Clinical Interventional Study Protocol

FULL PROTOCOL TITLE

Cognitive Stimulation Therapy for Dementia: A Two-Armed Pragmatic Trial

Study Chairman or Principal Investigator:

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Study Title

Cognitive Stimulation Therapy for Dementia: A Two-Armed Pragmatic Trial

Objectives

Cognitive Stimulation Therapy (CST) is an evidence-based non-pharmacological group therapy shown to benefit people with mild to moderate dementia. Despite increasing availability of CST worldwide, including in Connecticut and New York, access remains limited in the United States. This pilot pragmatic trial will embed a referral process to online community-based CST, known as virtual CST (V-CST) into the standard care protocol of two health care settings that serve people living with dementia in the state of Connecticut, assess the acceptability of V-CST to people living with dementia, and assess the feasibility of using data collected in standard practice by the referring health care systems and by the community-based V-CST facilitators to evaluate V-CST.

We will pilot a two-armed trial that will include an intervention group to receive the V-CST referral and a control group that receives standard care (no V-CST referral) to test the primary hypothesis,

H1: *Clinically meaningful cognitive decline will be less common in the intervention group than the control group.*

Additionally, the following secondary hypotheses will be tested:

H2: *Clinically meaningful cognitive improvement will be more common in the intervention group than the control group.*

H3: *New prescriptions for psychotropic medications will be less common in the intervention group than the control group.*

H4: *Increased dosages of psychotropic medications will be less common in the intervention group than the control group.*

H5: *V-CST will be favorably received by people with mild cognitive impairment and/or mild to moderate dementia, to be assessed by three process assessments*:

(a) the referral acceptance rate (percentage of people referred for V-CST who accept the referral);

(b) participant attendance (percentage of enrolled participants who attend each V-CST session); and

(c) participant attrition (percentage of enrolled participants who cease attending V-CST between session 1 (S1) and session fourteen (S14)).

Design and Outcomes

The study design that will be piloted is a two-armed randomized embedded pragmatic clinical trial (ePCT). This pilot trial aims to determine if it is possible to use the study design to determine if cognitive decline is experienced less commonly among intervention group (defined as those receiving V-CST referral) participants than control group members based on three widely used measures of cognition, the Montreal Cognitive Assessment (MoCA), St. Louis University Memory Screen (SLUMS), and Mini Mental State Exam (MMSE).

The study population will be persons with mild cognitive impairment and/or mild to moderate dementia identified by clinicians from two memory clinics: James E. C. Walker M.D. Memory Assessment Program at the University of Connecticut (UConn), and the Yale Memory Clinic at the Yale School of Medicine (Yale).

Participants will be randomized to the intervention and control groups stratified by site at the individual level. A total of 168 eligible participants will be enrolled in the study across the two sites. Participants will be randomized at each site by a random number generator to be allocated into the intervention or control arms in a 1:2 ratio. Analysis will examine baseline demographic, diagnosis, medication, and cognitive screening variables between the two groups to ensure their balance.

Patients randomly assigned to the intervention group will be referred by their clinical providers to participate in V-CST, and those who accept the referral will participate in one of seven V-CST groups. Up to eight participants will join each group. Open enrollment into the study will close once the groups are filled with up to 56 participants or when all seven V-CST groups have begun. 112 participants will be in the control group.

The primary clinical outcome is clinically meaningful cognitive decline per scores on standardized cognitive measures (i.e., MoCA, SLUMS, MMSE) and the secondary clinical outcomes are prescribed psychotropic medications. Both are obtained during standard of care in the two sites. Outcomes to assess implementation feasibility include the referral acceptance rate, participant attendance, and attrition.

Interventions and Duration

Referral for V-CST is the intervention that will be introduced in the two participating sites. CST is an evidence-based group therapy that is recommend for people with a diagnosis of mild cognitive impairment and/or mild to moderate dementia and has been recommended by the United Kingdom's National Institute for Health and Care Excellence since 2006 (NICE, 2006, 2018). It is a version of cognitive stimulation developed from the theory of reality orientation, which has been supported from a Cochrane review in a pilot trial (Spector et al., 2001) and a full randomized control trial (Spector et al., 2003). Analyses showed that CST had benefits comparable to those of accepted pharmacological treatments for dementia and was cost effective (Knapp et al., 2006). Additionally, RCTs have shown CST to have significant beneficial impacts on quality of life (QoL) (Butler et al., 2020), depression (Stewart et al., 2017), and cognition (Aguirre et al., 2013), and CST has been found to be efficacious for those with Alzheimer's disease and vascular dementia (Piras et al., 2017). CST is increasingly accessible in practice internationally and even accessible to low-income countries (Spector et al., 2019).

CST is a structured cognitive intervention involving 14 thematic sessions that promote participants to engage in various activities and discussions. Each session is typically 45-minutes, and it is offered twice per week over a seven-week period (Spector, 2003). The CST protocol is clearly defined and has been adapted for online delivery as Virtual CST (V-CST) to support social distancing (Cheung & Peri, 2020). CST-trained facilitators will adhere to the CST training manual, which outlines the 14-themed sessions and itinerary for each session (Appendix A), and will deliver the therapy online. The study duration will occur over 1 year starting with screening by the physicians at the two HCSs and end when data analysis is completed. The participants will be involved in the research protocol for up to 1 year from the start of the referral process to the end of the follow-up visit with their referring physician.

Sample Size and Population

The target population is people with mild cognitive impairment and/or mild to moderate dementia, and the study population will include those who are English-speaking and web users from one of the two health care system sites. 168 study participants will be enrolled into the study; 56 participants will be randomly assigned to the intervention group (V-CST referral) and 112 participants will be allocated to the control group to receive the current standard of care (no V-CST referral).

STUDY TEAM ROSTER

Principal Investigator:

Michael Lepore, PhD

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Amherst, MA 01003404-964-6686
mjlepore@umass.edu
Dr. Lepore, Principal Investigator, holds primary responsibility for overseeing the study's overall performance and quality, including eligible patient identification, randomization to intervention and control groups, intervention group referral and orientation processes, data retrieval from the referring health care systems, patient treatment and safety, data safety and monitoring, intervention fidelity monitoring, data analysis, and study communications and dissemination. Dr. Lepore will lead all phases of the project by collaborating with and providing direct supervision to all project team members in their respective roles and tasks, and he will also work closely with the site leads and site coordinators in planning for and implementation of patient identification, randomization, and referral processes, and data retrieval, safety monitoring, and analysis.

Co-Investigators:

Roee Gutman, PhD
Department of Biostatistics, Brown University
Providence, RI 02912 USA
401-863-2682
rgutman@stat.brown.edu
Dr. Gutman is the project biostatistician. He will oversee all data analyses. He will help advise on statistical and pragmatic study designs, which includes the handling of missing data that may arise and methods for addressing non-compliance. Dr. Gutman will also review project materials that are disseminated across the pilot sites, to stakeholders, and to experts.

PARTICIPATING STUDY SITES

Participating study sites include the University of Massachusetts, University of Maryland School of Nursing and Brown University, referral sites include the Yale Memory Center and UConn Center on Aging.

University of Massachusetts (UMass)

Michael Lepore, PhD
University of Massachusetts (UMass)
651 N Pleassant St

Amherst, MA 01003As the UMass Site Lead who also is the Project Lead (PI), Dr. Michael Lepore will oversee and coordinate all study activities and administration, including the identification of study eligible patients from the referring sites, the sharing of data on study eligible patients from the referring sites, the randomization of study eligible patients to intervention and control groups, the referral of patients for V-CST from the referral sites, data analysis procedures and dissemination, oversee adverse event

communication and documentation, and regulatory procedures. Dr. Lepore will be supported by a Study Coordinator who will provide direct support to the referral sites in identifying study eligible patients, making data on study eligible patients available for the research team, and referring patients for V-CST.

