods using other types of COAs, including PROs) and also potentially open-ended patient input in the form of surveys or patient interviews.

We also have the following comments and requests for information:

- Specify each patient's current activity level to be referenced as baseline, to be used for comparison after any intervention.
- Consider including patients who use and do not use assistive walking devices in your target patient population and describe how any use of assistive devices will be captured and accounted for in drug development studies.
- Provide detailed information about the actibelt®, such as size and weight.
- Provide further detail about how the accelerometer will be used (e.g., waist) and the instructions for use.
- Provide results of usability and human factor study (including safety data) and patients' compliance.
- It is unclear if 7 days is a sufficient length of time to detect a meaningful change in average walking speed for patients with multiple sclerosis (MS), as MS is a chronic illness. Please describe how you envision the implementation of the 7-day measurement into a longer study (e.g., repeated measures every few months?), how such data would be analyzed, and how you would ensure that the chance of data loss is minimized (storage, transmission, backup).
- Uncontrolled variables in a real-life setting (e.g., weather) should be considered as a source of variability in the data.

- We note in your briefing package the actibelt® overestimates walking speed in moderate and severe MS patients. As you continue your development work, you will need to address this issue, and its possible impact on the interpretation of the data.

Ultimately, FDA will review the following tool-related information to ensure the tool is fit-for-purpose:

- "Walking speed" (average or maximum) is identified as an output of the product. However, "step numbers" is also mentioned in the submission documentation. Measurements that actibelt® will report should be clearly defined. For example, when "walking" is stated, the intended report is currently unclear – time spent walking, walking distance, stride velocity or length, etc. The product's algorithm should be adequately described, including all inputs and outputs, and a description of how the raw data are processed (such as with a flow chart) to calculate the features/outcomes reported by the product.
- Each measurement that is reported by the actibelt® should be supported by sufficient validation data, which should include data that demonstrate (1) adequate content validity and (2) adequate test/retest reliability (precision) in the use population and intended environment.
- You should demonstrate that the tool is capable of collecting data that are sufficiently precise for its intended use, and you should assess the precision of its measurements in relation to reasonably expected differences in patient outcomes (clinically-meaningful).
- The tool should be demonstrated to provide reproducible measurements (i.e., accurate and reliable measurements by multiple actibelt® by multiple testers) in the populations tested.
- Because actibelt® is a wearable device, the effect of differences in placement should be assessed, to determine whether the tool's measurements are sufficiently insensitive to the reasonably-expected differences in tool placement, or a valid rationale should be provided as to why placement would not affect the tool's measurements.
- Since actibelt® is intended to be used by a lay user, the usability and human factors should be assessed to support the accuracy and reliability of the measurements over a 7-day period (or a longer period that is appropriate) in the subjects' home / community environment.
- You should demonstrate that the tool will provide accurate and reliable measurements over the entire length (i.e., 7 days) of a study. 10 MWT or 6 MWT validation testing may not adequately evaluate measurement error over the proposed 7 days of continuous measurement.

Appendix 1 of this letter contains the contents to include in your submission to reach the next milestone (qualification plan). Please contact the COA Staff at COADDTQualification@fda.hhs.gov should you have any questions before the next milestone. Please refer to DDT COA #000106.

Sincerely,

Elektra J. Papadopoulos -S

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APPENDIX 1: COA QUALIFICATION PLAN

The COA qualification plan should be accompanied by a cover letter and should include the following completed sections. This plan should contain the results of completed qualitative research and the proposed quantitative research plan. If literature is cited, please cite using the number assigned to the source in a numbered reference list.

Note: Sections 1 and 2 will be posted publicly under Section 507 (referring to section 507 of the Federal Food, Drug and Cosmetic Act [FD&C Act] which was created by Section 3011 of the 21st Century Cures Act).

Section 1: Proposed Plan for COA Qualification

1.1 Introduction and overview

- This should include a concise description of the disease and the clinical trial setting in which the COA would be used, the limitations of existing assessments, a brief description of the existing or planned COA, and the rationale for use in drug development.

