Scientific Research Publishing

Advances in Alzheimer's Disease, 2021, 10, 19-32
https://www.scirp.org/journal/aad
ISSN Online: 2169-2467
ISSN Print: 2169-2459

Virtual Cognitive Screenings and Interviews of Patients with Neurodegenerative Conditions Associated with Alzheimer's Disease and Parkinson's Disease

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How to cite this paper: Lenderking, W.R., Abel, C., Brookes, E., Sargalo, N., Filipenko, D., Smith, C. and Lo, R. (2021) Virtual Cognitive Screenings and Interviews of Patients with Neurodegenerative Conditions Associated with Alzheimer's Disease and Parkinson's Disease. *Advances in Alzheimer's Disease*, **10**, 19-32.
https://doi.org/10.4236/aad.2021.102002

Received: May 28, 2021
Accepted: June 26, 2021
Published: June 29, 2021

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Abstract

The current pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), commonly referred to as COVID-19, brings myriad challenges to research conducted among those more susceptible to the virus. According to the United States (US) Centers for Disease Control (CDC), eight out of ten reported COVID-19 deaths are among people > 65 years of age and older. Nonetheless, researchers must continue the crucial work of investigating and understanding diseases that affect the elderly. The focus of this white paper is to assess the challenges associated with research within the elderly population with neurocognitive conditions. Specifically, this paper addresses the need for the standardized administration of performance measures (e.g., neurocognitive assessments) among a dementia population while ensuring the physical safety of participants. Consideration is given to the administration of performance measures and the availability and feasibility of administering these measures remotely to a population that may have difficulty using novel technologies. In implementing remote research assessments, it is suggested that researchers follow a *G*AMMA approach by: 1) establishing clear *G*uidance on remote visit expectations and processes; 2) establishing *A*ppropriate exclusionary criteria in the development of the study design; 3) providing subjects *A*ppropriate study Materials for visual processing; 4) incorporating Multiple data sources in the overall study design (e.g., caregiver input); and 5) Acknowledging that there will be study limitations as researchers use emerging technology with this patient population, and using mitigation strategies for these limitations where possible.

Keywords

Parkinson's Disease, Alzheimer's Disease, Mild Cognitive Impairment, COVID-19, Virtual Cognitive Assessment

1. Introduction

Due to the widespread nature of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the number of deaths globally associated with COVID-19 continues to increase [1]. The groups most vulnerable to the virus in society are the elderly and those with underlying health conditions, resulting in higher mortality among these groups [2] [3] [4]. According to the World Health Organization [5], there are approximately 50 million people living with dementia worldwide, with 10 million new cases every year; this accounts for approximately 5% - 8% of the general population over the age of 60 years [6]. While the elderly population may be particularly vulnerable to COVID-19, the need continues for research into Alzheimer's disease (AD) and other forms of dementia.

The United States (US) Food and Drug Administration (FDA) has published *G*uidance for the conduct of clinical trials during the COVID-19 pandemic [6]. The FDA guidelines recommend utilization of alternative methods of completing study visits, for example, virtual visits held by telephone, to ensure the safety of vulnerable participants. Since it remains crucial to collect screening and performance measures (e.g., the Dementia Severity Rating Scale (DSRS) [7], Clinical Dementia Rating (CDR) [8], and Mini-Mental State Examination (MMSE) [9]), and to evaluate disease severity, other options are needed for collecting qualitative and performance data from the dementia population and their caregivers. In addition to assessing cognitive performance using performance-based outcomes (PerfOs), outcomes data are often collected from these patients using other clinical outcome assessment (COA) measures to assess how they are feeling as well as their level of functioning and quality of life (QoL).

The use of virtual technology in research is becoming both more necessary and more acceptable. Due to the characteristics of dementia such as disturbed emotions, perception, motor activity, mood [10], and cognitive impairment [11], and since populations with cognitive issues may face additional challenges when moving away from traditional, in-person data collection, there are considerable hurdles to overcome and logistical complications to consider.

