Official title: VIdeo Telehealth in ALzheimer's: NeuroPsychology (VITAL-NP)

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I. **Hypotheses and Specific Aims**:

Specific Aims

The outbreak of COVID-19 has raised critical questions regarding the implementation of teleneuropsychology (TeleNP) using video administration of cognitive assessments in patients' homes. Remote administration of brief cognitive assessments has been shown to be a valid alternative to in-person testing with typical, memory-predominant Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD) dementia. However, these studies have focused primarily on virtual testing services to a patient in a *remote clinic* rather than appraising feasibility and validity of virtual testing services to a patient in their *home.* Whether due to the COVID-19 pandemic, geographical barriers to healthcare access, or functional limitations, many older patients have limited access to remote clinic offices to participate in an evaluation.

Moreover, prior studies have selectively focused on research participants with typical presentations of AD, raising concerns as to the generalizability of TeleNP to patients who are diagnostically challenging and more representative of clinic settings. For example, patients with complex presentations of AD and related disorders (ADRD) are more likely to be referred to University clinics than patients with memory-predominant AD. Given that University clinics are typically located in urban areas, patients with complex ADRD often require more extensive travel and resources to obtain a dementia neuropsychological evaluation. **In order to increase access to neuropsychological assessments, improve the precision of neurodegenerative diagnoses, and ensure that TeleNP is generalizable to complex presentations of ADRD, appraisal of the feasibility and preliminary validity of home-based TeleNP in both typical and atypical AD is critically needed**.

The overarching goal of this proposal is to a) assess the feasibility and preliminary validity of **home-based delivery of TeleNP** to patients with suspected AD, referred for cognitive assessments in a Neurology Clinic; and b) elucidate whether TeleNP is equivalent to face-to-face evaluation (FF) for diagnostic adjudication of atypical versus typical AD. To accomplish these goals, we will conduct a **pilot clinical trial** of two testing modalities, TeleNP versus FF, for delivery of neuropsychological evaluations. Neurologist-referred patients with typical (i.e., memory-predominant; n=40) and atypical (i.e., complex and/or non-memory predominant; n=40) presentations of *possible* AD will be enrolled in the study. Care partners of participants will also be consented to the study and included in stakeholder surveys/interviews. Using a cross-over design, all participants will undergo evaluations (clinical interview + Core Battery of cognitive tests) in both modalities, approximately 4-6 weeks apart to account for potential practice effects. Although all participants will be referred due to suspected AD, the neuropsychologist will be blinded to the specific diagnosis (i.e. typical versus atypical) from the neurologist. The Core Battery will include measures of memory, executive, visuospatial, and language functions. To further minimize practice effects, alternate assessment forms will be implemented and order of test forms will be counterbalanced. Some tests are not readily adaptable to video-based delivery due to tactile/physical stimuli; as such, we will assess whether a Flexible Assessment (i.e., option to include additional tests, <u>after</u> completion of Core Battery) in the FF modality alters diagnostic conclusions. Finally, in an exploratory aim, we will identify stakeholder perspectives of TeleNP that inform pragmatic implementation of remote neuropsychological evaluations. Our Aims are:

Aim 1: Determine the validity of home-based video administration of neuropsychological tests (TeleNP) for assessing AD. 1a: Are cognitive test results equivalent across TeleNP and FF conditions in patients with suspected AD? 1b. Is this equivalence consistent across referral diagnoses (i.e., Typical vs. Atypical AD)? *This Aim will test the validity of cognitive measures assessed with TeleNP and determine whether the validity of TeleNP differs based on referral diagnosis.*

Aim 2: Evaluate the impact of home-based TeleNP on the differential diagnosis of typical and atypical AD. 2a. Is the neuropsychologist's diagnosis comparable across TeleNP and FF conditions? 2b. Does flexibility to incorporate additional tests (Flexible Assessment) that are not readily adaptable to video administration alter diagnostic conclusions? *Given that neuropsychologists' conceptualizations of patient presentations may differ from the referring neurologist, this Aim will appraise whether TeleNP results in the same diagnoses from neuropsychologists compared to FF (gold standard) conditions.*

Aim 3: Appraise the feasibility and acceptability of TeleNP in the evaluation of AD patients. 3a. What is the user experience of TeleNP by patients, care partners, neuropsychologists, and psychometrists? 3b. Are there barriers or unique benefits of TeleNP that may influence future use and scalability in clinical care? *This Aim will utilize mixed methods, including interviews about the user experience and surveys of intervention feasibility and acceptability, to address quantitative and qualitative aspects of TeleNP that may influence the pragmatic implementation of remote assessments in a future, definitive trial.*

II. **Background and Significance**:

In the context of the COVID-19 pandemic and other limitations to accessing face-to-face care, critical questions have been raised regarding the feasibility and validity of implementing teleneuropsychology (TeleNP) using video administration of cognitive assessments to patients in their homes. The knowledge gap regarding TeleNP resulted in a considerable decrease in cognitive assessments during this pandemic. Cognitive assessments, ranging from brief screens to comprehensive testing batteries, are an important clinical service to better elucidate the diagnostic presentation and severity of older adult patients, including Mild Cognitive Impairment (MCI) and Alzheimer's disease (AD) dementia[1-3]. Despite their integral use in clinical diagnosis, symptom tracking, and treatment planning, there are several barriers to the widespread translation of these services to a remote-delivery modality. Whereas remote administration of brief cognitive screens[4-8] and assessments[9-11] has been shown to be a valid alternative to in-person testing with typical, memory-predominant MCI and AD, these studies have focused primarily on virtual testing services to a patient in a *remote clinic* rather than appraising feasibility and validity of virtual administration of cognitive tests to a patient in their *home*.

