DDT #000103

REQUEST FOR QUALIFICATION PLAN

David Vissière:
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david.vissiere@sysnav.fr

Dear Mr. Vissière:

We have completed our review of the Letter of Intent (LOI) submission for DDT #000103 dated September 15, 2017, and received on September 21, 2017, by the Clinical Outcome Assessments (COA) Qualification Program.

You have proposed the development of an accelerometry-based measure to evaluate stride length, stride velocity, and distance walked in pediatric patients (≥ 5 years old) with Duchenne muscular dystrophy (DMD). We agree to enter this LOI into the COA Qualification Program given the unmet medical need and the potential utility of capturing patients' movement data in their uncontrolled natural environment.

Over the course of clinical outcome assessment development, specific details related to the qualification (e.g., concepts of interest, context of use) are likely to evolve over time. As there are still issues that need further clarification, we cannot agree to specifics until you have provided detailed materials for review and comment. We also note that the goal of the COA Qualification Program is to qualify outcome assessments that are judged to be fit-for-purpose for use as study endpoints in clinical studies for drug development. Specifically, our focus is the qualification of outcome measures; in this case, they are stride length, stride velocity, and distance walked. Note that our focus is not the device (i.e., ActiMyo) that is used to capture the aforementioned outcome measures.

The Qualification Review Team (QRT) has the following comments and recommendations at this time:

- Please clarify the exact study endpoint that you are proposing to qualify for use in clinical trial to support drug development. Specifically, please clarify whether the study endpoint will be one of the three variables (i.e., stride length, stride velocity, or distance walked per hour). We recommend that you collect patient or caregiver input to determine which of the three variables is most important to the patients regarding their walking ability to perform their activities of daily living.
- Please provide clinical interpretation of each of the three variables (stride length, stride velocity, and the distance walked per hour) and their associated measurement (median and 95th percentile). Specifically, please clarify whether the three variables provide supplemental information to each other in evaluating a patient's walking ability, as they do not appear independent and are likely derived from each other or from the same data.

- Please clarify whether your proposed context-of-use includes non-ambulatory patients. If non-ambulatory patients are included, please clarify the outcome measures (i.e., variables) and how they will be assessed for these patients.
- We are concerned that the dimensions and weight of the sensors used in your device may impede the patients' movement and/or compliance, especially in younger children. We recommend that you consider further reducing the dimension and weight of the sensors.
- Your recommendation of an acceptable minimal amount of time that the device should be worn in a study to obtain an acceptable variability in its measurements was not established on a mathematical basis, nor did your recommendation take into consideration how the variability would relate to meaningful treatment change. We recommend that you conduct more analysis and provide detailed information on any recommended minimum time that the device should be worn.
- Please provide information regarding the interpretation of the three variables and their change over time. Specifically, please provide information regarding the values or the amount of the changes of the three variables that may be considered a meaningful improvement or worsening of leg movement that impacts patients' daily function and activities. Your proposed minimally clinically important differences based on the standard deviation provides only supportive information as it does not directly convey the interpretation of meaningfulness (e.g., whether a 1.8 centimeter change in median stride length is a meaningful change to the patients).

Regarding the specification of the technical aspects of your device, please provide the following information for us to determine that the device produces a valid and reliable measurement in its intended use:

- An adequate description of the device's measurements (sensors), processing algorithm, and outputs.
- Test-retest reliability (precision) information to demonstrate that the device can reproduce the same measurement under the same conditions. For example, you could compare the results on consecutive days using the same task (e.g., 50-meter walk test) in a representative sample of patients.
- A detailed justification of the estimate of a turn radius of 0.6 meters.

Consider requesting a meeting with the QRT prior to moving forward with developing your Qualification Plan (Refer to Appendix 1):

- Develop and submit a draft version of your COA Qualification Plan. We acknowledge that the Qualification Plan does not need to be in final form; however, a draft version can be helpful to facilitate initial FDA review before proceeding forward with cognitive interviews and other development work.

If you have any questions, please contact the COA Staff at COADDTQualification@fda.hhs.gov. Please refer to DDT #000103.

Sincerely,

Elektra J. Papadopoulos -S

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Elektra Papadopoulos, MD, MPH
Associate Director
Clinical Outcome Assessments Staff
Office of New Drugs
Center for Drug Evaluation and Research

William Dunn -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.

Note: Sections 1 and 2 will be posted publicly under Section 507 of the FD&C 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

2.0 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

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

3.2 Literature review

3.3 Expert input

3.4 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)

3.5 Concept elicitation

3.6 Item generation

3.7 Cognitive interviews

3.8 Draft Conceptual Framework

Section 4 and 5: Proposed Quantitative Analysis Plan

4.1 Cross-sectional evaluation of measurement properties

4.2 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

5.0 Longitudinal evaluation of measurement properties (If Known)

5.1 Ability to detect change

5.2 Evaluation of individual patient change

6.0 Language translation and cultural adaptation (If Applicable)

6.1 Process for simultaneous development of versions in multiple languages or cultures

6.2 Process of translation/adaptation of original version

6.3 Evidence that content validity is similar for versions in multiple languages

7.0 Questions to CDER

8.1 Appendices

- References and copies of the most important references that the submitter feels CDER reviewers may want to review
- Study documents (e.g., protocols, analysis plan, interview guide, data collection form(s))