DDT COA #000107 **REQUEST FOR QUALIFICATION PLAN**

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Dear Dr. Keefe,

We have completed our review of the letter of intent (LOI) submission for pDDT COA 2018-03 received on October 5, 2018.

You have proposed to develop the Virtual Reality Functional Capacity Assessment Tool (VRFCAT), a performance outcome (PerfO) clinical outcome assessment (COA) to evaluate functional capacity in patients with schizophrenia. At this time, we agree to enter this letter of intent into the COA Qualification Program given the unmet medical need and lack of fit-for-purpose PerfO measures assessing cognitive function in patients with schizophrenia. The tracking number for this project has been assigned as DDT COA #000107. Please refer to DDT COA #000107 in all future communications.

The next step of the qualification process is for you to submit a qualification plan. This plan should contain the results of completed qualitative research and the proposed quantitative research plan (please see Appendix 1). During our review of your letter of intent, we concluded that insufficient information was provided related to the concept of interest and context of use. At this time, we cannot agree to specifics of the concept of interest and context of use until you have provided additional detailed materials for review and comment. We encourage you to request a meeting with the qualification review team (QRT) prior to developing your qualification plan.

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

Question 1:
As described above, the cognitive and functional capacity performance of patients with schizophrenia is largely stable over time. Therefore, there is little opportunity to track the clinical fluctuations of cognition and VRFCAT performance over time. Also, there are no approved drugs to treat cognitive impairment in schizophrenia. Given these characteristics of the longitudinal course of deficits in patients with schizophrenia, the MATRICS experts utilized standards for measures of cognition and functional capacity

that did not include sensitivity to treatment. Would it be possible to use the same standards used for the endorsement of the VRFCAT that were used for the MCCB? It is clear that with no drug known to improve cognition, sensitivity to treatment is not a currently viable standard.

QRT Response:

Helpful information for development of a PerfO measure can be found in the relevant published FDA Guidance (Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims (www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm193282.pdf)) and the paper "Developing and Implementing Performance Outcome Assessments: Evidentiary, Methodologic, and Operational Considerations"(Richardson E, Burnell J, Adams HR, Bohannon RW, Bush EN, Campbell M, Chen WH, Coons SJ, Papadopoulos E, Reeve BR, Rooks D, Daniel G. Developing and Implementing Performance Outcome Assessments: Evidentiary, Methodologic, and Operational Considerations. *Ther Innov Regul Sci*. 2018 Jan 1:2168479018772569. doi: 10.1177/2168479018772569).

FDA is open to reviewing evidence from clinical outcome assessments that measure cognitive domains of relevance and importance in patients with schizophrenia for the purposes of drug development. The qualification of VRFCAT, or any other clinical outcome assessment for use in drug development, will be based on the evidence that you submit for our review. We cannot determine if a medical product can improve cognition unless we have a sensitive tool; however, we note that a tool can be evaluated for sensitivity to change as long as longitudinal data is available and some patients have experienced changes regardless whether the changes are due to treatment or not.

Question 2:

This letter of intent highlights the existing evidence for the reliability and validity of the VRFCAT and the significant unmet need that the measure addresses. If the VRFCAT is accepted into the qualification program, would it be possible to move directly to the "Full Qualification Package" (Stage 3) step in the process, rather than first submitting a "Qualification Plan" (Stage 2)? We acknowledge that the available cross-sectional evidence would support qualification for exploratory use until data are available regarding the measure's longitudinal measurement characteristics. We assume that qualification for exploratory use would not prohibit the use of the measure as a primary endpoint in specific product development programs.

QRT Response:

The qualification process and stages as outlined in Section 507 of the FD&C Act do not allow for skipping or bypassing of the stages. Submitters have to follow the process as described in Section 507 of the FD&C Act. Please visit our website www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm593211.htm to see what information needs to be included in the qualification plan and the full qualification package.

The QRT also has the following comments and recommendations:

- Your proposed target population is very broad; i.e., people with schizophrenia rather than a subset of people with schizophrenia (such as people with schizophrenia who are not disorganized and who have stable psychotic symptoms). At this time, we cannot agree that this drug development tool will be appropriate for such a broad patient population. Ultimately, it will be based on the submitted evidence and the population studied. We recommend close communications with the Agency in refining the patient population(s).
- Your concept of interest is capturing improvements in functional capacity in relation to cognitive improvement. We recommend that you clearly define what is functional capacity and cognitive function. We also recommend that you clarify in describing how you identified the functional capacity that each of the VRFCAT task is assessing, and how you identified the cognitive function that each of the functional capacity is demonstrating. For example, it is unclear how task #7 represents working memory as opposed to the mathematical skills of the patient.
- In your letter of intent, you have presented data on correlations between each of the objectives in VRFCAT and the MCCB composite score, we suggest that you draw correlations between each objective and the corresponding domain in MCCB to better explain its relation to the appropriate cognitive function.
- As you develop your qualification plan, please make sure to describe how the VRFCAT was developed and if patient input was obtained during development.
- We are concerned that only tasks #3 and #9 showed separation in average number of errors made and average time to completion used between patients with schizophrenia and healthy subjects. The other tasks were not able to differentiate the two groups. This can attenuate the sensitivity of VRFCAT's ability to detect change. Please provide a rationale for retaining the items that do not differentiate between groups and may not be sensitive to change for purposes of scoring. Also, comment on whether you intend to develop new items that may better reflect the specific cognitive domains of importance that differ between patients with schizophrenia and healthy subjects.
- Please clarify how you plan to analyze the data in your qualification plan and justify the chosen time frame of 5 minutes (300s) to complete each task/objective. Please note that implementation of forced progressions at 300s will automatically create an arbitrary ceiling effect.
    - Additionally, according to table 2 in your LOI, 22 patients with schizophrenia for task #3 and 13 patients with schizophrenia for task #9 had undergone forced progressions. Please clarify if failure to complete a task within 300s had created any stress or frustration for patients in the past, as this could interfere with cognitive performance and ability to detect change.

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 #000107.

Sincerely,

Elektra J. Papadopoulos -S

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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. 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

4.1.2 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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