Moreover, prior studies have selectively focused on older adult participants with typical presentations of AD, often with previously confirmed memory-predominant syndromes adjudicated by interdisciplinary research conferences.[12-14] This approach is important and standard for initial validations; however, it raises questions regarding the **generalizability of TeleNP to patients who are diagnostically challenging and more representative of subspecialty Neurology clinic referrals**. For example, patients with atypical and/or complex presentations of AD and related disorders (ADRD) are more likely to be referred to subspecialty University clinics than patients with classic AD presentations[15]. Given that University clinics are often located in urban areas, patients may require more extensive travel and financial resources to obtain a comprehensive dementia evaluation. **To improve patient access to specialized neurodegenerative disorder evaluations, pragmatic appraisal of the feasibility and**

diagnostic validity of home-based TeleNP in patients with typical and atypical ADRD presentations is critically needed.

To overcome these significant gaps in prior research, we propose to demonstrate the feasibility and validity of home-based, comprehensive TeleNP. We will conduct a cross-over pilot trial to evaluate the feasibility and preliminary validity of standard, face-to-face (FF) neuropsychological assessment versus home-based video TeleNP in adults with suspected typical or atypical AD. Germane to the generalizability of TeleNP to clinical settings, the trial will be embedded in the University of Colorado Hospital (UCH) Memory Disorders Clinic, which will further facilitate an appraisal of whether TeleNP assessments are appropriate for diagnostic adjudication of typical vs. atypical ADRD phenotypes. In an exploratory aim, we will utilize a mixed methods approach to assess the feasibility and acceptability of TeleNP among key stakeholders: patients, their care partners, neuropsychologists, and a psychometrist. This approach will be guided by the Unified Theory of Acceptance and Use of Technology (UTAUT) model; this theoretical framework identifies "social influence" and "facilitating conditions", which can assess the potential influence of the home environment on user acceptance and intentions to use.[16] This pilot clinical trial will delineate the feasibility of implementing TeleNP in a Neurology clinic setting and thereby prepare us for a future definitive pragmatic trial of TeleNP effectiveness across multiple clinics.

III. Preliminary Studies/Progress Report:

This is an NIH-funded R21 application with no current pilot data. There are published studies of telehealth and neuropsychology; however, the vast majority of studies using remote neuropsychological testing have been delivery of services to another health care facility, with the presence of on-site support to the patient[8, 9, 17-20]. Although those studies emulated a "controlled" setting of a clinic, they did not address the feasibility of implementing TeleNP in a more real-world context, when the patient is at home with no staff support. **Whether due to rural-based access to care barriers, functional limitations**, **or COVID-19, many older patients have limited access to remote clinic offices for evaluation**, hence raising questions regarding scalability of clinic-to-remote clinic neuropsychological assessments. As such, we will appraise the feasibility and preliminary validity of TeleNP as a comprehensive neuropsychological assessment via home-based video telehealth administration.

IV. Research Methods

A. Description of Population to be Enrolled:

Clinical Trial Participants (Patients):

We will recruit 80 patients from the **UCH Memory Disorders Clinic (**considering possible screen fails, up to 150 may ultimately be recruited). To understand the feasibility and preliminary validity of TeleNP, we will enroll 1) 40 adults with suspected **typical** AD (i.e., memory-predominant) and 2) 40 adults wherein AD is on the neurologist's diagnostic differential, but the presentation is **atypical** (i.e., complex/non-memory predominant presentations). The typical and atypical AD groups will range in severity from MCI to mild dementia (based on referring neurologist's determination); this is consistent with current conceptualizations of AD, in which clinical syndrome (AD) is distinct from severity of presentation (MCI; dementia).[1, 2]

All participants with suspected AD will be referred by neurologists. Our specific inclusion/exclusion criteria will be:

Inclusion criteria:

Eligible participants will be adults ≥age 60 years and <90 years who are undergoing evaluation for possible AD and whose severity ranges from MCI to mild dementia. Of note, we are excluding individuals aged 90 and over, as recent studies suggest that individuals in the oldest-old category differ from other individuals with MCI or dementia in terms of risk factors for AD and prevalence of non-AD pathologies.[21-23] In addition, limited age-referenced normative data for neuropsychological tests are available for individuals 90 and over, which impacts our ability to address Aims 1 and 2.

Eligible participants must carry a diagnosis of either suspected typical AD or atypical AD, based on the referring neurologist's diagnosis.

- Typical AD: Defined as a memory-predominant presentation of AD.
- Atypical/Complex AD: Defined as a complex (i.e., AD is under consideration, but other diagnoses may be included in neurologist's differential diagnosis) and/or non-memory predominant phenotype of AD.

Both patient groups will be based solely on the neurologist's clinical diagnosis after the initial Neurology visit, and in the absence of formal neuropsychological test results, to minimize circularity.

Exclusion criteria:

We will exclude individuals with moderate to severe levels of dementia and individuals with active delirium (per neurologist's determination), as these patients are less likely to be referred for neuropsychological evaluation than individuals with mild presentations. We will exclude patients who are legally blind or deaf, due to the auditory and visual components of the study. We will exclude individuals with a brain tumor and individuals who have a confirmed non-AD neurological diagnosis (e.g, Multiple Sclerosis; FTD); moreover, we will exclude individuals who are being evaluated outside of the UCH Memory Disorders Clinic. Finally, we will exclude participants who report active (i.e., within the last 6 months) substance use of illicit drugs such as cocaine or methamphetamines, or who carry a diagnosis of a major psychiatric disorder (e.g., schizophrenia; bipolar disorder).