Virtual and telephone interviews have been used for some years in qualitative data collection among patient populations [12] and caregivers, for example in amyotrophic lateral sclerosis (ALS) [13]. A modified 26-item version of the MMSE has been validated for telephone use (TMMSE) [14] for patients with AD; the TMMSE omits items that are not possible to confirm during telephone completion (*i.e.*, "What floor of the building are we on?") and adds new or revised items for the telephone administration (e.g., the examiner asks the patient

to follow a three-step command, "Say, 'hello,' tap the mouthpiece of the phone 3 times, then say, 'I'm back.'") [15]. Educational information has been delivered to caregivers of patients with dementia via the telephone for support in self-efficacy and assessment of caregiver burden [16]. This paper will discuss the use of technology among patient populations with AD, Parkinson's disease (PD), and mild cognitive impairment (MCI), and the use of remote data collection, specifically qualitative interviewing and performance tools, to assess disease severity.

2. Methods

Targeted Clinical Trial Review

A review of ongoing and completed clinical trials conducted in neurodegenerative conditions including AD, PD, and MCI populations was conducted using the FDA clinicaltrials.gov database in April 2020. The search aimed to identify COA measures being used in these populations. Three separate searches were conducted using the following terms: "Alzheimer's disease (AD)," "Parkinson's disease (PD)," or "mild cognitive impairment (MCI)," Phase II and III, 2017 to present (past 3 years), adult, and older adults. Figure 1 illustrates the process used to determine the measures for review in the current paper.

We also searched products with patient-reported outcome (PRO) claims that had been approved by the FDA and European Medicines Agency (EMA), using the FDA and EMA databases to identify COA measures utilized to support label claims in AD, PD, and MCI.

Review of Electronic Platforms

A manual internet search of available electronic data platforms and videoconferencing systems was performed using the terms "videoconferencing platforms" and "web-based platforms." Each identified platform was reviewed for suitability

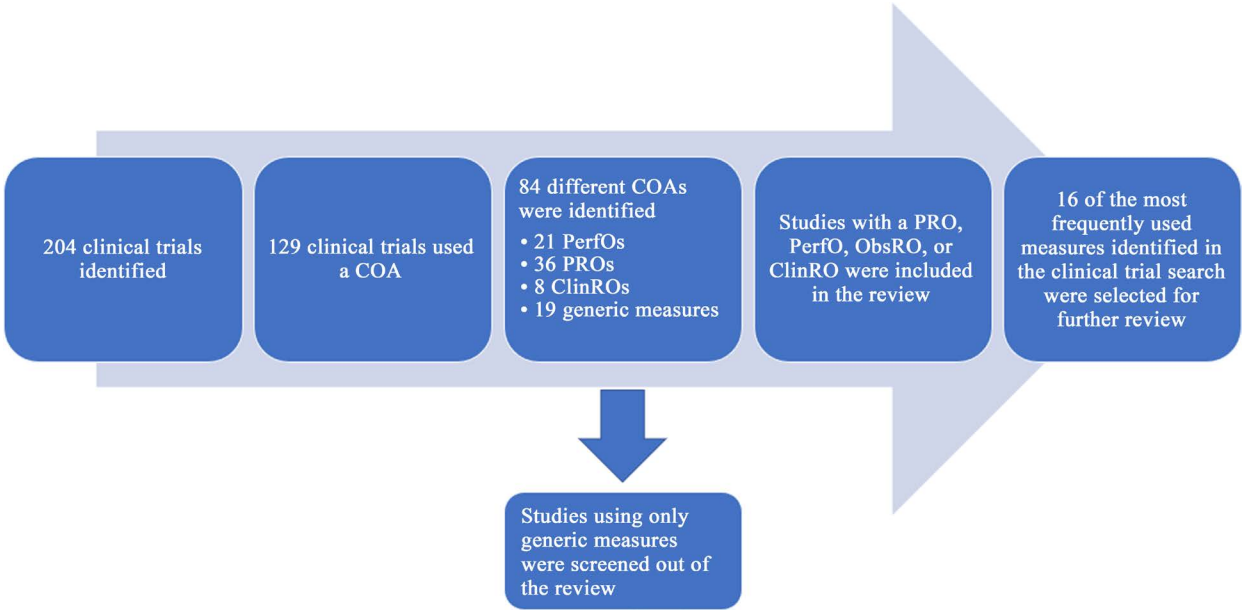

Figure 1. Selection of measures for review.

for use in data collection among patients with neurodegenerative conditions. Information about previous use of the platforms included whether they have been used in healthcare or research settings, and HIPAA compliance was assessed for each (Table 1). Other information such as video sharing capability, screen sharing, file sharing, technical support, and security was collected for each platform.

Table 1. Review of online data and videoconferencing platforms.

