Clinical Outcome Assessments (COA) Qualification Program
DDT COA #000107: Virtual Reality Functional Capacity Assessment Tool (VRFCAT)
Letter of Intent

Administrative Structure:

Description of the submitter including, but not limited to, principal investigator(s), working group member(s), institutions, and contact information not contained within the cover letter.

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Concept(s) of Interest (COI) for Meaningful Treatment Benefit:

A description of the meaningful aspect of patient experience that will represent the intended benefit of treatment (e.g., presence/severity of symptoms, limitations in performance of daily activities).

The treatment target for this Clinical Outcome Assessment (COA) is functional capacity, which refers to an individual's capacity for performing key tasks of daily living. To assess functional capacity, participants simulate in the clinic such real-world activities as handling finances, preparing a meal, shopping, taking public transportation, or holding a social conversation (Green et al, 2008; 2011; Harvey et al, 2007). Good performance on such measures does not mean that a person will perform the tasks in the community, but it does mean that the person could perform the task if he or she had the opportunity and was willing. Because performance on measures of functional capacity does not depend on social and community opportunities, they are more likely to be temporally linked with treatment-related changes in underlying cognition. Functional capacity has been shown in previous research to be related to impairments in everyday functioning in schizophrenia, which span employment, ability to live independently, and interpersonal functioning. Functional capacity measures have been recommended by the US FDA as co-primary outcome measures in clinical trials aimed at cognitive enhancement in schizophrenia. Functional capacity has been shown to be

intermediate between cognitive impairments and everyday outcomes in schizophrenia and to mediate the influence of cognitive deficits on functional outcomes (Harvey et al, 2009).

Provide a conceptual framework for the COA(s).

The COA has a series of 12 performance tasks that are performed in a fixed sequence. Each of the 12 task demands is related to specific cognitive processes as described in Table 1. These objectives are closely related to the main functional domains that are important in schizophrenia as previously defined by experts in the literature (Green et al, 2008; 2011; Harvey et al, 2007). Each task has a time to completion, an assessment of the number of errors, and a determination of whether the task was completed correctly or whether the participant was "progressed" to the next task demand ("forced progression"). The time to completion is the primary outcome. The framework for the number of errors is similar in that summing the scores from the individual items generates each domain. The forced progression domain is also derived using information from all items, but is a binary variable for each objective indicating whether or not forced progression occurred.

Table 1. VRFCAT list of objectives, cognitive domains and functional domains.

Mini Scenario		Objectives 1-12	Cognitive Domain	Functional Domain
Apartment	1.	Pick up the recipe on the counter	Visuospatial ability	Preparing for a meal
	2.	Search for ingredients in your cabinets and refrigerator	Visuospatial ability Executive Functioning	Preparing for a meal
	3.	Access your recipe and cross off the ingredients that you already have in your apartment	Verbal and Visual Memory, Working Memory	Preparing for a meal
	4.	Pick up the billfold on the counter	Visuospatial ability	Handling finances
	5.	Exit the apartment and head to the bus stop (Game Element)		Game element
Bus to Store	6.	Wait for the correct bus to the grocery store and then board it when it arrives	Attention, Verbal memory, Executive Functioning	Taking public transportation
	7.	Add up the exact amount of bus fare in your hand and pay for the bus	Working Memory	Taking public transportation and handling finances
Store	8.	Select a food aisle to begin shopping	Executive Functioning	Shopping
	9.	Continue shopping for the necessary food ingredients, and when finished check out	Attention Visuospatial ability, Visual Memory Verbal Memory, Executive Functioning	Shopping
	10.	Add up the exact amount for your purchase and pay for groceries	Working Memory	Shopping and handling finances
Bus to Apartment	11.	Wait for the correct bus to your apartment and then board it when it arrives	Attention, Verbal Memory, Executive Functionin	Taking transportation
	12.	Add up the exact amount of bus fare in your hand and pay for the bus	Working Memory	Taking transportation and handling finances

COU for COA Qualification:

Targeted study population including a definition of the disease and selection criteria for clinical trials (e.g., baseline symptom severity, patient demographics, comorbidities, language/culture groups)

This COA is targeted at schizophrenia patients. Also included would be patients with schizoaffective disorder. In terms of symptom severity, the MATRICS standards suggested that all patients with schizophrenia should be considered for participation in treatment trials because of the broad and global nature of cognitive deficits in this population. There were recommendations for a minimum duration of clinical stability and maximum levels of severity of both positive and negative symptoms of psychosis. These patients are the current target group for this COA. At this point in time, less information is available about cognitive enhancement and assessment standards in other psychotic disorders. Thus, the focus of the use of this COA will be limited to schizophrenia and schizoaffective disorders in this application.

There are no limitations on sex or racial or ethnic status in the MATRICS standards. Some previous studies using the MATRICS guidance have imposed upper age limits on studies, but we do not plan to do so and have normative data on a wide range of patients and healthy comparison subjects. Some studies have employed specific thresholds for years of education, but this approach may limit the generalizability of the use of the VRFCAT. Therefore, we will allow all education levels, but patients with pervasive developmental disability and those patients who appear not to understand the task instructions will be not be included.