Additional Consenting Participants:

Participants will be encouraged to bring a care partner, if available, with them to visits (i.e., FF and TeleNP), and the care partner will also provide consent to complete surveys and interviews. Consistent with the target sample for the primary participants, we will recruit up to 80 care partners; however, consistent with standard clinical practice, the availability of a care partner will not be a requirement. There are no age requirements or other inclusion/exclusion criteria for the care partner. We anticipate that most care partners will be co-residing caregivers, although participants may select a close friend as their care partner.

Total potential enrollment number including coverage for screen failures/withdrawals = 300. (Up to 150 patients, plus their care partners if applicable).

Recruitment and Screening:

We will work directly with the Memory Disorders Clinic to recruit participants. In the last two years, the UCH Memory Disorders Clinic served over 5,000 patients.

The referring neurologists (sub-investigators on this study) may directly approach their patients to discuss the proposed study and determine interest in study enrollment. They (i.e., referring neurologist) will provide baseline demographic and diagnostic information (typical vs. atypical AD), patient severity level (MCI vs. Mild Dementia), and their (neurologist) judgment of capacity to consent through a brief REDCap survey to the study psychometrist.

The psychometrist will contact the prospective participant to review the study procedures and obtain informed consent from the patient and/or legally authorized representative [LAR]. Although most patients with MCI retain capacity to consent to a research study, diminished capacity is present across the MCI and early dementia spectrum. We will consider the capacity judgment provided by the neurologist; in addition, the following questions will be used to assess whether or not the patient can consent for themselves. If they cannot answer these questions after consent discussion, consent will be obtained from an LAR:

- Describe in your own words the purpose of this study?
- What are you being asked to do?
- What are the side effects/risks of being in the study?
- Is this voluntary?
- What do you do if you have questions or possible side effects?

The psychometrist will present these questions; if any questions arise regarding capacity, then a neuropsychologist or physician will be available to complete a capacity to consent to research assessment.

The basis and conclusions of the capacity to consent assessment will be recorded. If cognitively capable of providing consent in the clinical opinion of the evaluator, the study participant will review and sign the consent form. If a study participant has an LAR (including durable/medical power of attorney or guardian) and are judged to be unable to provide consent, then the consent of the LAR will also be required. Verbal assent will be obtained from the decisionally challenged patient. The participant's LAR may also serve in the role of consenting care partner.

Informed consent, interviews, and surveys may be conducted via HIPAA-compliant platforms using remote assessments. Specifically, e-consent may be obtained remotely using HIPAA-compliant video programs (e.g., Zoom, Skype, Vidyo) and e-signature using REDCap and/or phone by the site investigator or study staff.

HIPAA privacy notification language will be incorporated into the informed consent document and will be signed by all participants prior to any procedures being carried out. Informed consent language will include key facts about the study, the study events, timeline, the study participant's role in the study, potential risks and benefits and highlight the fact that participation is completely voluntary and will signed by all study participants. The informed consent/HIPAA form will specify that the database will receive and store all research data. Information regarding the purpose and procedures for this project will be given in both oral and written form. All study participants will be consented in privacy and will be given as much time as they need to read, discuss and ask questions about study events and their respective roles and participation in the study. They will be reassured that the same ethical and legal codes that govern medical practice

also apply to clinical research and they will be given the opportunity to ask questions and receive information regarding the goals and details of this study. If the Principal Investigator or Co-Investigators do not initially participate in the discussion, they will be available to answer questions prior to obtaining written informed consent/authorization.

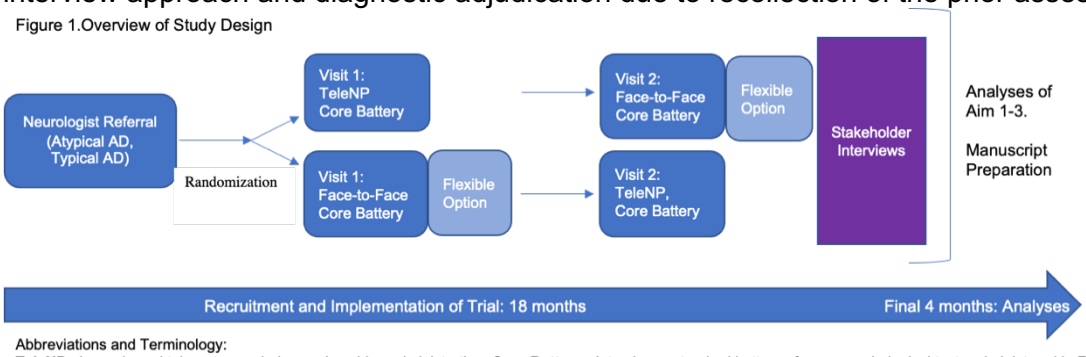
Subjects may withdraw participation in the study at any time by calling, writing, or emailing the Principal Investigator or study coordinator. Subjects will be unable to withdraw data that has already been analyzed, presented, or published.

B. Study Design and Research Methods

Randomization, Intervention and Neuropsychological Assessment Methods

Study participants will undergo both modalities (FF; TeleNP), conducted 4-6 weeks apart (allowing for maximum of 90 days). Order of modality will be randomized at baseline using a computerized process through REDCap, developed by Dr. Carlson. Similarly, assignment of supervising neuropsychologist will be randomized and counterbalanced across testing conditions. Our goal of using two neuropsychologists is to minimize bias; specifically, use of the same neuropsychologist for the same patient across both modalities would likely influence their interview approach and diagnostic adjudication due to recollection of the prior assessment.