University of Maryland Baltimore (UMB)

Joan Carpenter, PhD, CRNP, ACHPN, FPCN
Department of Organizational Systems and Adult Health
Baltimore, MD 21201
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As the UMB site lead, Dr. Carpenter will oversee all data storage at the UMB previous managed by Project lead Dr. Lepore during Dr. Lepore's transition to University of Massachusetts Amherst. Dr. Carpenter will be responsible for managing access to study data, ensuring data safety and integrity, and regulatory procedures. Dr. Carpenter will also be responsible for assisting in the data transfer to the new lead coordinating site, University of Massachusetts Amherst.

Brown University

Roee Gutman, PhD
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As the Brown University site lead, Dr. Gutman will oversee all data analyses for the study, including random allocation of study eligible patients to intervention and control groups for each referral site, assessing sociodemographic and clinical balance across these groups, and conducting data analyses relevant to the research questions including assessment of intervention outcomes. Dr. Gutman more generally will advise on statistical and pragmatic study designs, which includes the handling of missing data that may arise and methods for addressing non-compliance, and will also help confirm source data features from each pilot site. He will also help design the study's database.

The study includes two referral sites, which are listed below. Each referral site has a designated Site Lead and will have a Research Assistant (RA). Site Leads and RAs will engage and oversee the site's activities.

Referral Site 1: UConn Center on Aging (UConn)

Site lead: Karina Berg, MD, MS
UConn Center on Aging (UConn)
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kberg@uchc.edu

As the Site Lead at UConn on this project, Dr. Berg will oversee UConn's participation in this study by attending monthly project meetings in order to provide clinical guidance in the development and execution of this study with the project team, other clinical sites, and stakeholders. She will be involved in the enrollment process in screening for and referring eligible participants to CaringKind, as well as

contributing to the data transfer to UMass. She will also ensure that UConn's EHR generates a list of eligible patients; monitor study data; assure protocol compliance at her site; and conduct safety reviews on an ad hoc basis. During the review process, she will evaluate whether the study should continue unchanged or require modification/amendments.

Referral Site 2: Yale Memory Center (Yale)

Site Lead: Arman Fesharaki-Zadeh, MD
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Boyer Center for Molecular Medicine Yale
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arman.fesharaki@yale.edu

The Yale Memory Clinic will serve as one of the subject recruitment sites under Site Lead Dr. Fesharaki. This site is a leading diagnostic center for neurodegenerative diseases in the Northeast and approximately sees more than 1,200 patients per year. The clinic is staffed by six other memory providers, and it is located within the Yale Physicians Building in New Haven, CT.

As Site Lead, Dr. Fesharaki will oversee Yale's participation in this study by attending monthly project meetings in order to provide clinical guidance in the development and execution of this study; he will be responsible for ensuring that Yale's EHR generates a list of eligible participants, monitoring study data, assuring protocol compliance, overseeing transfer of study data to UMass, and conducting safety reviews on an ad hoc basis. During the review process, he will evaluate whether the study should continue unchanged, require modification/amendments, or close to enrollment. He will help participate in manuscript writing.

Operational Definitions for this protocol:
Intervention group: The group of participants randomly selected to receive a V-CST referral.
Intervention: The intervention introduced in this protocol is a referral process from the HCS to CaringKind for V-CST.
Standard of Care Procedures: The level at which the average, prudent provider in a given situation would manage that patient's care under the same or similar circumstances.
V-CST: A standard of care therapy provided by CaringKind.
HCS or referring providers: For the purposes of this protocol, HCS is equivalent to referring physicians/providers

1 STUDY OBJECTIVES

1.1 Primary Objective

Cognitive Stimulation Therapy (CST) is an evidence-based non-pharmacological group therapy shown to benefit people with mild cognitive impairment and/or mild to moderate dementia. A Cochrane Review of 15 RCTs of CST integrated data in meta-analyses for 718 participants (407 receiving cognitive stimulation, 311 in control groups) and showed "a clear, consistent benefit on cognitive function was associated with cognitive stimulation (standardized mean difference (SMD) 0.41, 95% CI 0.25 to 0.57). This remained evident at follow-up one to three months after the end of treatment" (Woods et al., 2012). Consistent with these meta-analysis findings, the present study will examine the impact of V-CST on

cognitive function in approximately the same time frame (i.e., within two months) after the end of treatment.

Despite increasing availability of CST worldwide, including in Connecticut and New York City, access remains limited in the United States. This pilot pragmatic trial will embed V-CST referral into the standard care protocol of diverse health care settings that serve people living with dementia in the state of Connecticut, assess the acceptability of V-CST to people living with dementia, and determine the feasibility of using cognitive test results collected as part of clinical care to evaluate study hypotheses. Collection of these data longitudinally will be leveraged to compare rates of clinically meaningful cognitive change between intervention and control groups.

The two-armed trial will use existing data collected in standard care to test the primary hypothesis,

H1: *Clinically meaningful cognitive decline will be less common in the intervention group than the control group.*

1.2 Secondary Objectives

Additionally, two secondary hypotheses (H2, H3) will be tested:

H2: *Clinically meaningful cognitive improvement will be more common in the intervention group than the control group.*

H3: *New prescriptions for psychotropic medications will be less common in the intervention group than the control group.*

H4: *Increased dosages of psychotropic medications will be less common in the intervention group than the control group.*

H5: *V-CST will be favorably received by people with mild to moderate dementia, to be assessed using data from CaringKind by three process assessments:*

(a) the referral acceptance rate (percentage of people referred for V-CST who accept the referral);

(b) participant attendance (percentage of enrolled participants who attend each V-CST session); and

(c) participant attrition (percentage of enrolled participants who cease attending V-CST between session 1 (S1) and session fourteen (S14)).

Using the final set of data, inclusive of the select EHR data on study participants from the HCS, we will also capture additional trial process measures, including:

c. percentage of complete data elements from each measure,

d. percentage of study participants who attend scheduled follow-up visits with the referring physician.

Finally, as described below in section 9.42, V-CST facilitators have participants in V-CST complete three measures prior to S1 and after S14:

a. Geriatric Depression Scale (GDS),

b. Engagement and Independence in Dementia Questionnaire (EID-Q) – Subscales 3-5,

c. Positive Psychology Outcome Measure (PPOM).

Using these data from CaringKind, aggregate results of these measures at both time points will be summarized in reports for participating HCS to share with participants and their legally authorized representatives.

2 BACKGROUND AND RATIONALE

2.1 Background on Condition, Disease, or Other Primary Study Focus

Despite the growing prevalence of neurodegenerative diseases, the treatment options available remain limited in mitigating the progressive cognitive and functional decline that PLWD face and poses serious health and economic burdens to society (Alzheimer's Association, 2020). To help minimize economic and social burdens, there has been a transition to keep PLWD living longer in their homes with non-pharmacological means due to the lack of advancements in pharmacological treatments. Despite several non-pharmacological approaches being effective and of low economic cost, they are still hard to access since many HCSs do not offer them (Gitlin et al, 2020). In Connecticut and New York City, CST is offered to people with dementia by a community-based care provider.

2.2 Study Rationale

Cognitive stimulation therapy (CST) is an evidence-based group therapy intervention and is built on eighteen key principles, which are outlined in the facilitator's manual. Each session has a theme with elements that are repeated weekly to reinforce learning. A key CST principle is choice. CST facilitators are encouraged to choose or add appropriate activities and offer group members choices to meet their needs. Facilitators are trained to recognize that everyone has different skills and strengths. Activities are geared to build successful participation. Participants are encouraged to share their opinions and engage in activities at their own discretion. Facilitators provide mental stimulation through discussions where new ideas, thoughts, associations, opinions, and choices are expressed. The manual guides CST facilitators to encourage an atmosphere where everyone's contribution is valued and respected, and a diversity of views is welcomed. The key principle of respect guides sessions to ensure the value and dignity of all participants are honored.

The structure of CST has developed from the theory of reality orientation, which has been supported from a Cochrane review in a pilot trial (Spector et al., 2001) and a full randomized control trial (Spector et al., 2003). Analyses showed that CST had benefits comparable to those of accepted pharmacological treatments for dementia and was cost effective (Knapp et al., 2006). Additionally, RCTs have shown CST to have significant beneficial impacts on cognition (Aguirre et al., 2013). The UK not only recommends this intervention for those with mild to moderate dementia, but it has been included in the United Kingdom's National Institute for Health and Care Excellence since 2006 (NICE, 2006, 2018).