	Device Type	Areas in Use	HIPAA Compliance	HITECH Compliance	Video Sharing	Screen Sharing	File Sharing	Security	Support
Microsoft Teams	Desktop, Tablet, Smartphone	Healthcare, Telemedicine	Yes	Yes	Yes	Yes	Yes		
Skype	Desktop, Tablet, Smartphone	Healthcare, Telemedicine	Yes (only Skype for Business Enterprise)	-	Yes	Yes	Yes		
Focus Vision (InterVu)	**Desktop**	Healthcare, Research	Yes	Yes	Yes	Yes (Not Smartphone users)	Yes		Live Support
Zoom for Healthcare	Desktop, Tablet, Smartphone	Healthcare, Telemedicine	Yes	Yes	Yes	Yes	Yes	Achieve HIPAA (signed BAA) and PIPEDA/PHIPA compliance with 256-bit AES encryption. SOC 2 (Type II) FedRAMP (Moderate) GDPR, CCPA, COPPA, FERPA, and HIPAA Compliant (with BAA) Privacy Shield Certified (EU/US, Swiss/US, Data Privacy Practices) TrustArc Certified Privacy Practices and Statements	
Mega-meeting	**Desktop**	General population	Yes	Yes	Yes	Yes	Yes	End-to-End Encryption Data Transport Layer Security (DTLS) Secure Real-Time Protocol (SRTP) Camera and Microphone Access WebSockets Meeting Security Account Security	
Doxy.me	Desktop, Tablet, Smartphone	Healthcare, Telemedicine (mental and behavioral health including AD and dementia)	Yes	Yes	Yes	Yes	Yes	End-to-end encryption	
Simple Practice	Desktop, Tablet, Smartphone	Healthcare, Telemedicine	Yes	Yes	Yes	Yes	Yes		Live Support

Continued

Vsee	Desktop, Tablet, Smartphone	Healthcare, Telemedicine	Yes	Yes	Yes	Yes	Yes		
GoTo Meeting/ Meeting (LogMeIn Edition)	Desktop, Tablet, Smartphone	Healthcare, Telemedicine (Not specific to telehealth but is used by professionals in this area)	Yes	Yes	Yes	Yes	No		Live support
thera-LINK	Desktop, Tablet, Smartphone	Healthcare, Telemedicine (mental and behavioral health)	Yes	Yes	Yes	No	Yes	Business Associate Agreement (BAA) provided Hashed and salted passwords All web traffic encrypted via HTTPS & TLS 1.2 All video encrypted via AES-256 bit encryption HIPAA certified support staff (24 × 7 × 365) HIPAA Policies and Procedures in place Encrypted database and file backups Browser protection via Content Security Policy Continuous system risk analysis Multi-factor biometric data center access Restricted employee access to PHI Credit cards and passwords are never stored PHI is encrypted Automatic Session Timeout HTTPS only, via Strict Transport Security (HSTS)	Live support
TheraNest	Desktop, Tablet, Smartphone	Healthcare, Telemedicine (specifically tailored to mental health applications)	Yes		Yes	No	Yes		Live support
Medici	Desktop, Tablet, Smartphone	Healthcare, Telemedicine	Yes (Medici Treatment Plan)		Yes	Yes	Yes		
Mend	Desktop, Tablet, Smartphone	Healthcare, Telemedicine (Tele-psychiatry)	Yes	Yes	Yes	No	Yes		
Chiron Health	Desktop, Tablet, Smartphone	Healthcare, Telemedicine	Yes	No	Yes	No	No		
VT/Connect	Desktop, Tablet, Smartphone	Healthcare, Telemedicine	Yes	Yes	Yes				

The existing FDA *G*uidance allows use of software in the context of health care and research. To protect patient privacy, remote data acquisition, transmission, and storage must be secure. This includes electronic platforms designed for

remote assessments that are required to have automated audit trails [6]. Although platforms for remote data collection are not considered to be medical devices as they are not specifically intended for use in the diagnosis, treatment, or prevention of disease, they must provide a secure way of communication [17]. When considering an electronic platform, it is critical to review its compliance with HIPAA requirements to ensure that the electronic health information collected through the software is protected.

3. Results

Review of measures

The targeted search identified a total of 204 clinical trials (n = 129 AD, n = 35 PD, n = 40 MCI). The studies were screened for utilization of a COA measure. Those that mentioned COAs used were included in the review. COAs were utilized in 129 studies to assess symptoms (AD: n = 82, PD: n = 26, MCI: n = 21).