Figure 1.Overview of Study Design



Abbreviations and Terminology:
TeleNP= home-based teleneuropsychology using video administration; **Core Battery**= Interview + standard battery of neuropsychological tests administered in FF and TeleNP modalities. **Flexible Option** = Menu of tests administered in addition to Core Battery in FF condition; tests include measures less adaptable to TeleNP (e.g., physical/tactile stimuli). **Stakeholder Interview:** Structured interviews with neuropsychologists, psychometrist, and a subset of participants and care partners

Intervention Components:

Pre-Visit Call: The psychometrist will place a pre-visit call to the participant and care partner up to 5 days prior to the scheduled FF visit or TeleNP visit. For the FF condition, the participant will be reminded to bring their care partner to provide additional details regarding symptom history during the interview. For the TeleNP condition, the psychometrist will have sent/delivered a study tablet, to the patient's home between the recruitment/screening call and the pre-visit call. During this pre-visit TeleNP call, the psychometrist will remind the participant to include their care partner on the assessment day, as the care partner will be encouraged to assist with setting up their home testing environment and to provide additional details regarding history during the TeleNP

interview. A test video call will also be conducted during this session, and the psychometrist will assist with troubleshooting.

Protocol and Core Battery (2 hours): In both conditions (FF; TeleNP), **the neuropsychologist will first conduct a structured, 30-minute interview with the participant and care partner, if available, which is a standard component of neuropsychological assessments**. The psychometrist will subsequently conduct a Core Battery of standardized neuropsychological assessments (see Data Collection below). The majority (60%) of clinical neuropsychologists employ psychometrists to administer their tests, thus our approach simulates clinical practice.[24] Tests in the Core Battery were selected based on: a) breadth: coverage of all primary domains (i.e., memory[25, 26], attention/executive functions[27, 28], visuospatial[29], and language functions[30]); b) use in clinical practice: frequent use in neuropsychological evaluations with established, validated norms in older adult populations; c) availability of alternate forms: presence of alternate forms, where possible, for tests most sensitive to practice effects (e.g., memory, verbally-mediated executive measures); and d) adaptability to TeleNP: inclusion of tests that minimize use of physical/tactile stimuli; i.e., inclusion of tests that may be screen shared via remote video technology and/or permit the patient to utilize their own piece of paper. The psychometrist will score the Core Battery based on published normative data for an older adult population using an automated excel calculator and provide the demographic-adjusted scores to the neuropsychologist. The neuropsychologist will document their diagnosis and severity of the participant's presentation.

Assessment Modality Details:

Face-to-face (FF) Assessment (control condition): The participant will undergo an in-person evaluation with the neuropsychologist and psychometrist at the Clinical & Translational Research Center (CTRC) or in Building 400 at CU-AMC. The standard protocol will be administered, including the interview and Core Battery. After completion of the Core Battery and submission of initial ratings, the supervising neuropsychologists may elect to have additional tests administered by the psychometrist as part of a Flexible Assessment. The Flexible Assessment will include a menu of tests that have physical/tactile stimuli (e.g., Design Fluency; Trail Making Test), all of which are excluded from the Core Battery due to lack of adaptability to video-based administration. Upon receipt of the scores from the Flexible Assessment, the neuropsychologist will complete a second form indicating any alterations to their diagnosis based on new information.

TeleNP Assessment (intervention condition): The participant will undergo a video-based TeleNP assessment using a HIPAA-compliant platform (e.g., Zoom). The participant will be at home using a study-provided tablet, and the neuropsychologist and psychometrist will administer the evaluation from either the CTRC or their CU-AMC office. During the scheduled TeleNP assessment, the standard protocol will be administered (i.e., interview and Core Battery). The psychometrist will assist with tablet collection at no direct cost to the participant (i.e., will provide a paid return box; alternatively, participant may drop off tablet if convenient to them)

Data Collection for Clinical Trial Participants:

Medical records:

--Participants will be asked to allow their past, current and future medical record information, to be placed in our RedCap database. The goal is to collect health information pertinent to cognitive functioning in older adults. Because concurrent medical conditions and treatments may impact the participants' health, it is likely that all pertinent past, current and future medical record information will be considered for inclusion in the RedCap database. This will include: symptom history and diagnostic considerations from the participants' neurology notes; laboratory results; health history (i.e., major medical problems); brain imaging results.

Demographics:

--Participants' age, birthdate, sex, gender, education level (Years), race/ethnicity, prior occupation, etc. will be obtained. Participant's contact information and address will also be obtained to facilitate scheduling baseline and follow-up appointments.

Interview:

--Participant's symptom history will be documented on a standard data collection sheet during the interview portion.

Neuropsychological Testing, Core Battery (May not be given in its entirety)*:*

- Cognitive/Mood Surveys:
    - Geriatric Depression Scale

- Cognitive Assessments:
    - Global:
        - MoCA, with alternate forms
    - Memory:
        - CVLT-II, with alternate forms
        - Benson Figure Recall / RBANS Figure Recall
    - Speed/Executive Functions:
        - Oral Trail Making Test
        - Oral Symbol Digit Modality
        - Digit Span, with alternate forms
        - Verbal Fluency, with alternate forms (FAS; BHR)
        - Color Word Inhibition
    - Language:
        - Sentence Repetition
        - Boston Naming Test-15 item, with alternate forms
        - Verbal Agility
        - WRAT Reading
        - Abbreviated Peabody Picture Vocabulary Test
        - Syntactic Comprehension
    - Visuospatial and Posterior Cortical Function
        - Judgment of Line Orientation (Short Form)
        - Benson Figure Copy / RBANS Figure Copy
        - Calculation Screen

