DDT# 000102

REQUEST FOR QUALIFICATION PLAN

May 10, 2018

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Dear Dr. Patel,

We have completed our review of the Letter of Intent (LOI) submission for DDT COA #2017-006 dated December 14, 2017.

You have proposed to develop an accelerometry-based clinical outcome assessment (COA) to evaluate physical activity related in non-cognitively impaired adults with osteoarthritis of the knee with a WOMAC pain rating of ≥ 4. We agree to enter this project into CDER's COA Qualification Program. The tracking number for this project has been reassigned to DDT# 000102. Please refer to DDT# 102 in all future communication

Over the course of instrument development, specific details related to the qualification (e.g., concepts of interest, context of use) are likely to evolve over time. We strongly encourage you to request a meeting with the Qualification Review Team (QRT) following completion of your literature review, concept elicitation qualitative interviews with patients, and experts input prior to proceeding forward with cognitive interview study.

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

Question 1: What are the COA's timeframes for reviewing the LOI, Qualification Plan, and Full Qualification Package?

As we continue to implement the qualification program under 21st Century Cures, we are reviewing and determining what would be reasonable timeframes for review for each milestone. We anticipate that for a LOI, the review timeline would be approximately 4 months, for a Qualification Package it would be approximately 8-10 months and for a Full Qualification Package it would be approximately 10 months. Please note that:
1. The timeframe does not begin unless it is determined that the submission is complete and reviewable, and
2. These timelines are goals and the actual response could be sooner or later depending on the complexity of the submission.

If you would like, we can set up teleconference with you to discuss the qualification process under 21st Century Cures.

We recommend that you take into consideration the following as you continue your development:

- 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. Provide information about the accelerometer, such as size and weight of the accelerometer.
- Provide further detail about how the accelerometer will be used (e.g., on hip, wrist, or both) and the instructions for use.

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

- Adequately describe the device's algorithm, including all inputs and outputs with a description of how the raw data are processed (such as with a flow chart) to calculate the features/outcomes reported by the device.
- Clearly define what measurements the device will report. For example, when they state "walking," it is currently unclear whether they would intend to report – time spent walking, walking distance, stride velocity or length, etc.
    - Each measurement that is reported by the tool 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.
- Demonstrate that the tool is capable of collecting data that are sufficiently precise for its intended use. The tool should assess the precision of its measurements in relation to reasonably expected (clinically-meaningful) differences in patient outcomes.
- Demonstrate that the variability of performance between devices are acceptable.
- Assess the effect of differences in placement (because the device is a wearable) to show that the tool's measurements are sufficiently insensitive to the reasonably-expected differences in device placement, or a valid rationale should be provided as to why placement would not affect the device's measurements.

Please contact the COA Staff via email at COADDTQualification@fda.hhs.gov should you have any questions regarding the next milestone. Please refer to DDT #000102.

Sincerely,

Elektra J. Papadopoulos -S
Digitally signed by Elektra J. Papadopoulos -S
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Date: 2018.05.31 13:39:04 -04'00'

Sharon H. Hertz -S
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Date: 2018.05.24 13:15:34 -04'00'

Elektra Papadopoulos, MD, MPH
Associate Director
Clinical Outcome Assessments Staff
Office of New Drugs
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Sharon Hertz, MD
Director
Division of Anesthesia, Analgesia and Addiction Products
Office of New Drugs
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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.

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)
- Provide a hypothesized conceptual framework for the outcome assessment(s)

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.

1.4 Critical details of the measure to the degree known

- Reporter, if applicable
- Item content or description of the measure
- Mode of administration
-Data collection method build on the letter of intent outline at the q2-4

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: Qualitative Evidence

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

2.2 Literature review
2.3 Concept elicitation
2.4 Item generation
2.5 Cognitive interviews
2.6 Draft Conceptual Framework

3.0: Proposed Quantitative Analysis Plan

3.1 Cross-sectional evaluation of measurement properties

3.1 Item Level Description

3.1.1 Item descriptive statistics including frequency distribution of both item response and overall scores, floor and ceiling effect, and percentage of missing response

3.1.2 Inter-item relationships and dimensionality analysis (e.g., factor analysis or principal component analysis and evaluation of conceptual framework)

3.1.3 Item inclusion and reduction decision, identification of subscales (if any), and modification to conceptual framework

3.2 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.

3.3 Reliability

3.3.1 Test-retest(e.g., intra-class correlation coefficient)

3.3.2 Internal consistency (e.g. Cronbach's alpha)

3.3.3 Inter-rater (e.g. kappa coefficient)

3.4 Construct validity

3.4.1 Convergent and discriminant validity (e.g., association with other instruments assessing similar concepts)

3.4.2 Known groups validity (e.g., difference in scores between subgroups of subjects with known status)

3.5 Score reliability in the presence of missing item-level and if applicable scale-level data

3.6 Copy of instrument, conceptual framework, provisional scoring algorithm

3.7 User manual and plans for further revision and refinement

3.7.1 administration procedures

3.7.2 Training administration

4.0 Longitudinal evaluation of measurement properties (If Known)

4.1 Ability to detect change

4.2 Evaluation of individual patient change

5.0 Language translation and cultural adaptation (If Applicable)

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

5.2 Process of translation/adaptation of original version

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

6.0 Questions for CDER

7.1 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))