



# **Development and qualification of the Virtual Reality Functional Capacity Assessment Tool-Short List for early Alzheimer's disease**

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- Virtual Reality Functional Capacity Assessment Tool-Short List is owned by Clario.

# Background

- Critical Path Institute (C-Path)
  - Established in 2005 by the University of Arizona and the U.S. Food and Drug Administration (FDA)
  - An independent, non-profit organization
    - Dedicated to implementing FDA's Critical Path Initiative
    - Enables pre-competitive collaboration that includes regulatory input/expertise
- Patient-Centered Evidence (PCE) Consortium (formerly PRO Consortium)
  - Formed in late 2008 by C-Path in cooperation with FDA's CDER and the pharmaceutical industry to facilitate pre-competitive collaboration between sponsors and FDA
  - Membership: 25 pharmaceutical firms
  - Part of C-Path's Clinical Outcome Assessment (COA) Program

# Overview

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- FDA's Clinical Outcome Assessment Qualification Program
- PCE Consortium's experience with qualification
- Cognition Working Group's history
- Virtual Reality Functional Capacity Assessment Tool-Short List for early Alzheimer's disease: evidence generation for qualification

# Goal of Working Groups: Qualification by FDA

To produce and/or compile the necessary evidence to enable new or existing COAs to be qualified by FDA for use in clinical trials where COA-based endpoints can be used to support product labeling claims.

Intent: To expedite development of publicly available COAs that can be widely used in drug development

FDA's definition of COA qualification:

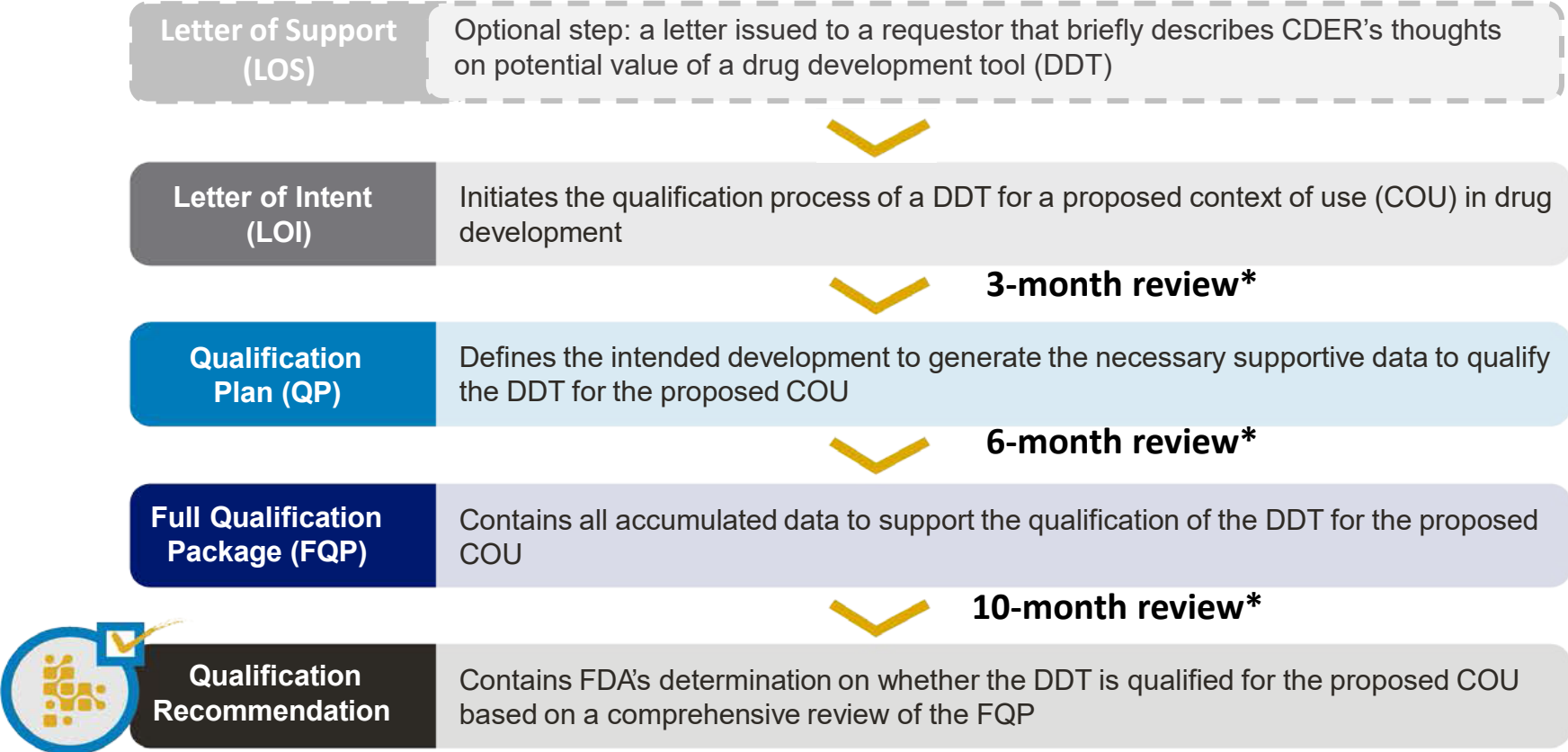
“COA qualification is a regulatory conclusion that the COA is a *well-defined and reliable assessment* of a specified **concept of interest** for use in adequate and well-controlled (A&WC) studies in a specified **context of use**. COA qualification represents a conclusion that within the stated context of use, results of assessment can be relied upon to measure a specific concept and have a specific interpretation and application in drug development and regulatory decision-making.”