Neuropsychological Testing, Flexible Assessment:

- Cognitive Assessments in addition to Core Battery (May not be administered in its entirety):
    - Grooved Pegboard
    - Clock Drawing Test
    - Rey-Osterrieth Complex Figure
    - BVMT
    - Navon Figures
    - Face Perception/Affect Naming
    - VOSP Number Localization
    - Design Fluency
    - Written Trail Making Test A & B

Surveys:

- 4-item measures of acceptability and feasibility
- 19-item modified UTAUT after TeleNP portion

Cognitive Composites, Neuropsychologist Diagnosis, and Interviews: See Outcome Measures Below

Data Collection for Care Partner Participants:

Demographics:

--Care partner's age, birthdate, sex, gender, education level (Years), race/ethnicity, prior occupation, etc. will be obtained. Participant's contact information and address will also be obtained to facilitate scheduling baseline and follow-up appointments.

Surveys:

- 4-item measures of acceptability and feasibility
- 19-item modified UTAUT after TeleNP portion

Interviews: See Outcome Measures Below

Incorporation of Results into Clinical Care: Because the set battery used in the FF assessment uses validated tests that are normally used for these patients in clinical care, it is likely that patients in this study *will not* undergo a separate standard of care neuropsychological assessment. Therefore, a brief research overview of the results of the FF assessment will be provided to the referring neurologist and the participant after both conditions are complete (and posted to Epic Medical Record as a research note), for use in their clinical care. Based on a

national survey, the median time between neuropsychological assessment and completion of reports is 3 weeks; our proposed time is slightly longer than the median, but remains within an expected *range* for clinical reports.[31] Of note, when considering the amount of time between referral and scheduled date of assessment in SOC (often on the order of months), our window will likely be shorter/faster than SOC given dedicate research time. If any safety, psychological or other signs of distress related to potential diagnosis of AD are noted during either assessment, appropriate referrals will be coordinated by Drs. Bettcher and Greher. Drs. Bettcher and Greher will coordinate with the neurologist to determine if prompt discussion of the first assessment is clinically prudent. The research note posted to Epic EMR will include a brief background/history, table of scores for FF condition, and summary/recommendations, consistent with standard of care approaches.

C. Outcome Measure(s):

Aim 1: Equivalence of Cognitive Test Results: *The goal of this Aim is to test the concurrent validity of cognitive measures across testing modalities and determine whether the test results differ based on referral diagnosis.* Z-scores will be calculated based on age-referenced normative data for each cognitive test (Table 1) in the Core Battery. For data reduction purposes, a mean z-score for each cognitive domain will be used (i.e., memory, executive functions, spatial abilities, language). This will allow us to address whether neuropsychological test results are equivalent across modality (i.e., FF vs. TeleNP) and whether complexity of referral impacts comparability of test results.

Aim 2: Equivalence of Neuropsychologist's Diagnosis: *Considering that neuropsychologists' conceptualizations of patient presentations **may differ from the referring neurologist**, the goal of this Aim is to appraise whether TeleNP results in the same diagnoses from neuropsychologists compared to FF (gold standard) conditions, and determine whether inclusion of flexibility to incorporate additional tests (Flexible Assessment) that are not readily adaptable to video administration alters diagnostic considerations.* Neuropsychologist-determined diagnosis (i.e., typical AD, atypical/complex AD, not AD) and severity (i.e., subjective concerns; MCI; dementia) will be assessed immediately after the standard protocol via a REDCap survey. To clarify whether the Flexible Assessment alters the neuropsychologists' conceptualizations, neuropsychologist diagnosis and severity will also be documented after the Flexible Assessment is completed.

Aim 3: Feasibility and Acceptability of TeleNP: *This Aim will utilize mixed methods, including patient, care partner, neuropsychologist, and psychometrist interviews about the user experience and surveys of intervention feasibility and acceptability (i.e., modified UTAUT), to address quantitative and qualitative aspects of TeleNP that may influence the pragmatic implementation of remote assessments in a future, definitive trial.*

Qualitative:

- Patients and Care Partners: **A subset of diverse patients (n=20) and any associated care partners** will be invited to participate in semi-structured interviews with the psychometrist within one week of completing both FF and TeleNP conditions. We will sample for diverse perspectives, including participants from both genders and typical vs. atypical AD. These interviews will focus on the participant's user experience, guided by

UTAUT domains and specific attention to home setting and potential care partner involvement.

- Psychometrist and Neuropsychologists: The psychometrist and neuropsychologists will also participate in brief, separate interviews to garner information regarding feasibility, acceptability, and strengths/weaknesses of TeleNP; these interviews will be conducted by Dr. Lum on four occasions, with each interview occurring after completion of 20 study visits.

Quantitative: To appraise feasibility of TeleNP, we will include measures of enrollment tracking (i.e., enrolled vs. decline), protocol assessment time, tracking of protocol adherence (i.e., completion of Core Battery), and presence of technological difficulties (e.g., termination of assessment due to technological difficulties). **The psychometrist will ask all patients (n=80) and associated care partners (up to n=80)** to complete validated 4-item Acceptability and Feasibility of Intervention Measures[32, 33] after both conditions, and a 19-item UTAUT questionnaire (adapted to TeleNP) after the TeleNP condition to measure determinants of intention to use.

We will document the fidelity of assessment administration and scoring using a fidelity checklist in a random 20% sample of participants.

Costs and Payments

All costs associated with the implementation and maintenance of the study shall be supported by Dr. Bettcher's grants. There is no charge to participants or participants' insurance for participation.