1.2 Concept of Interest for meaningful treatment benefit

- Describe the meaningful aspect of patient experience that will represent the intended benefit of treatment (e.g., the specific symptom and/or sign presence or severity or limitations in performance or daily activities relevant in the targeted context of use)

1.3 Context of Use

- Identify the targeted study population, including a definition of the disease and selection criteria for clinical trials (e.g., baseline symptom severity, patient demographics, language/culture groups)
- Identify the targeted study design. Most commonly the COA will be used to assess the change (compared to a control) induced by a medical treatment
- Identify the targeted study objectives and endpoint positioning (i.e., planned set of primary and secondary endpoints with hierarchy). Usually, the COA will serve as a primary or secondary study endpoint measure

1.4 Critical details of the measure to the degree known

- Reporter, if applicable
- Item content or description of the measure
- Mode of administration (i.e., self-administered, interview-administered)
- Data collection method

1.5 Description of the involvement of external expertise, including scientific communities or other international regulatory agencies, if applicable (i.e., working group, consortia)

Section 2: Executive Summary

- High-level summary of what is included in the qualification plan and results to be described in the sections below

Section 3: Qualitative Evidence and Draft Conceptual Framework

- Evidence of content validity (i.e., documentation that the COA measures the concept of interest in the context of use)

3.1 Literature review
3.3 Expert input
3.3 Reporter input (e.g., for PRO measures, concept elicitation, focus groups, or in-depth qualitative interviews to generate items, select response options, recall period, and finalize item content; for PerfO measures, evidence to support that the tasks being performed are representative of the meaningful health aspect of the concept of interest and are relevant to ability to function in day-to-day life)
3.4 Concept elicitation
3.5 Item generation
3.6 Cognitive interviews
3.7 Draft Conceptual Framework

Section 4, 5, and 6: Proposed Quantitative Analysis Plan

Section 4: Cross-sectional evaluation of measurement properties

4.1 Item Level Description
- 4.1.1 Item descriptive statistics including frequency distribution of both item response and overall scores, floor and ceiling effect, and percentage of missing response
- 4.1.2 Inter-item relationships and dimensionality analysis (e.g., factor analysis or principal component analysis and evaluation of conceptual framework)
- 4.1.3 Item inclusion and reduction decision, identification of subscales (if any), and modification to conceptual framework

4.2 Preliminary scoring algorithm (e.g., include information about evaluation of measurement model assumptions, applicable goodness-of-fit statistics). The scoring algorithm should also include how missing data will be handled.

4.3 Reliability
- 4.3.1 Test-retest (e.g., intra-class correlation coefficient)
- 4.3.2 Internal consistency (e.g., Cronbach's alpha)
- 4.3.3 Inter-rater (e.g., kappa coefficient)

4.4 Construct validity
- 4.4.1 Convergent and discriminant validity (e.g., association with other instruments assessing similar concepts)
- 4.4.2 Known groups validity (e.g., difference in scores between subgroups of subjects with known status)

4.5 Score reliability in the presence of missing item-level and if applicable scale-level data
4.6 Copy of instrument, conceptual framework, provisional scoring algorithm
4.7 User manual and plans for further revision and refinement
- 4.7.1 Administration procedures
- 4.7.2 Training administration
- 4.7.3 Scoring and interpretation procedures

Section 5: Longitudinal evaluation of measurement properties (If Known)
5.1 Ability to detect change

Section 6: Interpretation of Score (If Known)
6.1 Evaluation and definition of meaningful within person change (improvement and worsening)

Section 7: Language translation and cultural adaptation (If Applicable)
7.1 Process for simultaneous development of versions in multiple languages or cultures
7.2 Process of translation/adaptation of original version
7.3 Evidence that content validity is similar for versions in multiple languages

Section 8: Questions to CDER

Section 9: References

- References and copies of the most important references that the submitter feels CDER reviewers may want to review.

Section 10: Appendices and Attachments

- Study documents (e.g., protocols, analysis plan, interview guide, data collection form(s)).