Given CST's clearly defined structured protocol and adaptability for online delivery to support social distancing guidelines during COVID (Cheung & Peri, 2020), V-CST has the potential to serve as an effective intervention that can be easily disseminated worldwide since its online delivery has mitigated some of its prior barriers to access: cost, distance, and time constraints. V-CST is also favored by clinicians because not only are most of its components of delivery flexible, but this intervention is of minimal risk. The minimal risk of participation in CST has been established by numerous studies, and participants have reported an overall, positive experience from V-CST. Also, given the evolving conditions of COVID, the delivery of this intervention online will help support ongoing access to treatment despite any changes to social distancing guidelines while keeping vulnerable participants safe.

Despite the established efficacy of CST (Spector et al., 2003), its implementation remains circumscribed as many HCS do not offer this community-based service. To address this gap in access, a multi-modal approach is needed, and the collaboration between clinical sites and community-based partners becomes essential in delivering such non-pharmacological interventions to patients that would likely benefit from them (Harrison et al., 2020). In this pilot trial, two clinical sites (Yale and UConn) will refer patients to one community-based partner (CaringKind) to provide V-CST.

2.3 Potential Risks and Benefits

Potential Risks:
Both Intervention and Control Group Risks:

As we are collecting Personal Health Identifiers (PHI), there is a risk for loss of confidentiality. We will minimize this risk by utilizing a secure file transfer protocol established with UMass and storing all PHI on HIPAA compliant data servers called Sharepoint. Sharepoint is maintained by UMass information technology (IT) department. Additionally, all data will be deidentified at UMass prior to transferring to Brown for analysis. Additionally, we will not be collecting any sensitive or potentially harmful information if a loss of confidentiality occurs.

Intervention Group only:

Minimal risks to PLWD are expected and no Adverse Events (AEs) or Serious Adverse Events (SAE) of CST have been reported in over 15 years of studies. The minimal risk of participation in CST has been established through implementation of CST in numerous studies and countries, as an international CST implementation research study protocol summarizes: "CST has no documented adverse effects and, therefore, risk to participants will be low" (Spector et al., 2019). Despite the established low risk for any AEs or SAEs, our stakeholder engagement processes include attention to risk minimization, including the risks of in-person treatments posed by the COVID-19 pandemic. To eliminate these risks, CST will be delivered online in this trial. The team's experience delivering CST online has further confirmed the dearth of risks from participating in CST. There is a risk for breach of privacy. To address the risk for breach of privacy, participants will be encouraged to attend virtual sessions in a private setting. However, due to the nature of a virtual setting, the facilitators cannot guarantee privacy. Additionally, the V-CST site will follow standard of care protocol and HIPAA compliance policies within their institution to protect participant privacy. Finally, subjects will be in group therapy and already identified by everyone else in the group. This breach in privacy is not feasibly avoidable due to the nature of the therapy. This breach in privacy will be reviewed and discussed during the clinical assent process. Finally, a potential risk for this patient population is increased stress related to the virtual aspect of the intervention. To mitigate this risk, the facilitators created and implement an orientation prior to beginning V-CST.

Potential Benefits:

Studies have provided substantial evidence for the efficacy of CST in reducing depression and in improving cognition and quality of life (QoL) in older adults with dementia. A recent Cochrane review on CST combined data from 15 randomized controlled trials of CST with PLWD and showed significant effects on cognition in intervention versus control conditions. The findings of this Cochrane review are similar to the findings yielded in previous systematic reviews which indicated improved cognition among patients treated with CST. In a descriptive study to assess the impact of CST on cognition, quality of life, and depression, among six CST groups (like the present study), a paired sample t-test run among pre- and post-test measures showed statistically significant improvements in cognition and depression. Furthermore, CST is commonly described as an enjoyable experience by participants, and many

participants want more CST sessions after the completion of the treatment. This desire for more sessions inspired the development of Maintenance-CST, a longer-term delivery that extends beyond the initial 14 sessions. Participants in an online CST group studied by this team in Fall 2020 provided weekly responses about their experiences, commonly sharing comments that reflect their enjoyment of CST and their desire for more sessions (e.g., "Very good discussion today because the topic brought everyone into the conversation. I would like to know if there is a plan for an ongoing group") (Lepore et al., 2021). This study will hopefully encourage the establishment of a referral process between the study sites allowing for participants and fellow patients to continue benefiting from CST.

3 STUDY DESIGN

The study design that will be piloted is a two-armed randomized pilot ePCT. This pilot trial aims to evaluate it is possible to use the study design to determine if cognitive decline is experienced less commonly among intervention group participants than control group members.

The study population will be persons with mild cognitive impairment and/or mild to moderate dementia, and subject participants will be randomly sampled from two institutions: UConn and Yale. Eligible participants will be identified from medical records, verified appropriate for V-CST by physician review, and randomized in a 1:2 ratio into the interventional or control arms. The intervention will be referral for V-CST and the control will receive no referral. Unequal randomization is used in this trial because randomizing more participants to the control arm allows greater overall participation.

A total of 168 eligible participants will be enrolled into the study, and enrollment will close once the intervention group has 56 participants and the control group has 112 participants. Analysis will examine baseline demographic, diagnosis, and medication variables between the intervention and control groups to ensure they are balanced. Any identified imbalances will be addressed using regression adjustments.

4 SELECTION AND ENROLLMENT OF PARTICIPANTS

The HCS clinicians will use the study inclusion and exclusion criteria for participant selection and screening. Study enrollment will entail random allocation to control and intervention groups, and referral of the intervention group to V-CST by the HCSs, as described below.

Eligible subject participants will be identified by clinicians from each of the HCS clinical sites via utilization of their electronic clinical records. In order to pragmatically and accurately screen for participants meeting inclusion and exclusion criteria, we will obtain a HIPAA authorization waiver to review medical records prior to enrollment. Cognitive assessment cut-off scores in the inclusion criteria align with those previously used with the MoCA (Binns et al., 2020), SLUMS (Stewart et al., 2017), and MMSE (Aguirre et al., 2010). The referral process (from Yale and UConn to CaringKind) that is detailed in this protocol follows the standard of care for referral method at the participating sites. Participation in the protocol does not change the standard of care methods at any of the sites. The referral of intervention group members will end once all 56 intervention group members have been offered a V-CST referral or when the seven V-CST groups have begun.

4.1 Inclusion Criteria

Participants must meet all the inclusion criteria to participate in this study, to be assessed in clinic or by record review at each site:

- Diagnosis of Mild Cognitive Impairment or Mild to Moderate Dementia
- MoCA score of 10 to 26 OR SLUMS score of 10 to 26 OR MMSE score between 13 and 24 recorded as present $\leq$ 24 months before the record review
- English-speaking
- Visit expected to be scheduled to include cognitive screening 6 to 12 months after record review.

4.2 Exclusion Criteria

Candidates who meet any of the exclusion criteria will be excluded from study participation, to be assessed at each clinical site by file review and during V-CST enrollment:

- Auditory or visual impairment, combative behaviors, or other clinician-assessed condition that would interfere with group treatment
- No access to online meeting platform
- Patient has specified to HCS not to engage patient in research or to use patient data in research
- Patient has previously participated in V-CST
- Physician determines a caregiver is needed to support V-CST participation, but no caregiver available to assist with technology.

4.3 Study Enrollment Procedures

Pre-enrollment Screening:

Eligible participants who fulfill the inclusion criteria will be identified by clinicians from the HCSs via utilization of their clinical records. Clinicians will review the list of participants identified as eligible to remove any whom they consider unfitting for V-CST. Reasons for removing any patients from the eligible list will be documented by the clinicians to inform potential refinements to the inclusion criteria in the screening log. The clinicians will maintain a screening log that includes the patients' identifiers for medical record search, diagnosis, I/E criteria requirements, enrollment status (referral or control group), outcome of referral for intervention arm, and reasons for not enrolled if applicable. This screening log will be kept on site at the HCS on a local encrypted server. To ensure pragmatism for the clinical HCS sites and to align with the goal of this pilot trial, the screening log will include PHI for ease of use. The screening log will be securely transferred to UMB via Sharepoint where it will be scrubbed of all PHI/PII and each participant will be assigned a unique study identifier. After the data set is de-identified, the UMB team will send the data to Brown University for randomization. The screening log will be stored on Microsoft Teams (MS Teams) at UMB for data cleaning. Screening procedures were completed while UMB was the lead coordinating site. All data in screening process will be transferred after regulatory approval of UMass as the lead coordinating site.