The VRFCAT is being developed for languages, countries, and cultures beyond United States English. While the validation data for the VRFCAT and the extensive normative data that have been collected thus far are all in US English, we have developed versions of the VRFCAT for US Spanish, Russian, Polish, German, Spanish for Spain, UK English and Canadian English. These versions have been pilot-tested in all of these languages and countries and are currently being revised for use in large-scale validation studies.

***Targeted study design and statistical analysis plan (includes the role of the planned COA in future drug development clinical trials, including the planned set of primary and secondary endpoints with hierarchy, if appropriate*)**

The primary goal of the development of the VRFCAT is for use as a clinical outcomes measure in clinical trials. There are several different study designs employed in clinical trials targeting cognition in schizophrenia, but the gold standard is a randomized, placebo controlled, double blind clinical trial. There is nothing in the nature of the VRFCAT that would preclude its use in cross-over and single arm studies.

A variety of different dependent variables are collected with the VRFCAT, including total time to completion, number of errors made, and number of objectives that were never achieved in a fixed time period. The primary outcome measure for the VRFCAT is total time to completion of the total assessment scenario. This measure was selected on the basis of having the best psychometric properties as described below. Further, total errors and objectives achieved are to be used as secondary outcomes variables. The analysis plan for treatment outcomes studies with the VRFCAT would be to use the total time to completion of the assessment scenario as a

repeated-measures outcome across assessment time points, using previously validated alternate forms at each assessment. Secondary variables would be examined similarly.

Thus far, the development of these variables has included studies of the psychometric characteristics considered to be important for a clinical trials outcome measure: baseline and follow up distributional properties such as normality of primary outcome variables, and the presence of ceiling and floor effects. Critical to its role as a co-primary measure, convergent validity of the VRFCAT has been estimated with measures of cognition and everyday functioning, and discriminant validity has been assessed by an analysis of the overlap of VRFCAT measures with symptom measures such as severity of psychosis and affective symptoms. Key repeated-measures statistics such as test-retest reliability and practice effects have been determined. Further, as the COA has multiple alternate forms, similarity of the forms in terms of level of performance and validity indices has been examined. Finally, an NIH-sponsored study of the VRFCAT in a normative sample of 650 healthy controls matched to the United States census on age, education, race and sex has recently been completed. This study enables calculation of norm-based standardized scores for the primary and secondary outcomes measures.

In addition to these studies conducted on the psychometric characteristics of the VRFCAT, it has been included in ongoing industry-sponsored trials in schizophrenia, depression and older research participants with a high genetic risk for Alzheimer's disease. While not directly related to schizophrenia trials, the data from the major depression trial, as well as supportive psychometric data is available and can help to illuminate the feasibility of using the VRFCAT in a 40-site clinical trial. The data from the AD-risk study is not available yet.

Data from the ongoing 50-site double-blind schizophrenia treatment study is still being collected, so there are only preliminary blinded data available to conduct analyses on the psychometric characteristics of the VRFCAT in a multi-site schizophrenia clinical trial setting. However, this trial will provide critical information on the use of this COA in treatment studies. Cognitive performance is the primary outcome, but extensive data are being collected on clinical symptoms, which will allow for continued evaluation of the independence of the COA from other clinical features of schizophrenia. The study involves all of the characteristics of a suitable treatment-sensitivity study, with alternate forms of the VRFCAT administered at repeated assessments of cognitive performance.

Applicable study settings for future clinical trials

- ***Geographic location with language/culture groups***

The multinational similarities in the prevalence and nature of schizophrenia symptoms has led to worldwide clinical trial efforts. Thus, the COA in development has different versions designed for use in different countries, including modifications in the central tasks, the methods of transportation, and regional variation in shopping strategies, in addition to modifications of the language of the instructions and the stimulus materials. These multinational considerations are central to the development plan.

Further, consideration of worldwide differences in educational standards and access to

technology is central to the development plan. This includes using instructions that are equivalent to the US 4th grade reading levels and an embedded tutorial that includes orientation to the technology prior to assessment.

- ***Other study setting specifics (e.g., inpatient versus outpatient)***

Due to the severity of psychotic symptoms that often accompany inpatient stays for patients with schizophrenia, the kinds of cognitive enhancement and disability reduction studies for which the VRFCAT is designed have almost exclusively been conducted in outpatient settings. However, there is considerable variation in the potential participant samples. Younger first episode patients are a priority treatment target for cognitive enhancement studies, and a recent academic study has used the VRFCAT successfully in a first episode sample (Ventura et al, 2018), which demonstrated that first episode patients are impaired on the VRFCAT, and that their impairment is robustly correlated with all measures of real-world functioning assessed, including role functioning, social functioning, work functioning, and independent living. In contrast to previous paper and pencil functional capacity measures, the VRFCAT is solidly based in skills that are applicable to younger patients as well as older ones.

COA Type: Performance Outcome (PerfO)

The VRFCAT is a performance-based outcome (PerfO) that does not require self-report on the part of the patient-participants and requires no ratings or judgments regarding clinical symptoms or functional abilities.

References:

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