Clinical Trial participants will receive $25 to compensate for their time after both visits are completed. Care partners will not be compensated.

C. Description, Risks and Justification of Procedures and Data Collection Tools:

Description of Risks:

Potential risks to participants, by intervention, including physical, psychological, social, cultural, financial, and legal risks: For both conditions, there are no expected physical or legal risks. Participants will be advised that the clinical trial is voluntary, and that they may obtain a clinical neuropsychological evaluation in lieu of the research study as part of standard of care.

Risks associated with neuropsychological assessments:

- Both conditions (FF [control] and TeleNP [intervention]): The potential risks associated with participation in the study are minimal and include the risk of anxiety and/or fatigue, boredom or frustration during the completion of the neuropsychological testing sessions. An additional potential risk is loss of confidentiality, which could lead to potential social or cultural risks, if personal sensitive information is shared outside of the intervention.
- TeleNP: For the TeleNP condition, there are no expected physical, social, cultural, financial or legal risks. One potential risk is loss of privacy and/or confidentiality, as described below. We will employ video-based assessments for the TeleNP section, using HIPAA-compliant platforms.

Mild practice effects may be observed regardless of order of administration, which is commonly noted in standard of care with serial testing; however, given that results will be provided from the FF condition (i.e., the condition most comparable to standard of care), there is a small possibility that this may result in a slight overestimation of participant's cognitive abilities for those who undergo the FF condition second. See mitigation of risks below, as we will use validated mitigation strategies used in standard of care for serial testing.

The neuropsychological tests selected for this research study are identical to measures used in standard of care, with the FF condition being comprehensive and comparable to SOC. Standard of care for neuropsychology is not set in stone, meaning that the duration of the assessment is often provider-dependent. For reference, the tests and the length of the assessment are comparable to the standard neuropsychology battery – both in terms of content and duration – that the PI (Bettcher) uses in clinic for the same patient population. All tests selected were chosen based on their standard use in clinic, their ability to carefully characterize cognitive strengths and weaknesses, and their utility in assisting with differential diagnosis. Thus, we do not think that that the participant would receive a less comprehensive assessment in the research study than they would receive as part of standard of care.

Risks to privacy and/or confidentiality: Participants face a potential risk to privacy or loss of confidentiality related to private identifiable information and the research materials (test results) that they may provide as a study participant.

Risk of a delay in diagnosis: Based on a national survey, the median time between assessment date and report is approximately 3 weeks; however, this does not include available windows to schedule neuropsychology visits in clinic, which often is on the order of months (i.e., once a patient is referred to neuropsychology at UCH, it frequently takes more than a month to schedule them with a provider). Our study will involve a 4-6 week process (maximum of 3 month window), during which time both the FF and TeleNP conditions will be conducted. This is still within the range of expected result times when considering the SOC provider scheduling process. In addition, the clinical neuropsychological assessment is one portion of a much larger assessment conducted by the neurologists; the neurologist is ultimately the provider that will provide a definitive diagnosis to the patient, and their diagnostic regimen typically occurs over a 3- to 6-month period, during which reversible dementia labs, brain MRI, and cognitive testing are ordered. Our proposed timeline fits within the expected parameters of a neurology assessment; thus, we do not expect a risk for a delay in diagnosis.

Alternative treatments and procedures: Because patients will all be seen by the UCH Memory Disorders Clinic, patients have access to the Neuropsychology Service as part of usual care. Based on neurologist determination, patients are frequently referred for a neuropsychological assessment as part of the interprofessional care team approach.

Adequacy of Protection Against Risks

Informed Consent and Assent: Because the targeted patient groups suffer from degenerative diseases, safeguards, and guidelines are in place for assessing the capacity of potential subjects and the use of surrogates/legally authorized representatives in the setting when an individual is determined unable to consent for themselves. Participants will be recruited through the UCH Memory Disorders Clinic, which is a subspecialty clinic in the department of Neurology. Dr. Holden and other neurologists at the UCH Memory Disorders clinic may directly approach

their patients to participate in the study, and they will also document their initial determination of capacity to consent based on clinical assessment. If the patient is interested in participating, the neurologist will provide brief (e.g., contact information; diagnosis; capacity) information to the psychometrist and the psychometrist will set up the initial screening and consent call. All potential participants will be encouraged to include a care partner in the process (i.e., screening/consent, study visits).

All participants will subsequently participate in an informed consent process; if the referring neurologist notes a lack of capacity, the participant will be asked to include their legally authorized representative (LAR) during the screening/consent call. All aspects of the project will be reviewed by the University of Colorado Multiple Institutional Review Board (COMIRB). Before enrollment, study personnel will ensure the subject's full understanding of the research project, including the study objective, risks and benefits, the right to non-participation, review processes, emergency medical treatment, and financial responsibility. Informed consent will provide explicit details regarding confidentiality and sharing of de-identified data with qualified researchers; more specifically, consent forms will indicate that: de-identified data may be shared with qualified investigators outside the University; identifiable information from their in-person assessment will be provided to them and their referring neurologist in a research note. Dr. Bettcher, Dr. Greher, and Dr. Holden will also be available to answer questions regarding consent and procedures.

Strategies to minimize risk: Risks to subjects are minimal and may include loss of confidentiality and psychological discomfort about discussing issues related to their neuropsychological assessment. Prior to enrollment, the study will be explained in a clear and detailed manner by the study coordinator (serving in role as coordinator and psychometrist) and investigators. All participants will be reminded at the beginning of all assessments of their right to terminate the assessment at any time. In the study consent procedure and study activities, we will clearly state that all participants can refuse to answer any questions or to review any of the study materials. Research staff will be trained to address psychological distress and will follow standard procedures for referral for mental health evaluation. We will also reassure patients that if they choose not to be in the study, it will not affect the medical care they normally receive.