A total of 84 COA measures were identified as having been used in those 129 trials (21 performance-related outcomes (PerfOs), 36 PROs, 8 clinician-reported outcomes (ClinROs), and 19 generic measures (PROS not specific to neurodegeneration). Studies that incorporated the use of a PRO, PerfO, or ClinRO were included in the review.

Sixteen COA measures (14 disease-specific PerfOs, 2 generic PerfO measures) were identified as having been used most frequently across the three conditions, and were selected for further review of their suitability for completion in a virtual/remote, non-face-to-face setting with technological devices (**Table 2** and **Table 3**). The Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog), Alzheimer's Disease Cooperative Study-activities of daily living scale (ACDS-ADL), and Clinician Interview-Based Impression of Change (CIBIC) measures were also mentioned as part of label claims in these conditions. Each of the sixteen COA measures was assessed for suitability for virtual/remote completion. Props and tools required as part of the assessment (*i.e.*, paper, pen, stopwatch, and objects for item recognition) as well as worksheets and scoring methods were reviewed in detail.

Verbally Administered Measures for Virtual Administration

The Clinical Dementia Rating Scale Sum of Boxes (CDR-SOB) is a global assessment dementia screener used to assess severity of dementia using a 5-point scale system. The CDR-SOB does not require the use of props for administration; the interviewer conducts separate interviews with both the participant and the study partner (e.g., caregiver), recording their responses for comparison using the score sheet. The CDR-SOB can be conducted via telephone or web-conferencing and, in a recent study, showed no significant statistical difference from in-person administration [15]. The Logical Memory Test (LMT), Hopkins Verbal Learning Test (HVLT), Free and Cued Selective Reminding Test (FCSRT), and Controlled Oral Word Association Test (COWAT) are widely used measures designed to assess episodic memory, verbal learning, and verbal

Table 2. COA measures utilized in AD, PD, and MCI clinical trials.

Instrument Name	Concepts Measured	Tools Required (Props/Forms/Software)
Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog)	Word recall, Naming Objects, following commands/instructions, Constructional praxis (drawing), Ideational Praxis (post a letter), Orientation (Date/time/place), Language, comprehension of spoken language, Word Finding difficulty, Remembering test instructions	Pen, paper, pages with drawings to copy, word lists, Objects (flower, bed, whistle, pencil, rattle, mask, scissors, comb, wallet, harmonica, stethoscope, tongs)
Mini-mental State Exam (MMSE)	Orientation, Registration, Attention and Calculation Recall, Language, Copying	MMSE Form Paper for copying image Paper for attention and calculation task
Clinical Dementia Rating Scale—Sum of Boxes (CDR-SOB)	Memory, Orientation, Judgment & Problem Solving, Community Affairs, Home & Hobbies, Personal Care	CDR Interviewer Guide
Montreal Cognitive Assessment (MoCA)	Visuospatial/Executive, Naming, Attention Language, Abstraction, Delayed Recall, Orientation	MoCA Form Paper and Pen for the tracing exercise and clock drawing exercise
Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)	Immediate Memory, Visuospatial/Construction Language, Attention, Delayed Memory, Total Score	RBANS Kit (contains items for item recognition, word cards, line drawing)
Cambridge Neuropsychological Test Automated Battery (CANTAB)	Working memory, learning and executive function, visual/verbal memory, episodic memory, attention, information processing, reaction time, decision making	CANTAB Software, usually completed using a Tablet computer
Cogstate	17 tests covering; memory, learning, psychomotor function, upper limb function, executive function, attention, verbal learning, processing speed, emotion recognition,	Cogstate Software on computer or paper based tests
Neuropsychological Test Battery (NTB)	Memory, verbal recall (immediate and delayed), auditory learning, verbal fluency,	Word lists, digit span, stopwatch
Hopkins Verbal Learning Test (HVLT;Digital Symbols, Trail Making)	Attention, Processing Speed	Digit Symbol Page, Trail making page, pen/pencil
Logical Memory Test (LMT)	Recall (immediate and delayed)	Short Story, score sheet
Rey Auditory Verbal Learning Test (RAVLT)	Auditory learning, delayed recall	Word lists, score sheet
NIH Toolbox Cognition battery (NIHTB-CB)	Working memory, Executive Functioning, intelligence	NIHTB-CB Software
Free and Cued Selective Reminding Test (FCSRT)	Episodic Memory	Score sheet
Controlled Oral Word Association Test (COWAT)	Verbal fluency	Stopwatch, pen and paper
9 Hole Peg Test	Hand dexterity	9 Hole Peg test
6 Minute Walk Test (6MWT)	Exercise capacity and coordination	Stopwatch, distance markers

Table 3. COA measures mentioned in label claims search.

