DDT COA #000112 **REQUEST FOR QUALIFICATION PLAN**

Stephen Joel Coons, PhD
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Critical Path Institute
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sjcoons@c-path.org

Dear Dr. Coons:

We have completed our review of your December 21, 2018 letter of intent (LOI) submission for **Chronic Heart Failure-Symptom Scale (CHF-SS)**, DDT COA #000112.

You have proposed to develop a patient-reported outcome (PRO) instrument to evaluate chronic heart failure (CHF) symptoms in CHF patients. At this time, we agree to enter this LOI into the COA Qualification Program given the unmet drug development need for instruments for this context of use. The tracking number for this project has been reassigned to DDT COA #000112. Please refer to DDT COA #000112 in all future communications.

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 acknowledge your thorough summary of instrument development activities for the CHF-SS under Amgen's drug development program and agree you are moving in the right direction. However, as limited information was provided, we cannot agree to specifics until you have provided detailed materials for review and comment.

Please see the following general comments that will help further prepare the instrument for qualification.

1. We request that you provide source materials (i.e., qualitative study reports) for all relevant studies outlined in the IBP (i.e., evidence submitted to the IND for Amgen's drug development program, including what was summarized in Wiklund et al., 2016) for review in order to help establish the content validity of the CHF-SS domains. We recommend you request a meeting with the qualification review team (QRT) before implementing your cognitive interview study.

2. We have the following comments regarding your cognitive interview protocol:
    a. Your LOI includes a 9-item version of the CHF-SS while the cognitive interview protocol includes a 10-item version with a patient global impression of severity item. Please clarify which version of the CHF-SS you will continue to develop.

i. If you plan to move forward with the 10-item version, please clarify the purpose for including both the CHF-SS global item and the Patient Global Rating of Severity – Symptoms (PGRS-XS) item.

3. If supported by the qualitative research, we encourage you to consider providing separate questions for swelling symptom locations (e.g., swelling in the feet, ankles or legs) in Question 6, as they appear to represent different levels of swelling severity and might improve precision in measurement.

4. The CHF-SS item stems don't specify what aspect of symptom severity (e.g., worst, on average, overall symptoms) patients should report on over a 7-day period. Please provide the rationale for this approach.

Appended is an outline of the contents to include in the next milestone submission (qualification plan). Please contact the COA Staff at COADDTQualification@fda.hhs.gov if you have any questions. Please refer to DDT COA #000112.

Sincerely,

Elektra J. Papadopoulos -S

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Date: 2019.04.29 12:46:14 -04'00'

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Norman Stockbridge, MD, PhD
Director
Division of Cardiovascular and Renal Products
Office of New Drugs
Center for Drug Evaluation and Research

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 (for existing instruments, the specific version of the instrument and copy of the tool from which quantitative evidence has been or will be derived)
- 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 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 (for existing instruments, the final version 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

4.1.2 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., intraclass 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

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))

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