We will provide neuropsychological test results from the FF condition (i.e., condition that is most congruent with standard of care) to the referring neurologist and the patient, and this information will also be placed in a research note in their UCH EMR. This will be explicitly noted in consent form and reviewed in detail with the participant. In terms of study results, there is a possibility of practice effects, particularly on memory tests and fluency tests, with serial testing. Studies suggest minimal practice effects in individuals with symptomatic Alzheimer's disease; however, given that we will provide results from the FF assessment to be used in clinical care and potentially for diagnosis, we will mitigate risk in the following way: a) use of alternate forms, where possible and b) require of at least one month between conditions. Based on these strategies, which are also used in standard of care with neuropsychological serial testing, we do not think enrollment in the study poses a significant risk of a clinically meaningful practice effect.

Strategies to manage and protect the privacy of participants and confidentiality of research data: A copy of the consent for will be given to each participant. Maintenance of subject confidentiality is a high priority for the proposed research project. Video-based TeleNP will be conducted using

HIPAA-compliant platform supported by UC Health and CU Anschutz Medical Campus. Video assessments will not be recorded. All written and audio-recorded data (i.e., stakeholder semi-structured interviews) and consent materials will be given anonymous identification numbers and will be stored on a password protected private database on computers in locked offices. The consent forms and the key for identification of subject names corresponding to identification numbers will be stored in a separate locked file cabinet. For audio-recorded data (i.e., semi-structured interviews), research assistants will redact any spoken identifiers (names, etc.) from transcripts and will label audio-files with a sequential de-identified number. Study data will be collected and managed using REDCap (Research Electronic Data Capture). Only key study personnel will have access to these data. REDCap is a secure web application designed to support data capture for research studies, providing user-friendly web-based case report forms, real-time data entry validation (e.g. for data types and range checks), audit trails, and a de-identified data export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus).

Plans for ensuring professional intervention if indicated: Participants will be given the PI's contact information for any questions or concerns about the study. Staff will be trained to identify and address psychological distress, reportable events, or threats to society including elder abuse, suicide or homicide ideation or intent, violent behavior or threats, excessive emotional outbursts, a witnessed psychotic break with visual or auditory hallucinations, verbalization of anxiety or flashbacks to past traumatic experiences, and reports of major depression (assessed in the study). For acute issues, hospital security will be called (720-848-7777). For nonacute issues, the research team will be available in clinic to help avert crises and to schedule potential needed follow-up. If elder abuse is suspected, we will contact the patient's Colorado county law enforcement agency and county-specific adult protective services intake phone number through standard reporting mechanisms. The informed consent forms state that if elder abuse is suspected it will be reported, in accordance with State of Colorado law. A toll free crisis line will be made available to participants who may be in abusive situations (1-888-885-1222), and the referring neurologist will be alerted to suspected elder abuse.

Plans for handling incidental findings: Participants will receive results from their FF research assessment. Through the process of completing the study procedures, the most likely potential incidental findings will be new or worsened physical or psychological distress, or delirium. If the intervention is stopped due to discomfort and/or the patient desires for the research staff to share information about their current needs with the patient's UCH Memory Disorders Clinic neurologist, the psychometrist will communicate this information on the patient's behalf. Of note, if information emerges during either the TeleNP or FF visit that requires immediate clinical action, or clearly would impact treatment, the neuropsychologist will immediately notify the participant and neurologist to streamline care and minimize any delays in treatment. Moreover, if any safety, psychological or other signs of distress related to potential diagnosis of AD are noted during either assessment, appropriate referrals will be coordinated by Drs. Bettcher and Greher.

To improve reach to participants who have limited access to technology and conduct TeleNP using a standardized technology platform, we will provide a 4G tablet to all participants via a research lending library. Participants will be encouraged to bring a care partner, if available, with them to visits (i.e., FF and TeleNP); however, consistent with standard clinical practice, the availability of a care partner will not be a requirement.

E. Potential Scientific Problems:

Practice Effects: Repeated administration of cognitive tests is sometimes associated with practice effects, which may impact interpretation of results. Practice effects have been shown to be lower in symptomatic (MCI, dementia) patients relative to asymptomatic adults[34]; with respect to individual domains, verbal memory tests and verbally-mediated executive function measures appear to be most vulnerable to practice effects, with visuospatial measures less impacted. In estimating practice effects over a 3- to 6-month period, maximum effect sizes have ranged from 0.10 to 0.15 based on drug trials, which are quite small.[34] Our proposed period (4-6 weeks) occurs over a shorter duration. Based on recommendations for clinical trials[34], we will use alternate forms, where available (i.e., memory tests; fluency measures; attention/working memory). Of note, we will provide feedback to the patient and referring neurologist based on the FF assessment. In cases where the participant undergoes the FF assessment *after* the TeleNP condition, it is possible that aforementioned practice effects, albeit very small, may influence the mean scores obtained for each cognitive domain. Serial testing is common in standard neuropsychological practice, thus we will use validated approaches (i.e., alternate forms) for tests that are most vulnerable to this effect.