Instrument Name	Concepts Measured	Tools Required (Props/Forms/Software)
Unified Parkinson's Disease Rating Scale (UPDRS),	Motor and non-motor symptoms associated with PD.	Patient and clinician questionnaires, pen and paper
Sickness Impact Profile (SIP)	Perception of health status, physical and emotional functioning	Pen and Paper
Severe Impairment Battery (SIB) [36]	Orientation, language, memory, praxis, attention, social interaction and visual perception.	Pen and Paper, spoon (for language and praxis)

fluency. These measures are all administered verbally by an interviewer and could also be administered remotely without adjustments to the measures [18] [19]. Indeed, in studies conducted in healthy, elderly populations without dementia, the Wechsler LMT, HVLT, Bushke Selective Reminding Task, and COWAT [18] [19] measures showed no statistically significant differences when administered face-to-face versus via telephone, with the exception of the delayed portion of the Bushke Selective Reminding Task [18].

Pen-and-Paper Measures for Virtual Administration

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and the ADAS-Cog are frequently used measures designed to assess attention, language, immediate and delayed memory, as well as visuospatial skills. These measures require props (*i.e.*, a pen, watch, flower, harmonica, or other things) in the item recognition and recall sections. These items could be shown to participants via web-conferencing, or alternative tasks could be developed that do not require props. Worksheets are required for completion of pen-and-paper tasks in the RBANS, ADAS-Cog, MMSE, and Montreal Cognitive Assessment (MoCA) by the participant. These worksheets could be mailed to participants in advance of the assessment, with instructions noting that patients are not to open the packet until instructed to do so by the administrator. The ADAS-Cog has been conducted remotely in older adults with and without cognitive impairment successfully [20], with strong correlation between in-person and web-conference data collection in those with MMSE < 17. However, potential barriers could include access to and ease of use of technology [21]. Use of web-conferencing and cameras could enable props such as word cards to be shown to the participant. The 26-item TMMSE has been previously utilized in studies where data were not collected in person and showed strong correlation with the in-person administration of the MMSE [14].

Device-based Measures for Virtual Administration

The Cambridge Neuropsychological Test Automated Battery (CANTAB) and those from Cogstate Ltd are designed to detect changes in neuropsychological ability and are conducted electronically using a tablet computer provided to the participant during the interview. Devices could be shipped to participants ahead of the interview provided that participants are able to log into and use the device without assistance from the interviewer. Alternatively, a caregiver could receive training on how to set the assessment up for the participant. One potential risk is that sponsors and researchers may be loath to send out valuable hardware that may not be returned in a timely manner.

The MoCA has been modified for virtual use by the developer, with telephone, video-conference, and app-based options available [22]. The telephone option removes the visual elements of the test, while the video-conferencing and app options allow administration of the full measure [22]. A recent study among an elderly population of veterans indicated that in-person and video-administration methods showed comparable accuracy and inter-rater reliability [23] [24].

Additionally, the RBANS has been validated for virtual administration through the use of video-conferencing and interfacing iPads [23] [25]. Analyses have shown that scores obtained via virtual administration are highly correlated with those obtained via face-to-face administration, with minimal differences in measure index scores [25] [26].

Phone App Measures for Virtual Administration

The 9 Hole Peg test and the 6-Minute Walk test are performance-based measures designed to detect hand dexterity and aerobic capacity. These measures are not widely available for remote completion; the challenge remains that they require equipment and observation by an interviewer. However, the 9 Hole Peg test has been developed for use in an app [27] using Apple's ResearchKit [28] and tested for use in patients with multiple sclerosis.

The product label claims search identified five COAs in total (all ClinRO measures), which have been used in clinical trials to support label claims for Alzheimer's treatment. The measures identified were the CIBIC with Caregiver Input (CIBIC+), ADAS-Cog, ADCS-ADL, Severe Impairment Battery (SIB), and Post-traumatic Stress Diagnostic Scale (PDS). With regards to PD, a total of five COAs (ClinROs, ObsROs, and PROs) were identified. These measures were the Unified Parkinson's Disease Rating Scale (UPDRS), Scale for the Assessment of Positive Symptoms (SAPS-PD), Sickness Impact Profile (SIP), home daily diaries, and Investigator/clinician global impression (CGI).