Enrollment and Informed Consent Considerations:

As described in more detail in section 11, the study will have a waiver of informed consent for research purposes, but subjects will be able to give clinical consent/assent for the V-CST referral and participation. As with usual care, patients do not have to enroll in any program they are not interested in and can stop at any time.

Randomization:

The UMB team will de-identify and sort screening log and create an enrollment log with each participant assigned a unique study identifier for randomization. Participants will be allocated by a random number sequence in a 1:2 ratio into the intervention or control arms within each site. The study biostatistician will create the random sequence that the HCSs will apply for the random allocation of participants. The sequence will be created using block randomization with size of 4 to ensure balance across time.

At each HCS, clinicians will offer referral for V-CST to participants who were randomly assigned to the intervention group. The referring physician will meet the patient in clinic or contact the patient by phone to offer the referral. The referral will describe what participation entails, including the schedule of V-CST sessions, the use of the online meeting platform, and the expectations of participants' caregivers. To be consistent with real-world clinical practice, blinding will not be used (Dal-Re et al., 2018): the referral

sites will make referrals to the V-CST facilitator team following standard treatment referral protocols, which include the names and contact information of the patients who will be referred.

Patients who are referred for V-CST will be contacted by CaringKind using their standard procedures to enroll referred patients in V-CST.

Attendance in a V-CST orientation session, scheduled at least one to two weeks prior to S1, will be required to verify each participant's capacity to participate in V-CST. The V-CST orientation sessions will be held per CaringKind's SOC protocol. The orientation process is internal to CaringKind, not a part of this study protocol. During the orientation session, the V-CST facilitator will provide an overview description of V-CST, will review caregiver expectations, will verify participants' abilities to use both the audio and visual components of Zoom, and will provide participants an opportunity to meet the V-CST facilitator and to ask questions. Orientation participants who are verified to be able to participate in V-CST will be emailed a Zoom link calendar invite for the 14 sessions. Orientation participants who are determined during the orientation session to be unable to participate (e.g., if they are unable to access Zoom) will be advised by the CaringKind team that they are unable to participate and their HCS clinician will be notified of this outcome. Referrals for V-CST will stop once 56 participants are referred to CaringKind or when all seven V-CST groups have begun.

Enrollment and randomization were completed while UMB was the lead coordinating site. All data in screening process will be transferred after regulatory approval of UMass as the lead coordinating site.

5 STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

The intervention introduced in the pilot pragmatic trial is V-CST referral by physician. V-CST referral will be provided to 56 patients who are randomly allocated to the intervention group. CST is an evidence-based group therapy that is recommend for people with a diagnosis of mild to moderate dementia. In this study, CST will be delivered online via Zoom and referred to as virtual CST (V-CST). CST is administered twice weekly over a seven-week period for a total of 14 sessions. At each group session, there will be a total of up to eight participants, and the sessions typically last between 45 minutes to 1 hour and are co-facilitated by two CST-trained facilitators from CaringKind: One facilitator leads the V-CST sessions (lead facilitator), while the other provides participant support (facilitator). To help with adherence rates, reminder emails are sent to participants on the morning of the session, and adherence is captured by CaringKind recording participant attendance at each session per standard of care.

Facilitators ensure privacy and protect safety by providing password protected Zoom sessions. A meeting password is required, and the 'waiting room function' is used to ensure that only those who are intended to join the meeting are admitted.

Adverse effects: Some people with dementia may have difficult or traumatic memories, and sensitivity is required not to push group members into sharing painful memories. Additionally, current affair discussions involve topics that members may find uncomfortable to discuss. To mitigate these events, the group members will be able to choose from a list of topic discussions. However, should a participant become upset during the discussion, the facilitators will determine if the person can remain in the group; if the participant is unable to remain in the group (e.g., due to uncontrolled anger), the facilitator will remove that participant from the group to provide him or her private space to discuss what happened. The lead facilitator will inform the HCS of adverse events. Facilitators will respond to adverse events per their SOC protocol at CaringKind. Adverse events will be reported to the HCS clinicians following reporting

guidelines detailed below in section 7. Topics that elicit such events will be removed from the V-CST protocol.

5.2 Handling of Study Interventions

V-CST referral will be handled by the patient's physician following guidelines that align with the physicians' standard referral practices and that use the V-CST facilitators' orientation guide to describe the nature of V-CST, describe risks of participating (such as risk to privacy due to the nature of group therapy), and verify patient assent for the physician to make the referral. When providing V-CST referrals, physicians will meet the patient in clinic or contact the patient by phone to offer the referral. The referral will describe what participation entails, including the schedule of V-CST sessions, the use of the online meeting platform, and the expectations of participants' caregivers. The referral sites will make referrals to the V-CST team following standard treatment referral protocols, which include the names and contact information of the patients who will be referred. V-CST will be administered per SOC protocol at CaringKind. The V-CST procedures described below are part of standard of care at CaringKind and have not been augmented or changed for this protocol.

When delivering V-CST, facilitators will adhere to its 18 principles as specified in the CST facilitator manual and standard of care procedures (Spector et al., 2006):

1) Mental stimulation: Improving cognition and communication through mentally stimulating discussions. The first aim of CST is to mentally stimulate and get participants' cognitive functions active and engaged.

2) New ideas, thoughts, and associations: Encouraging new ideas and opinions by making new semantic connections. This encourages new ideas, thoughts, and associations, rather than mere memory recall of information previously learned. For example, during the current affairs discussions, rather than introducing familiar topics, participants are encouraged to discuss new topics.

3) Using orientation, sensitively and implicitly: Integrating orientation information into general discussion. Formal orientation is to be conducted individually with each participant prior to participating in V-CST. Informal orientation will be conducted in a subtle way in the beginning of each group. Orientation information will be displayed by the V-CST facilitator via the Zoom "share screen" function, and during the discussion the facilitator will offer orientation questions, such as, "Do you think the weather today is hotter/colder than usual for this time of year?"

4) Opinions rather than facts: Using topics to generate opinions rather than testing facts to mitigate incorrect answers from participants. The V-CST group should never feel like a memory test. Rather, the strengths of individual participants will be the focus of intervention delivery.

5) Using reminiscence as an aid to the "here and now": Comparing old and new information to promote orientation. Using memories helps to tap into a strength that many people with dementia have for recalling experiences from much earlier in their lives. Additionally, such reminiscence is often an enjoyable activity for participants.

6) Physical movement: Exercising motor skills through movement and games. Mild exercise components such as lifting arms in sequence are incorporated into V-CST sessions when appropriate. Movement is encouraged at the beginning of every session, but also is limited both to maintain safety and to maintain visual and audio connection with the participants.

7) Providing triggers and prompts to aid recall and concentration: Supporting learning through multisensory cues and an information board. A combination of senses are stimulated through the activities in the session. Memory works much better when not relying on only one sense. Oftentimes, visual cues are used during the sessions, such as by using the "share screen' feature, and a variety of sounds are incorporated into the sessions as well.

8) Continuity and consistence between sessions: Using consistency throughout sessions helps promote continuity and familiarity. Groups always start and end in the same way. Memory and learning are supported through the provision of continuity and consistency between sessions.

9) Implicit (rather than explicit) learning: Let learning and remembering happen naturally. Genial facilitation will encourage participants to experience V-CST groups in a fun way as opposed to viewing these sessions as learning experiences.

10) Stimulating language: Promoting communication and conversation. The sessions are designed to stimulate language and promote communication and conversations amongst participants.