Diagnosis: While neuropsychologists will be apprised of the study design, they will be blinded to the *specific* referral diagnosis (i.e., typical vs atypical AD); moreover, the neuropsychologist will be asked to provide *their own determination* and given the option of including "Not AD" as their provisional diagnosis. The goal of this approach is to minimize bias and circularity; however, it remains possible that neuropsychologist-specific effects will be present (i.e., tendency to rate participants as "complex"). We will assess in exploratory analyses whether there were provider-specific effects on outcomes. We acknowledge that the division of diagnoses into three categories (i.e., subjective concerns; MCI; dementia) does not fully map onto NIA-AA diagnostic criteria for MCI[2] and AD dementia[1]; however, most neuropsychologists do not have access to fluid/PET biomarkers in clinical practice, thus our approach more pragmatically represents standard of care. Nonetheless, neuropsychologists often do provide specific diagnoses for complex phenotypes, including focal presentations (e.g., posterior cortical atrophy). As an exploratory strategy, we will consider providing an additional diagnostic field for the neuropsychologist to indicate specific considerations in their differential.

Statistical Analysis Framework: We are evaluating equivalence by examining mean Z-scores per cognitive domain, aggregated across multiple tests; however, individual tests have different test-retest reliabilities, which are often evaluated on a patient-specific level through the use of reliable change indices (RCIs). Given the pilot nature of this clinical trial, it is possible that a .5SD difference in mean domain score will not accurately reflect a clinically meaningful difference in individual test scores. As such, we will consider examining test-specific differences across modalities using published test-rest reliability.

Technological Difficulties: We have incorporated several approaches to minimize and troubleshoot technological difficulties, including a pre-visit test call, inclusion of care partner in the process, and provision of a study tablet to all participants. Consistent with Aim 3, **we will track technological issues throughout the study procedures to inform changes that might be beneficial to a larger clinical trial.** In addition, we will include a discussion during monthly team meetings regarding any technological issues that arise.

F. Statistical Analysis Plan:

For **Aim 1**, we will adopt an equivalence testing framework. The null hypothesis is that there is an average difference of at least .5 SD units in the difference in the z-scores, where .5 SD defines a potentially clinically meaningful difference. The alternative hypothesis is that the mean of the

difference in the z-scores is zero. This is the reverse of standard statistical testing. We elected a .5 SD margin as an initial threshold for a clinically meaningful difference; the reason for this decision is that once an individual reaches a level deemed to be clinically significant impairment (e.g., mild impairment = -1.5 SD; moderate impairment =-2.0 SD), a change in .5 SD equates to a categorical difference in their overall severity rating. To conduct our equivalence test, we will compute the difference in the z-score between the FF and TeleNP conditions and compute the mean difference and a 90% confidence interval based on a t-test. This results in an equivalence test with an alpha=0.05. If the entirety of bounds of the 90% confidence interval are between (-.5SD, .5SD), then the two assessments will be considered equivalent. We will repeat this computation stratified by referring diagnosis (typical vs. atypical), and also by sex or race/ethnicity (white vs. non-White).

For **Aim 2**, we will compute a 3x3 table with the rows as TeleNP diagnosis and the columns as FF diagnosis to summarize the results. To assess the equivalence of TeleNP and FF for each condition we will create 3, 2x2 tables. For example, when assessing for differences in typical AD we will collapse over atypical AD and Not AD. Following prior work[35], we will compute the difference proportion of typical AD for the TeleNP and FF setting and construct a 90% confidence interval. A difference of proportions greater than 5% will be considered a clinically meaningful difference. If the 90% confidence interval is between (-5%,5%), then the two modalities will be considered equivalent. We will repeat this process for the two other neuropsychologist-determined categories (atypical AD, Not AD). We will conduct the same analyses, stratified by severity. We will assess whether the neuropsychologists' diagnosis is equivalent to the Flexible Assessment by repeating the above analysis using the Flexible vs FF diagnosis (i.e., diagnosis reported prior to initiating Flexible Assessment).

For Aim 3, Feasibility and Acceptability of Intervention Measures and the UTAUT will be analyzed descriptively with means and interquartile ranges. Analysis of qualitative data will be a continuous process beginning with initial interviews and continuing throughout the data generation period. All interviews will be audio-recorded and transcribed verbatim. Directed by Dr. Lum, rapid qualitative analysis[36] will be used to understand multiple user perspectives on feasibility, acceptability, and other potential factors affecting use, including home context, of TeleNP compared to FF. At least 2 team members will analyze transcripts.[37] All data will be entered into ATLAS.ti v8.0 (GmbH, Berlin) for data management. Transcripts will be analyzed to develop the major themes or concepts reported by interviewees. Using the quantitative and qualitative data, we will conduct sequential mixed methods analyses using data from Aim 3.[38] The synthesis stage of data analysis involves triangulating the findings from interviews and quantitative data related to feasibility (i.e., assessment time, protocol adherence, technical issues, etc.), acceptability ratings, availability of a care partner, etc. We will interpret and summarize feasibility and acceptability for each modality from the different user perspective

G. Summarize Knowledge to be Gained:

Appraisal of the feasibility and validity of TeleNP in patients with complex AD presentations will provide a critical platform for the future development of a pragmatic, multi-site trial. Validation of TeleNP in a real-world setting will further increase access to neuropsychological evaluations and reduce patient burden. Specific knowledge to be gained includes:

- Comparison of two testing modalities for neuropsychology: telehealth and standard, face-to-face assessment
- Comparison of diagnostic adjudication for these two neuropsychology modalities
- Test- and interview-specific differences in feasibility and validity in these two modalities

- Qualitative information regarding feasibility, participant experience and acceptability, care partner experience and acceptability, and psychometrist & neuropsychologist experience.
- Greater understanding of technological concerns that may arise in telehealth
- Preliminary understanding of potential benefits of telehealth, both qualitatively and quantitatively

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