Types of qualification: “limited” context of use and “full” context of use

FDA’s *Guidance for Industry and FDA Staff: Qualification Process for Drug Development Tools*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf>






# FDA COA Qualification Process based on 21<sup>st</sup> Century Cures Act passed in 2016



- Qualitative Research and Transcripts
- Quantitative study protocol(s)
- Statistical analysis plan(s)

\*Not including "initial assessment" / reviewability period of approximately 3-6 months  
[Qualification Process for Drug Development Tools Guidance for Industry and FDA Staff](#)

# FDA Qualification Successes -> Measures

	Year	Working Group	Qualified Measure(s)
	2017	Depression (DDT008)	<ul style="list-style-type: none"> <li>• <i>Symptoms of Major Depressive Disorder Scale (SMDDS)</i></li> <li>• 19 trials to date</li> </ul>
	2018	Non-Small Cell Lung Cancer (DDT009)	<ul style="list-style-type: none"> <li>• <i>Non-Small Cell Lung Cancer Symptom Assessment Questionnaire (NSCLC-SAQ)</i></li> </ul>
	2019	Asthma (DDT006)	<ul style="list-style-type: none"> <li>• <i>Asthma Daytime Symptom Diary (ADSD)</i></li> <li>• <i>Asthma Nighttime Symptom Diary (ANSD)</i></li> </ul>
	2020	Irritable Bowel Syndrome (DDT005) <ul style="list-style-type: none"> <li>• Included in FDA labeling</li> </ul>	<ul style="list-style-type: none"> <li>• <i>Diary for Irritable Bowel Syndrome Symptoms-Constipation (DIBSS-C)</i></li> </ul>
	2018	Measure accepted by FDA <ul style="list-style-type: none"> <li>• Included in FDA, EMA, PMDA, Health Canada, and MHRA labeling</li> </ul>	<ul style="list-style-type: none"> <li>• <i>Myelofibrosis Symptom Assessment Form v 4.0 (MFSAF v4.0)</i></li> </ul>