11) Stimulating executive functioning: Using activities to support planning and organizing. Executive functioning involves sequencing, planning, and organizing. Several of the V-CST sessions exercise executive functioning skills.

12) Person-centered: Seeing the person and their uniqueness. Each person in the group is unique, with a lifetime of experiences that have shaped their personality and attitudes, leading to a variety of skills, interests, preferences, and abilities. Participants' strengths will be focused on, rather than concentrating on areas of weaknesses.

13) Respect: Respect and dignity for all. It is imperative to show respect by learning what is important to each participant, and to value the diversity of views, opinions, and beliefs in the group.

14) Involvement and inclusion: Keep everyone involved. The group facilitator should not be doing most of the talking. Group members should be encouraged to address their contributions to one another. The group can also be involved in helping to plan future sessions, such as deciding upon what topics to discuss at the next session.

15) Choice: Activities are flexible and should be adapted to each participant's strengths. The group program is not prescriptive. Group members should always be offered choices, and alternative activities and approaches should be available to fit the needs of the group. Offering choices allows group members to become more involved, especially in activities that allow them to identify with their group when selecting a group name and group song. A choice of activities is offered for each session. The facilitator can choose from two activities designed for each session, mix ideas across sessions, or incorporate their own ideas into the session if appropriate.

16) Fun: Make it fun and enjoyable. Groups should provide a learning atmosphere that is fun and enjoyable. Members' brains should be stimulated, as should their sense of humor.

17) Maximizing potential: Optimize the learning environment to support the peoples' potential. People with dementia can learn, given the right environment. Give people time, do not overwhelm participants with information and provide them just enough prompting to enable them to carry out the activities independently. This will increase exposure to success, which will also aid in learning and enjoyment.

18) Building/strengthening relationships: Becoming friends. The group sessions will help members to get to know each other better and can strengthen relationships between the members and facilitators.

Each of the V-CST sessions is comprised of an introduction, a main activity, and a conclusion. There is a manual to provide guidance and examples for trained facilitators (Spector et al., 2016), and it emphasizes the flexibility of CST delivery to align with group interests, needs, and preferences. An outline description of the three main parts of a V-CST session is provided below.

I. Introduction (Duration: 10 minutes)

i. Group name and theme song: During the first session, identify a group name and group theme song. After today's session, please begin all future sessions by greeting each group by their group name and sing your group song.
ii. Orientation: Discuss day, month, year, season, weather, time, name and location
iii. Icebreaker: Question for all to enhance group cohesion
iv. Discussion: Current events (using newspapers or photographs)

II. Main Activity (Duration: 25 minutes):
Most sessions include a choice of two activities selected to align with the level of function and interests of the group. All activities can be adapted to align with group interests and capacity. Activity suggestions from the manual for group facilitators are shown in Appendix A. The activity themes for each of the 14 sessions are listed below.

1. Physical Games
2. Sounds
3. Childhood
4. Food
5. Current Affairs
6. Faces/scenes
7. Word Association
8. Being Creative
9. Categorizing Objects
10. Orientation
11. Using Money
12. Number Games
13. Word Games
14. Team Quiz

III. Conclusion (Duration:10 minutes)

i. Thank everyone for participating
ii. Members sing the theme song again
iv. Introduce next week's content
v. Seek feedback about the session

5.3 Concomitant Interventions

5.3.1 Allowed Interventions

All drugs and/or treatments/interventions are allowed, including rescue medications, while in the study.

5.3.2 Required Interventions

No concomitant interventions are required.

5.3.3 Prohibited Interventions

No classes of medications, devices, etc. are prohibited while the participant is in the study.

5.4 Adherence Assessment

Adherence will be assessed by documenting several process measures using data captured in standard practice by CaringKind, including:

1. referral acceptance rate (percentage of participants offered V-CST referral who accept referral)
2. enrollment rate (percentage of participants offered V-CST referral who enroll in V-CST)
3. attendance at each of the 14 V-CST sessions. Attendance will be tracked over the course of the pilot.

6 STUDY PROCEDURES

Study procedures, including the schedule of evaluations and description of evaluations, are described below.

6.1 Schedule of Evaluations

Assessment	*Pre-Treatment Data Screening (Day -90 to -30)*	*Treatment Enrollment (Day -30 to -1)*	*Treatment Group 1-7 (Day 0 to 200)*	*Post-Treatment Data Screening (Day 61 to 275)*
Inclusion/Exclusion criteria	*X*			
Randomization	*X*			
Demographics	*X*			
Diagnoses	*X*			
Medications	*X*			
Cognitive function	*X*			*X*
Referral acceptance rate	*X*			
Enrollment rate		*X*		
Attendance			*X*	
Attrition			*X*	
Therapy administration form			*X*	
Weekly Monitoring Participant Progress reports			*X*	
Adverse Events			*X*	

NOTE: Day 0 = Date of V-CST Group 1, Session 1

6.2 Description of Evaluations

Evaluations will occur at 5 points during the study: (1) Pre-Treatment Screening of Baseline Data, (2) Treatment enrollment, (3) Treatment Group 1 through 7, (4) Treatment closeout, and (5) Post-Treatment Follow-up Data. This schedule is summarized in the table above and a detailed description of each phase of the study is described below. The evaluations and timepoints described below in 6.2.2 and 6.2.3 are part of standard practice at CaringKind and collected universally as part of the V-CST treatment program. We will be accessing the information from these evaluations secondarily for our study.

6.2.1 Pre-Treatment Data Screening

Pre-treatment data screening will be conducted first to determine which patients at each HCS are eligible for the study. These evaluations will be conducted by the HCSs examining their electronic health records to identify eligible participants based on the study's inclusion and exclusion criteria.

Eligible participants will be randomized at each site and allocated into either the control or intervention arms. At this time, the following data will be abstracted from HCS records on the eligible participants: ICD-10 code(s) for dementia; demographics; medications; and cognitive screening scores.

Participants randomized to the intervention arm will be referred for V-CST.

Pre-Treatment Data Screening will conclude with HCSs uploading the abstracted data to the project Sharepoint file.

6.2.2 Treatment Enrollment

During V-CST enrollment, V-CST facilitators will conduct an orientation session for the intervention group and obtain clinical consent for participation.

6.2.3 Treatment Sessions

Over the course of 14 treatment sessions in 7 V-CST groups, five process measures will be collected by the V-CST facilitators at each session:

- Patient attendance (percentage of 14 sessions attended)
- Protocol fidelity: CST protocol followed per Therapy Administration Form
- Attrition: Patient dropping out of V-CST group and stopping attendance
- Weekly Monitoring CST Participant Progress reports
- Adverse Events

V-CST will end after the 14 sessions (plus orientation and closeout sessions) and participants continue with their standard of care treatment at their HCS.

6.2.4 Post-V-CST Data Screening

Post-V-CST data screening will be conducted by the referring physician after the 14 V-CST sessions have been held.

At this time, post-intervention data on medications and cognitive screening scores will be abstracted from HCS records on the study participants. Post-treatment data screening will conclude with HCSs uploading the abstracted data to the project Sharepoint file.

7. SAFETY ASSESSMENTS

This study is of minimal risks, and there are no known risks to participants in the proposed trial. Furthermore, online delivery of CST adheres to COVID social distancing guidelines keeping this vulnerable population safe. Currently, memory clinics do not standardly provide non-pharmacological interventions to their patients, so no alternative treatments will be provided besides V-CST.

Minimal risks to participants are expected, and no Adverse Events (AEs) or Serious Adverse Events (SAE) of CST, V-CST, or referral for V-CST have been reported over the last 15 years. Numerous studies have established CST to be of minimal risks to participants and report: "CST has no documented adverse effects and, therefore, risk to participants will be low" (Spector et al., 2019). Despite the established low risk, our processes will mitigate the risk for in-person interventions by offering CST online.