Review of Electronic Platforms

Online data and videoconferencing platforms were also searched using a manual internet search, and were reviewed for suitability for use in data collection in this population using a checklist developed by the study team (**Table 1**). All of the 15 platforms identified were HIPAA compliant [29] [30]; all 15 were suitable for use on a desktop computer, 13 for use on a Tablet, and 13 for use on a Smartphone. Screen sharing was enabled on all but three of the platforms. All platforms, except for MegaMeeting, have been used in healthcare settings previously.

4. Discussion and Conclusion

Our review indicates that there are indeed viable performance and other outcome measures available for virtual administration among a mild-to-moderate dementia population. Furthermore, secure data-transfer platforms are available to ensure data privacy. With the rapid rise in smartphone and computer use, global technology continues to advance and bring new opportunities for research and data collection. However, the elderly are often at a disadvantage when presented with new technology due to a lack of fluency with, or apprehension about, devices and program applications [31] [32]. In light of the current pandemic, it is incumbent upon researchers to provide easily accessible platforms and procedures to ensure the physical safety of this vulnerable population during study assessments, while concurrently ensuring that the assessments are

conducted in a standardized fashion. These considerations can be adequately met by employing a combination of strategies, referred to by the authors as the *G*AMMA Approach. This approach is described subsequently and is a suggested guide for researchers as they implement remote research assessments among patients with dementia.

Guidance on expectations—Prior to assessing and/or interviewing patients, researchers should provide clear *G*uidance on what the patient can expect and how the assessment and/or interview will be conducted. A document outlining procedures and any technological requirements should be provided to patients well in advance of the study interaction. If possible, the document should also include screenshots and a step-by-step guide to ensure patients can easily navigate any technology that they are required to use and/or set-up prior to the assessment and/or interview. Some recent qualitative studies in older, healthy adults have shown that older populations are interested in adopting new technology [33] [34], but are hesitant to do so due to how quickly technology changes and concerns with data privacy [33].

Appropriate Exclusionary Criteria—Importantly, researchers must ensure *A*ppropriate exclusionary criteria are used. Recognizing the severity of the disease and level of impairment should be a key driving factor as researchers develop study designs. The use of virtual platforms and advanced technology may prove too burdensome among patients with more advanced disease, and may result in increased agitation or frustration among patient participants. Patients with more severe cognitive deficits may not be the proper candidates for virtual assessments, and paper-and-pencil administration of performance measures may ultimately be the best choice for the more clinically advanced dementia populations. For data collection purposes, it is recommended that cognitive assessment of patients with severe dementia continue to be conducted in person.

Materials for Visual Processing—During the interview or assessment, patients should be provided materials for visual processing, either through a shared computer screen or a mailed hard copy of documents to be discussed. This allows an additional level of engagement and opportunity to process materials and can troubleshoot potential issues such as poor attention or mild hearing impairments.

Multiple Data Sources—The incorporation of multiple data sources should be considered in the overall study design. For example, including caregivers (e.g., spouses, adult children, professional caregivers, etc.) can provide an additional level of robustness to the data, as well as an additional level of comfort to the patient. Caregivers can be incorporated into the study design to allow assistance with technology and provide proxy-reports on the patient's level of cognitive functioning, either via interview or completion of an ObsRO. Additionally, the patient's referring clinician can provide another level of detail that neither the patient nor caregiver can convey. Specifically, the clinician can provide detailed clinical feedback through interviews or through the completion of a Cli-

nRO. Ideally, patients, caregivers, and clinicians could complete complimentary questionnaires that are widely used and validated for comparison with each other to determine the degree of alignment across observations and reports. A variety of complimentary measures are available from multiple sources, such as Health Measures (https://www.healthmeasures.net/), such as the PROMIS, NIH Toolbox, and the NeuroQoL measures [35].

Acknowledges Study Limitations—Finally, it is important to note that, as with any emerging technology and research, there will be study limitations. For example, measures may be administered in a non-standardized fashion, patients and caregivers may under-report disease symptoms or impacts, or patients may not have the level of insight needed to answer the research questions. Current research validating alternative administrations of measures will continue to be critical as we navigate technological resources and continue research under what has become the "new normal." Anticipating study limitations and trying to find additional solutions in advance is important to the success and generalizability of the research.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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