DDT COA #000104 **REQUEST FOR QUALIFICATION PLAN**

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Regarding: pDDT #2018-04 Letter of Intent for Qualification of the Duchenne Video Assessment

Dear Ms. Leffler:

We have completed our review of the letter of intent (LOI) submission for DDT COA #000104 received on October 24, 2018, by CDER's Clinical Outcome Assessment (COA) Qualification Program.

The submission included an LOI for the Duchenne Video Assessment (DVA), a clinician-reported outcome (ClinRO), proposed for the assessment of quality of movement in Duchenne muscular dystrophy (DMD) patients who are ambulatory and at least 4 years old. Following a review of your submission, we agree to enter the DVA tool into the COA Qualification Program given its potential for capturing data that might reflect real-world functioning and complement clinic-based assessments in DMD patients. The tracking number for this project has been assigned to DDT COA #000104. Please refer to DDT COA #000104 in all future communications.

Please find below our comments in response to the questions included in your submission:

Question 1: *Does CDER agree with the Concept of Interest being proposed?*

Response:

We agree, in principle, that movement is an important concept in patients with DMD. Information linking the measurement to patients' ability to perform daily activities should be developed. You should consider also assessing additional concepts representing potential areas of concern for patients with DMD. For example, do patients consider time to perform a motor task important? You should conduct concept elicitation interviews with patients with DMD to understand what aspects of movement are important to them. Overall, these concepts should represent clinically meaningful concepts that are distinct, clearly defined, and non-overlapping.

Question 2: *Does CDER agree with the Context of Use for this outcome measure?*

Response:

We agree with your context of use in ambulatory DMD patients age 4 years and above. However, your study protocol lower age bound is 7 years. It is unclear why patients ages 4-6 years are excluded from the study. We recommend broadening the eligibility criteria for the study to include patients ages 4 years and above and ensuring adequate sampling of this age range in the study. We note and encourage your plan to expand the context of use to non-ambulatory DMD patients as it has the potential to fill a measurement gap in patients with DMD.

Question 3: *Will our proposed studies be sufficient to demonstrate the content validity of this assessment?*

Response:

No, your proposed studies are not sufficient to demonstrate the content validity of the instrument for your target population. To further assess the content validity of the DVA tool, we recommend carrying out a qualitative study in which you conduct concept elicitation (i.e., open-ended questioning) in DMD patients and examine what constitutes clinically relevant and important concepts to them and what would be meaningful change. This will contribute to evidence in support of the content relevance of your proposed tool.

Question 4: *Will this outcome measure be accepted into the CDER qualification program?*

Response:

We agree to enter the DVA tool into the COA Qualification Program. We have provided additional comments below in addition to our responses to Questions 1-3 on ways to improve the DVA tool.

Additional Programmatic Comments

- We recommend that you evaluate the measurement properties and performance of the DVA tool (i.e., floor and ceiling effects, internal consistency reliability, test-retest reliability, convergent and divergent validity, known-groups validity, and potential responsiveness) in a well-conducted study that includes a sample of patients greater than 4 years of age.
- Please provide details of your proposed scoring algorithm. Items should be scored in a manner such that any score change (both improvement and decline) clearly reflects a clinically meaningful change in DMD patients' ability to perform their daily activities (e.g., mobility, activities of daily living, personal hygiene tasks).
- You should consider the use of patient reported outcome (PRO) measures and other clinical outcome assessments to complement other measures that you plan to develop to provide the patient and caregiver perspective as well as help to assess meaningful change among affected patients. We recommend inclusion of existing clinic-based assessments currently used in studies in DMD patients to evaluate the relationship with existing measures.
- When you move forward with expanding your population to non-ambulatory DMD patients, you should consider including a clinically meaningful assessment of upper extremity performance outcome measures in order to best capture the proposed concepts of interest and clinical benefit in non-ambulatory DMD patients.
- Please provide details on how you propose to standardize video recording.

Additional Comments on the Mobile Software Platform

- While you have completed some usability testing, you may want to consider performing additional usability testing to demonstrate that the tool can be used by the intended users without serious use errors or problems for the intended uses and under the expected use conditions. The testing should be comprehensive in scope, adequately sensitive to capture use errors caused by the design of the user interface, and should be performed such that the results can be generalized to actual use. The usability validation testing should be designed to include:

    - Test participants that represent the intended (actual) users of the tool
    - All critical tasks that are performed during the test
    - The device user interface that represents the final design
    - Test conditions that are sufficiently realistic to represent actual use conditions
    - To the extent practicable, the content, format, and method of delivery of training given to test participants should be comparable to the training that actual users would receive

- Reliability of the tool should be demonstrated to ensure the DVA mobile software technology may be used correctly and consistently by an intended user and across all intended users (i.e., repeatability and reproducibility). You should consider how your software application tool may be used reliably by all intended mobile platforms (e.g., Android, iOS), including different models (e.g., various Samsung Galaxy models, various Apple iPhone models) and operating system updates (e.g., various versions of Android and iOS). Variations of the mobile platform may influence the quality of video captured as well as influence the necessary training and labeling material required to adequately use the tool. For example, the mobile platform variations may influence the lighting required, the field of view captured by the camera, and internet/network connections needed to transmit data. You should also consider all the potential environments the tool may be used in and demonstrate the tool (as well as the training and labeling material) adequately accounts for the environmental variations (e.g., indoor, outdoors).

- The interoperability of the DVA tool and mobile software technology should be demonstrated to ensure the video assessment can be used safely and securely, and that is can effectively exchange and use information across all platforms and products connected in and across the tool's systems. Some examples you should consider include:

    - Verify and validate that when data is corrupted it can be detected and appropriately managed
    - Implement a fault-tolerant design and verify its performance
    - Verify only authorized users are allowed to exchange information with the interoperable tool
    - Assure that any reasonably foreseeable interactions do not cause incorrect operation of other networked systems

- The tool's internet- and network-connected design should account for cybersecurity risks. To ensure the tool is a trustworthy platform, the following examples should be considered when developing the mobile software application:

    - Prevent unauthorized use
    - Ensure trusted content by maintaining code, data, and execution integrity
    - Maintain confidentiality of data
    - Design the tool to detect cybersecurity events in a timely fashion

- Design the tool to respond to and contain the impact of a potential cybersecurity incident
- Design the tool to recover capabilities or services that were impaired due to a cybersecurity threat
- Informing users of relevant security information (e.g., use of a VPN, backup and restore features)

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 #000104.

Sincerely,

Elektra J. Papadopoulos -S

Digitally signed by Elektra J. Papadopoulos -S
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Billy Dunn, MD
Director
Division of Neurology Products
Office of New Drugs
Center for Drug Evaluation and Research

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 as well as any appendices or attachments referred to in those sections. Section 507 refers 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
3.2 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

Sections 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
4.1.1 Inter-item relationships and dimensionality analysis (e.g., factor analysis or principal component analysis and evaluation of conceptual framework)
4.1.2 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. Please number references.

Section 10: Appendices

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