No safety events are expected. A possible AE may be participant stress during a group discussion. Some people with dementia may have difficult or traumatic memories, and sensitivity is required not to push group members into sharing painful memories. Additionally, current affairs discussions involved topics that members may find uncomfortable to discuss. To mitigate these events, the group members will be able to choose from a list of topic discussions. Should a participant report or exhibit increased stress during participation in V-CST, two primary actions will be taken: First, the V-CST facilitator will try to address and reduce the participant's stress, and if the participant is unable to remain in the group, the facilitator will remove that participant from the group to provide him or her private space to discuss what happened. Facilitators will respond to adverse events per their SOC protocol at CaringKind. The facilitator will inform the HCS of adverse events. Topics that elicit such events will be removed from the V-CST protocol.

7.1 Specification of Safety Parameters

The primary safety parameter used in this study is online versus in-person CST delivery. In addition, each session will have two facilitators who completed CST training, one who leads facilitation and one who monitors and supports participants throughout the discussion to address any challenges that may arise. Also, to protect confidentiality, methods to protect identifying information and participant data will include the use of password protected programs, encrypted software, and use of secured servers, and password protection into Zoom meetings. See section 2.3 for specific safety measures against loss of confidentiality and breach of privacy.

7.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

There are no documented harmful side effects from receiving a referral for or participating in CST (Orrell et al., 2017; Spector et al., 2003). Although the minimal risk of CST has been established and our online delivery further reduces risk for harm, care will be taken to assess, record, and analyze safety parameters.

V-CST facilitators will monitor participants for harm at all times during therapy delivery. Should a safety event occur, the event will be addressed by the PI upon receiving the adverse event report and reported to the Safety Officer.

7.3 Adverse Events and Serious Adverse Events

Definitions for adverse events (AEs), serious adverse events (SAEs), and Unanticipated Problems (UP) to be used for this trial are provided below:

Adverse Event (AE): Any unfavorable medical occurrence in a clinical research study participant, including any abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participants' involvement in the research, whether or not considered related to participation in the research.

Serious Adverse Event (SAE): Any adverse event that:

- Results in death,
- Is life threatening, or places the participant at immediate risk of death from the event as it occurred,
- Requires or prolongs hospitalization,
- Causes persistent or significant disability or incapacity,
- Results in congenital anomalies or birth defects,
- Is another condition which investigators judge to represent significant hazards.

Unanticipated Problems (UP): Any incident, experience, or outcome that meets all of the following criteria: unexpected, in terms of nature, severity, or frequency, given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the study population; related or possibly related to participation in the research; suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

As stated above, one possible AE for this study is increased stress. For example, it is possible that the group discussion that takes place will increase participant stress. Increased stress is a possible mild AE of CST. This study has no other AEs.

No SAEs are expected. No AEs or SAEs of CST have been reported in over 15 years of studies. CST involves group discussions, and in this trial, CST will be delivered online to prevent infectious disease transmission.

Although hospitalizations and death or not uncommon in this population in general, they are unlikely to be related to the study. In the event of hospitalizations or death of V-CST participants identified by the V-CST facilitators, the lead facilitator will report this information to the referring physician per standard of care practice. In the event of hospitalizations or death of any study participant (intervention or control group) identified by the referral site, the referral site will report this information to the study coordinating site (UMass).

7.3.1 Reporting Procedures

No SAEs are expected to relate to participation in this study. Hospitalizations and death are expected in this population and will be assessed by the V-CST facilitators and referring sites but are not expected to be related to study participation. The minimal risk of participation in CST has been established through implementation of CST in numerous studies, which have concluded: “CST has no documented adverse effects and, therefore, risk to participants will be low” (Spector et al., 2019). Although the risks of participating in CST are established to be low, it is possible that the group discussion that takes place during CST will increase participant stress. Increased stress is a possible mild AE of CST. AEs will be reported to the PI and to the HCSs within 5 business days of their occurrence.

AEs will be reported per IRB policies and also to IMPACT Collaboratory Regulatory and Data Team for dissemination to the NIA IMPACT Collaboratory PO (Dr. Partha Bhattacharya), and the project’s IMPACT Safety Officer, six months after the start of enrollment and again at the end of enrollment/data collection (whichever is later) , or at the frequency requested by NIA or the IMPACT Safety Officer.

Process for identifying AEs, SAEs, and UPs:

In the unlikely event of an AE, the lead facilitator will complete an adverse event form with supporting documentation of the event such as lab values, hospital/discharge summaries, and clinical evaluations to

be submitted to the patient's HCS within 5 business days of the incident. An IMPACT Collaboratory-approved report form will be used, with adaptations made as identified to be needed. The patient's referring provider will review the adverse event form and complete the form with a determination on relatedness and severity then submit documentation to the PI/UMass team within 5 business day from being notified of the incident.

Regarding adverse events that are serious and unexpected and unanticipated problems, the lead facilitator will follow the same procedure as for AEs and will be required to submit documentation immediately upon becoming aware of the incident.

All adverse event reporting will be done through a secure file transfer protocol established by the UMass IT services to ensure protected transfer of AE documentation. The PI or study coordinator will initiate communication with the sponsor to notify of an AE event per the reporting schedule below.

The following subsections include a discussion of how AEs will be classified. Data and safety monitoring reporting will classify SAEs and AEs as to their severity, expectedness, and potential relatedness to the study intervention as per the definitions below:

Severity

- **Mild**: Awareness of signs or symptoms, but easily tolerated and are of minor irritant type causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient.
- **Moderate**: Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning.
- **Severe**: Events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating.

Expectedness

- **Unexpected** - nature or severity of the event is not consistent with information about the condition under study or intervention in the protocol, product brochure, or investigator brochure.
- **Expected** - event is known to be associated with the intervention or condition under study.

Unexpected events will be subject to expedited reporting requirements as described in the NIA Guidance on Clinical Trials.

Relatedness

All adverse events (AEs) will have their relationship to V-CST assessed by a V-CST facilitator who examines and evaluates the participant based on temporal relationship and her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related**: The adverse event is clearly related to the investigational agent/procedure – i.e., an event that follows a reasonable temporal sequence from administration of the study intervention, follows a known or expected response pattern to the suspected intervention, that is confirmed by improvement on stopping and reappearance of the event on repeated exposure and that could not be reasonably explained by the known characteristics of the subject's clinical state.
- **Possibly Related**: An adverse event that follows a reasonable temporal sequence from administration of the study intervention follows a known or expected response pattern to the suspected intervention, but that could readily have been produced by a number of other factors.
- **Not Related**: The adverse event is clearly not related to the investigational agent/procedure - i.e., another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent with the onset of the event and the study intervention and/or a causal relationship is

considered biologically implausible.

Note, given the nature of this pragmatic study, all deaths and hospitalizations will be considered expected and not related to the study.

Reporting schedule:

- All **adverse events that are serious** (SAE) **and unexpected** (i.e., have not been previously reported for CST) will be reported to the IMPACT Collaboratory Regulatory and Data Team and NIA IMPACT Collaboratory PO for dissemination to the project's IMPACT Safety Officer within 48 hours of the study's knowledge of SAE.
    - Only those adverse events that are serious (SAE), unexpected, ***and related to the intervention*** must also be reported to Advarra IRB. Unexpected and ***unrelated*** SAEs will be reported to Advarra IRB on a case-by-case basis if requested by the IMPACT Collaboratory Safety Officer or NIA IMPACT Collaboratory PO.

- All **unexpected** deaths will be reported to IMPACT Collaboratory Regulatory and Data Team and NIA IMPACT Collaboratory PO (Dr. Partha Bhattacharyya) for dissemination to the IMPACT Collaboratory Safety Officer within 24 hours of study's knowledge of death.
    - Advarra IRB does not require the specific reporting of death outside of the SAE reporting requirement above, but they will be notified on a case-by-case basis if requested by the IMPACT Collaboratory Safety Officer or NIA IMPACT Collaboratory PO.

- All **unanticipated problems** (**UPs)** will be reported to the IMPACT Collaboratory Regulatory and Data Team and NIA IMPACT Collaboratory PO for dissemination to the project's IMPACT Collaboratory Safety Officer and IRB (if required) within 48 hours of the study's knowledge of the event.