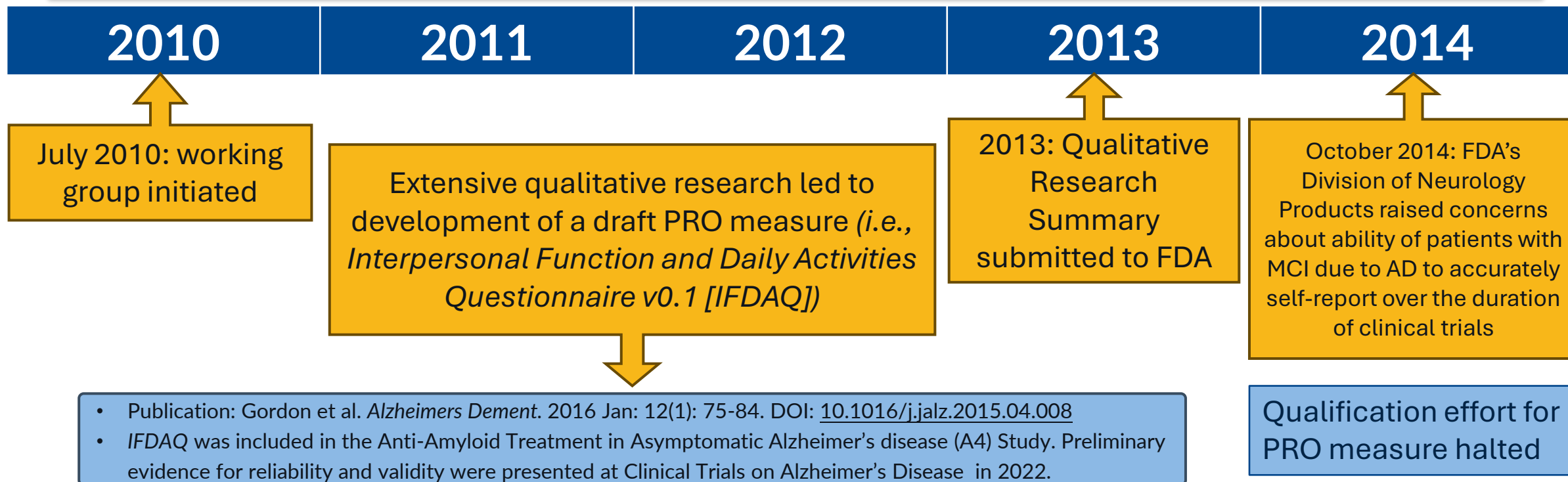


FDA qualification statements are regulatory conclusions that specific COAs can be used in drug development for a defined context of use, **helping streamline trials and facilitating regulatory review**

Qualification Statements can be found here: <https://force-dsc.my.site.com/ddt/s/>

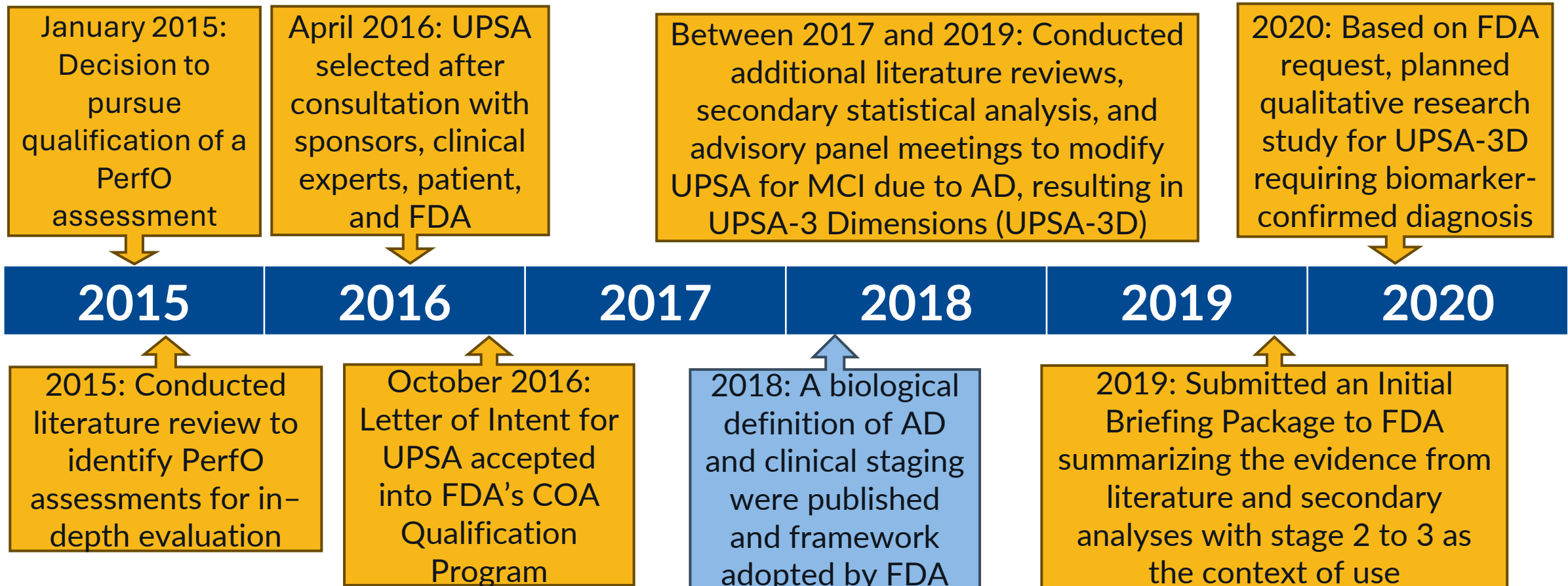
# Cognition Working Group: Initial Focus on Patient-Reported Cognition (2010-2014)

