DDT COA #000115 **REQUEST FOR QUALIFICATION PLAN**

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Dear Dr. Domingo,

We have completed our review of the letter of intent (LOI) submission dated March 30, 2019 and received on April 3, 2019 by CDER's Clinical Outcome Assessments (COA) Qualification Program.

You have proposed to develop a performance outcome (PerfO) assessment to evaluate cognitive impairment in patients with schizophrenia. At this time, we agree to enter this LOI into the COA Qualification Program given the unmet medical need and lack of fit-for-purpose PerfO measures in patients with schizophrenia. The tracking number for this project has been reassigned to DDT COA #000115. Please refer to DDT COA #000115 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. As limited information was provided related to concepts of interest and context of use, we cannot agree to specifics until you have provided detailed materials for review and comment.

The Qualification Review Team's (QRT's) responses to the questions included in the submission can be found below:

Question 1: *We would like to know what steps remain and what documentation we should to submit to FDA in order to have the Qualification of a COA for clinical trials in CIAS for primary outcome.*

We know that some research is still pending to clarify the psychometric validity for its use in clinical trials for CIAS, however this could be done in US directly. We acknowledge that to be a COA for Clinical Trials some psychometric properties that are still pending to be confirmed:

- *Generate alternative equivalent versions (at least 1 or 2 additional, one for screening and another one for interim evaluations when study visits are just few weeks a part).*
- *Confirm test-retest stability of subtests and composite scores at short time periods.*
- *Ascertain the sensitivity to change of Composite Scores.*
- *Explore its utility as a safety measure for cognitive health in clinical trials for INDs for schizophrenia.*
- *Calibrate algorithm for FWCS in US population.*

We will appreciate your advise to became a full qualified COA for new study drug protocols for CIAS indication.

> **QRT Response:** The next milestone in the DDT qualification process is to submit a Qualification Plan (QP). Refer to Appendix 1 of this letter for information regarding submission of a QP.

Question 2: *Given the fact that the subtests included in the new COA already exist, we would like to know to what extend it would be acceptable to re-use already completed studies to validate the battery for clinical trials in CIAS (assuming the use of FWCS as derived from Spanish data).*

> **QRT Response:** There is insufficient information for the QRT to provide a specific recommendation. You will need to submit detailed information regarding your proposal to use data from existing studies, including protocols for all studies that you propose to use data from, and your plan to adapt the FWCS (functional regression-weighted composite score) algorithm to the U.S. population. For each study that you propose to use data from, the study protocols should include detailed information regarding the study patient population, the inclusion/exclusion criteria, the study design (including study arms, assessment schedule, and duration), the study treatments, the study locations, and the exact versions of the subtests that are proposed in the EPICOG-SCH. Details of your plan to re-use the existing data using the FWCS as derived from the Spanish data should be provided. Your plan should also include how this existing data and Spanish FWCS will be used to develop the scoring for the U.S. population. Please also clarify whether you will be able to submit these existing data for FDA's analysis when requested.

The QRT has the following comments and recommendations:

1. Provide a detailed development history of how the subtests in EPICOG-SCH were selected.

    a. The subtests you have selected appear to be under copyright by Pearson. We recommend reviewing the licensing agreements associated with purchase and use of these subtests to determine whether there may be conditions or limitations regarding their use in this context. You may also consider contacting Pearson regarding your development of the EPICOG-SCH and your intention to qualify it.

    b. Please describe the reasons why older versions of subtests were selected (e.g., WAIS-III/WMS-III) when newer versions are available (e.g., WAIS-IV/WMS-IV). We are concerned that qualifying a DDT that uses older versions of instruments may limit its utility as the content and scoring may be obsolete, or it may limit access to the DDT (i.e., it may be difficult for end-users to obtain older versions of subtests when they become unavailable on the market). Please provide your rationale that this will not be an issue for EPICOG-SCH; or, if it is an issue, please clarify whether you plan to modify the EPICOG-SCH (particularly, the FWCS), using the most up-to-date versions of the subtests.

2. Provide evidence of content validity of the EPICOG-SCH that demonstrates that the selected subtests assess cognitive functions that are relevant and important to patients with schizophrenia. In addition, provide evidence that no other important cognitive functions are omitted.

3. Please provide a detailed explanation of how the FWCS was developed and how it is used.

    a. You state that the FWCS is a predictor of functional outcomes (i.e., a patient's potential to live independently). However, it appears that the FWCS was derived using cross-sectional data. Longitudinal data are needed to demonstrate whether FWCS is predictive of future outcomes.

        i. Without longitudinal data and substantial evidence to support this concept of interest and context of use, qualification of your proposed EPICOG-SCH may be limited to measurement of cognitive function in patients with schizophrenia with stable disease (i.e., it may not be qualified for use as a COA that predicts future ability of independent living).

    b. You propose the FWCS as a primary and secondary endpoint measure, but your proposed clinical trial inclusion criteria require patients to have stable schizophrenia symptomatology and a stable living situation for ≥ 3 months prior to screening. In patients with schizophrenia, worsening of cognitive symptoms leading to inability to live independently is not expected to occur rapidly. That is, patients may maintain their independence for a long period of time such that the FWCS is not able to either show improving or worsening of independent living. We recommend that you further clarify how FWCS will be used as study endpoint in clinical trials for the purpose of drug development.

    c. You will need to provide evidence to justify interpretation of the FWCS (e.g., proposed cut-off scores).

4. To support that EPICOG-SCH assesses cognitive function in patients with schizophrenia, it is necessary for you to provide evidence that it produces the same (or similar) results as other existing instruments when used in the same context. If you intend to claim that EPICOG-SCH can be an alternative to more comprehensive instruments such as the MATRICS Consensus Cognitive Battery (MCCB), then it is necessary for you to provide evidence to demonstrate that EPICOG-SCH produces the same (or similar) results as MCCB when used in the same context.

5. We strongly recommend collaborating with other investigators and outcome measures developers to facilitate successful qualification of your proposed COA. Submitters seeking DDT Qualification generally represent multidisciplinary consortia with a variety of resources and expertise that can be leveraged throughout the qualification process. Certain necessary components of the qualification process, such as validation of your proposed COA in the U.S. population, will benefit from formal collaborative partnerships with stakeholder organizations in the U.S.

Appendix 1 of this letter contains the contents to include in your submission to reach the next milestone. Please contact CDER's COA Qualification Program at COADDTQualification@fda.hhs.gov should you have any questions (refer to DDT COA #000115).

Sincerely,

Elektra J. Papadopoulos -S

Digitally signed by Elektra J. Papadopoulos -S
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Elektra Papadopoulos, MD, MPH
Associate Director
Clinical Outcome Assessments Staff
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Tiffany Farchione, MD
Director (Acting)
Division of Psychiatry 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 (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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