- The summaries of all AEs, SAEs, deaths, and UPswill be reported to the IMPACT Collaboratory Regulatory and Data Team, NIA IMPACT Collaboratory PO, and the IMPACT Collaboratory Safety Officer 6 months after the start or enrollment and at the end of enrollment/data collection (whichever comes later), or at a frequency requested by the IMPACT Collaboratory Safety Officer or NIA IMPACT Collaboratory PO.

The timelines established above will allow for the study team to adhere to the reporting schedule required by the IMPACT Collaboratory. Additionally, all AEs, SAEs, and UP will be tracked in a log stored in the regulatory binder. All AEs, SAEs, and UP will be reviewed at the biweekly Quality Control Committee.

7.3.2 Follow-up for Adverse Events

Although the risks of participating in CST are minimal, it is possible that the group discussion that takes place during CST will increase participant stress. Increased stress is a possible mild AE of CST. AE reporting will follow the schedule and methods detailed in section 7.3.1. The referring physician will follow up with participants following an AE according to standard of care practice.

7.4 Data and Safety Monitoring Plan

This study will be monitored by an IMPACT/NIA appointed Safety Officer (SO). The PI will be responsible for monitoring and protecting the data under the laws of HIPAA. They will ensure that those involved in the study are adhering to the study protocol that is provided to the Institutional Review Board (IRB) and will conduct safety reviews according to the schedule above. During these review processes,

the PI will assess whether the study's protocol should continue unchanged, require amendments, or close to enrollment. Changes in protocol will only be made in the interest of protecting participants' safety. Before these changes are made, the PI will inform the IRB. The PI, Safety Officer, and the IRB will have the authority to stop or suspend the study or require modifications. All research methods will only be carried out by trained professionals who have completed the training module "Ethics on Human Research."

The outcome data will be collected in standard care and abstracted from the sites' clinical records for this study. The V-CST practitioners and Site Lead and Coordinators are appropriately trained medical professionals to deliver these interventions and address any complications should they arise. In terms of risks unrelated to health, there is low risk associated with collection and attainment of subjects' protected health information (PHI). These risks will be mitigated by the study team's adherence to the adequate plans that have been designed to prevent against the improper use and disclosure of identifying information.

To protect confidentiality, all PHI will be maintained in a HIPAA compliant Sharepoint file, all data will be deidentified at UMass before being transferred to Brown University for analysis, and all results will be published as group data to avoid using identifying information. UMass will be the primary location for all data management, maintenance, and distribution. Any identifying information will be destroyed at the earliest opportunity, unless such retention is required by law in the interests of patient safety. Lawful authorities will include members overseeing the research, such as the IRB and SO. In the event of illegal disclosure, the event will be documented in the "accounting for disclosures log" and participants will be subsequently made aware of the disclosure.

Raw data will be extracted from the research sites electronic medical record each participant's name, age, ICD-10 dementia diagnosis code(s), psychotropic medications and dosages, and cognitive test scores. These data will be stored in a HIPAA-compliant Sharepoint file. The referring sites will be granted access to upload their patient data, and access to patient data will be restricted to the PI and study coordinator. Sharepoint is an encrypted secure file transfer platform maintained by the UMass IT department, with access to Sharepoint granted and maintained by the UMass IT department. All data will then be transferred from Sharepoint into MS teams to be maintained and clean accessible to only the UMB team. Sharepoint will only be used to transfer data and will not be the primary storage platform. MS teams is a HIPAA compliant and password protected platform maintained and stored on a UMass IT server.

Data previous stored at UMB will be transferred via Sharepoint to UMass to be permanently stored/maintained by the UMass study team and PI. All UMB servers will be scrubbed of all data for this project and will not store any data.

8 INTERVENTION DISCONTINUATION

Participants may decline the V-CST referral and also may withdraw voluntarily from the study at any time and for any reason without consequence. Additionally, specifications are established for discontinuing participant involvement in V-CST if ongoing involvement poses undue risk of AEs, such as if a participant is frequently combative and/or verbally abusive to other participants.

During V-CST sessions, the facilitators will observe all participants for expressions or signs of extreme stress or argumentative or confrontational behavior, such as yelling, cursing, or arguing with other participants. Facilitators will intervene when such signs are observed, such as to redirect the discussion to another topic. Participant involvement in V-CST will be discontinued temporarily or for the remainder of the study depending on the frequency and severity of the AEs and the responsiveness of the participant to redirection. Participant involvement in V-CST will be temporarily discontinued (for the remainder of the session) when more than one instance of such heightened stress is observed during a single V-CST

session. Additionally, participant involvement in the trial will be discontinued when instances of such heightened stress are observed in three separate V-CST sessions.

9 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

Referral for V-CST is the intervention that will be introduced in this study. The study design is a two-armed, open-labeled randomized pilot ePCT to evaluate V-CST's effectiveness for promoting cognitive function in people with mild-to-moderate dementia. Clinically meaningfully cognitive change will be determined based on change in scores on the MMSE, MoCA, and SLUMS, and will be compared across intervention and control groups.

9.2 Sample Size and Randomization

168 people with mild cognitive impairment and/or mild to moderate dementia will be enrolled into the study, and 56 will be assigned to the intervention group through randomized allocation to receive V-CST referral, and 112 participants will be randomly allocated to the control group to receive the current standard of care (no V-CST referral). Randomization will be stratified by site by a random number sequence in a 1:2 ratio.

9.21 Treatment Assignment Procedures

During study enrollment, the designated Site Lead/and or RA from each participating HCS will be supported by the UMass study coordinator to generate a list of eligible participants, based on this study's inclusion criteria, and to randomize the list by a random number sequence in a 1:2 ratio to either the intervention group (V-CST referral) or control group (no V-CST referral).

The HCS Site Lead will refer eligible patients in the intervention group for V-CST. Referrals for V-CST will stop when all 56 intervention group members have been offered a referral or when all 7 V-CST groups have begun.

9.3 Interim Analyses and Stopping Rules

Although no AEs are anticipated, the possibility of AEs will be monitored at every V-CST session, and specifications are established for discontinuing participant involvement in V-CST should they arise, as described above. The primary potential risk of V-CST is an increase in stress among participants, such as if participants are argumentative or confrontational with each other.

During V-CST sessions, the facilitators will observe participants for expressions or signs of increased stress or argumentative or confrontational behavior, such as yelling, cursing, or arguing with other participants. V-CST facilitators will immediately intervene when such signs are observed, such as to redirect the discussion to another topic. Participant involvement in V-CST will be discontinued temporarily or for the remainder of the treatment pending the frequency of these extreme stress instances and the responsiveness of the participant to redirection. Participant involvement in V-CST will be temporarily discontinued (for the remainder of the session) when more than one instance of such heightened stress is observed during a single V-CST session. Additionally, participant involvement in V-CST will be discontinued altogether when instances of such heightened stress are observed in more than two separate V-CST sessions.

In any V-CST group where more than one participant's involvement in V-CST is discontinued altogether due to multiple AEs, findings will be presented to the study statistician to review the events by group to determine whether there are statistical as well as clinical concerns. The statistician will report his findings to the project Safety Officer. The findings will be used to determine what steps will be taken.

9.4 Outcomes

Both primary and secondary outcomes will be examined, as described below.

9.41 Primary Outcome

The primary outcome to be assessed is clinically meaningful reduction in cognitive impairment. Reduction in cognitive impairment from baseline to post-intervention will be determined by comparing pre- and post-scores on standardized measures of cognition (i.e., the MOCA, SLUMS, or MMSE). A change—either increase or decrease—of 2 points or greater will indicate a clinically meaningful change. Primary outcome data will be retrieved from participating site records.

The MOCA, SLUMS, and MMSE are standardized screening tools commonly used by clinicians to determine a person's cognitive status. Although each of these instruments is relatively quick and easy to use and calculated to a total score of up to 30, each also has different sensitivity to mild cognitive impairment and length of time for completion, and clinicians use a combination of the different instruments to assess cognition rather than any one instrument exclusively. Based on prior literature, a decrease of about 1 point on each instrument is anticipated in the control group over the study period.