- Problem: Existing cognition measures lacked sensitivity in mild cognitive impairment (MCI) population or were developed without patient or caregiver input
- Need: Capture patient's perspective on functioning – complex activities of daily living (ADL) performance and interpersonal functioning
- Goal: Develop PRO measure for MCI due to Alzheimer's disease (MCI due to AD) for qualification



# New Focus on Performance Outcome Assessment (2015-2020)

- New goal: To capture patient's performance on aspects of day-to-day functioning (i.e., instrumental activities of daily living [iADLs]) that are expected to be impacted at pre-dementia stages of AD



# A Need for Remote Assessment (2021-current)

May 2021: Measurement approach reassessed following COVID-19 pandemic

- Some UPSA tasks had become outdated (e.g., check writing, using directory assistance).
- With the accelerated movement toward technology-enabled remote assessments, desire for a touchscreen computer-based assessment rather than requiring task completion using physical props in person.

Measure selected: Virtual Reality Functional Capacity Assessment Tool – Short List (VRFCAT-SLx)

- Administered by trained study personnel on a touchscreen tablet computer
- Intended to be used to support labeling claims of therapies aimed at preventing or delaying the progression of cognitive impairment in persons with AD

Meeting with FDA's Qualification Review Team confirmed alignment with this decision

- **Concept of interest:** Day-to-day functioning based on performance of cognition-dependent instrumental activities of daily living (iADLs)
- **Context of use:** Persons 50 years of age and older with biologically defined AD and clinical staging of 2 to 3 on the AD continuum (transition from MCI due to AD) as defined by Jack et al. 2018

# Virtual Reality Functional Capacity Assessment Tool (VRFCAT)

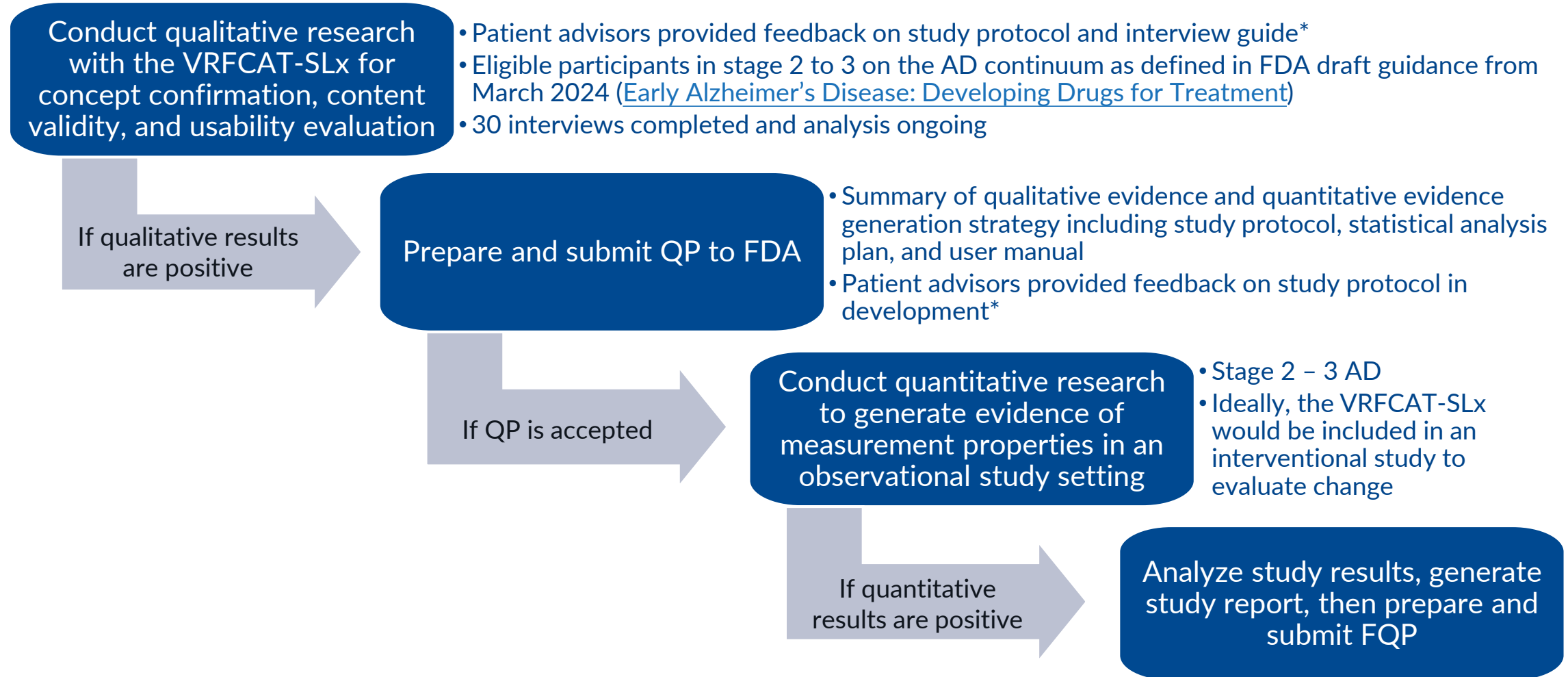
- An assessment of cognition-dependent iADLs including meal planning, transportation, handling money, and shopping (executive functioning, episodic memory, overall cognitive performance)
- Scientifically validated in schizophrenia participants
- Available in multiple languages and culturally adapted environments
- FDA 21 CFR part 11 compliant
- With demonstrated sensitivity to functional capacity deficits, the VRFCAT was developed to improve clinical trials by:
  - Detecting functionally meaningful improvements in patients' everyday lives
  - Reducing reliance on informant report
- Accepted into the FDA's COA Qualification Program as a measure of functional capacity for schizophrenia treatment trials (DDT-COA-000107)
- Despite extensive quantitative evidence supporting the VRFCAT in schizophrenia, qualitative research was required for qualification effort; results published:

Horan et al. Qualitative Analysis of the Content Validity of the Virtual Reality Functional Capacity Assessment Tool (VRFCAT) in Schizophrenia: A Multi-Stakeholder Perspective. *Schizophr Bull Open*. 2023 May 6;4(1):sgad012. doi: 10.1093/schizbullopen/sgad012.

# VRFCAT-Short List (VRFCAT-SLx)

- A version of the VRFCAT developed specifically for use in patients with mild cognitive impairment (MCI) and early Alzheimer's disease (AD)
  - Reduced task complexity and length
  - Graphics simplified based on patients' feedback in a qualitative study
  - Includes an interactive practice module to provide orientation to tablet, provides examples, and corrective feedback
- Well-tolerated by patients
  - 99% of patients met a priori set criteria for performance validity on the *VRFCAT-SLx*
- Average completion time in patients with MCI and mild AD
  - 15 minutes

# Next Scientific Steps for the Development of the VRFCAT-SLx



\*We acknowledge the consultation of patient advisors from Alzheimer's Associations Early Stage Advisory Group in the study design of our qualitative research and the consultation of patient advisors from Us Against Alzheimer's in our quantitative protocol development.

# Learnings from Pursuit of a Cognition Measure (1/2)

- Early alignment with clinical division within regulatory agency is essential
- Qualification process enables ongoing interaction and communication with FDA's Qualification Review Team at key decision points
- Qualification effort has been impacted by changes in the field: 21<sup>st</sup> Century Cures Act redefining the process since 2016 and biological definition of AD since 2018 requiring new data collection

# Learnings from Pursuit of a Cognition Measure (2/2)

- Selection of appropriate COA type depends on target population and context of use
  - PRO measures may not always be suitable in conditions with primary cognitive impairment
  - For less severe stages, unclear when self-report becomes untenable
  - For PerfO assessments, need evidence that tasks reflect activities that are meaningful in daily life
    - PerfO measure gets us closer to directly providing the patient's perspective in AD trials, given the known challenges with self-report using PRO measures and the fact that other measures are either clinician-reported outcome measures or observer-reported outcome measures completed by caregivers.
- Other factors come into play in selecting tools to assess cognition
  - Participant burden
  - Remote assessment in post-COVID era
- Proper and robust data collection takes time. It may be tempting to skip steps, but this may result in a measure that is not considered fit-for-purpose in clinical trials. Same steps would be taken whether pursuing qualification or not.

# Thank you!

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