MMSE is a widely used, 12-item assessment of cognitive function that evaluates orientation to time and place, language, registration and recall of words, attention and calculation, and visual construction, and takes about 10 minutes to complete (Howland et al., 2016). MMSE assesses several areas, including orientation, immediate memory, short-term memory, and language functioning, each of which is scored independently for a total of 30 points (Slavych, 2019). MMSE has significant ceiling effects, reliably detecting dementia but not MCI (Howland et al., 2016). MMSE's brevity and ease of administration are strengths, whereas MMSE's disadvantages include its inability to detect subtle memory losses (Slavych, 2019). In a Cochrane review of CST, 10 studies involving 600 participants used the MMSE, finding the overall mean difference was 1.74 points (95% CI 1.13 to 2.36) and statistically significant ($Z = 5.57$, $P < 0.00001$) (Woods et al., 2012). In studies of people with stroke/transient ischemic attack, cerebrovascular disease, Tan et al (2017) and Kalmijn et al (1996) defined cognitive decline as a reduction of ≥ 2 points in the MMSE over two consecutive screenings from 3–6 months to 1 year.

MoCA takes the longest time of the three screening tools to complete, about 15 minutes. MOCA is useful with several populations and disorders, including Parkinson's disease, vascular dementia, traumatic brain injury, and others. MOCA addresses several concepts, including visuospatial/executive functions, naming, memory, attention, language, abstraction, delayed recall, and orientation, each of which is independently scored and combined for a total possible score of 30. MoCA's sensitivity as a screening tool for mild cognitive impairment, Alzheimer's disease, and dementia, and its ease of use are all strengths. The length of time required for MOCA administration is a disadvantage (Slavych, 2019). Consistent with their use of the MMSE, Tan et al (2017) also defined cognitive decline as a reduction of ≥ 2 points in the MoCA over two consecutive screenings from 3–6 months to 1 year. In a study of 175 subarachnoid hemorrhage patients, the minimum clinically important difference of the MoCA was 2 at 3-month follow-up (Wong et al., 2017). By calculating Reliable Change Index (RCI) confidence intervals (95%) from MoCA test–retest results, Krishnan et al (2017) identified a change of 1.73 points as representing a clinically meaningful difference in MoCA scores, a threshold beyond which the likelihood is high that an individual's change in performance reflects actual change in cognitive ability rather than noise.

SLUMS takes the shortest time of the three screening tools to complete, about 7 minutes. It includes 11 questions addressing several concepts—orientation, short-term memory, calculations, naming of animals, clock drawing test, recognition of geometric figures—and each response gets scored for a total of 30. The brevity of the SLUMS and its sensitivity for mild cognitive impairment are strengths. Limited research regarding psychometric properties of the SLUMS and its use with different populations are disadvantages (Slavych, 2019). Stewart et al (2017) compared pre-/post-CST SLUMS scores with 40 participants and found on average scores were 1.78 points higher after the intervention.

The study will leverage the use of these three instruments in standard practice to evaluate the primary outcome, clinically meaningful cognitive change, among patients who are assessed with any of the three different instruments. Clinically meaningful cognitive change will be determined based on a 2-point change in scores on the three instruments from pre-to post-treatment. Additionally, distribution-based analysis to determine clinically meaningful cognitive change is described in section 9.5.

Another potential indicator of meaningful change is the clinical decision to utilize an alternate cognitive assessment at post-intervention due to the presence of a ceiling or floor effect of the assessment originally utilized at pre-intervention. Based on input from clinicians participating in this study, pre- to post-intervention change from using the MoCA or the SLUMS to using the MMSE will initially be used to indicate a clinically meaningful *reduction* in cognitive function, and a change from using the MMSE to the MoCA or SLUMS will initially be used to indicate a clinically meaningful *improvement* in cognitive function. Any such *reductions* or *improvements* in cognitive function determined based on change in instrument use will be verified by the study coordinator directly with the HCS.

9.42 Secondary Outcomes

Because some trials have shown improvement in cognitive function for V-CST compared to control procedure, we will also compare the proportion of participants who experience clinically meaningful improvement in cognitive function between the two arms.

The other two secondary outcomes to be assessed through each site's pre- and post-intervention EHR data review for the intervention and control groups is the prescription of new psychotropic medications or the change in dosage of psychotropic medications. These secondary outcome study hypotheses are that fewer intervention than control group members will be newly prescribed psychotropic medications or have an increase in dosage of these medications. Study data on psychotropic medications will be retrieved from participating site records.
The following process measures also will be calculated using data from V-CST facilitators to assess trial feasibility:

- Referral acceptance rate at each health care setting (the percentage of PLWD in the intervention group who are referred for V-CST);
- Enrollment rate (the percentage of PLWD referred for V-CST who enroll in V-CST)
- V-CST adherence, which will be measured by monitoring participant attendance at V-CST sessions and calculating the percentage of sessions attended by enrolled participants;
- V-CST attrition, which will be assessed by documenting when participants cease attending V-CST between session 1 (S1) and session fourteen (S14).

To support quality improvement in these process measures, adherence and attrition also will be examined qualitatively when they occur. Specifically, when enrolled participants do not attend V-CST sessions, or when they cease attending V-CST sessions altogether, the intervention delivery team will inquire via email with the individual to query the reason(s) for their missed attendance or attrition. Additionally, in

the case of attrition, the HCSs will be notified, and the sites will inquire about the reasons for attrition at the patient's next regularly scheduled appointment. Participants' reasons for adherence and attrition will be reported to the PI, study coordinator, and/or lead facilitator as they are identified to continuously inform CST delivery and to determine any refinements that may be needed for successfully delivering CST online.

Finally, participants in V-CST will complete three measures in conjunction with an orientation session prior to S1 and a close-out session after S14 as these assessments are conducted in standard V-CST programming: Geriatric Depression Scale (GDS), Engagement and Independence in Dementia Questionnaire (EID-Q) – Subscales 3-5, Positive Psychology Outcome Measure (PPOM). Results at both time points will be summarized in reports for participating sites to share with participants.

9.5 Data Analyses

Data analysis will be conducted in two phases: after baseline data retrieval; and after all study data have been retrieved.

After baseline data retrieval, data analysis will be conducted to compare and assess the equivalence of baseline cognitive impairment, medications, and demographic characteristics across the intervention group and control group. Statistical analyses of baseline characteristics between participants for primary and secondary outcomes are the following: The Shapiro-Wilk test will be used to confirm that the random sample is normally distributed for the outcome variables studied. Student t-test will be used to confirm that mean variables are not significantly different between intervention and control groups (e.g., percentage with moderate versus mild cognitive impairment). Chi-square test will be used to confirm that dichotomous variables (e.g., sex) are not significantly different between intervention and control groups. Wilcoxon rank-sum will be used to confirm that ordinal variables (e.g., cognitive screening score) are not significantly different between groups.

Three outcome measures in this pragmatic study are used to assess cognition: MoCA, MMSE and SLUMS. 2-points change in the MoCA, MMSE or SLUMS will be used to indicate clinically meaningful cognitive change (either improvement or decline). Additionally, the number of points change on the cognitive screening instruments that are indicative of meaningful change will be evaluated using a distribution-based approach based on baseline cognitive assessment data from the three sites to inform the selection of instruments and threshold cut-offs for clinically meaningful change for a full-scale trial.

After all study data have been retrieved, including baseline and follow-up data from intervention and control groups, MoCA, SLUMS, and MMSE data elements will be examined for their completeness/missingness, and findings of missing data will be reported to the respective HCS. In addition to evaluating the completeness/missingness of data (i.e., the percentage of complete (non-missing) data elements), we also will determine the frequency of use of the three instruments (i.e., the percentage of study participants who were assessed with each instrument). If the outcomes could not be retrieved for some individuals, we will use multiple imputation with chains equations to address the missingness.

We will follow an intention-to-treat protocol whereby all patients who are randomized are included in statistical analyses according to the group (intervention or control) to which they were assigned, regardless of whether they participate in V-CST (McCoy, 2017). We will determine the distribution of each measure's change in scores and will apply the Cohen criteria whereby the values of the standardized response mean and effect size (i.e., the change in mean scores divided by the standard deviation (SD) of the baseline scores) are used as the indices of responsiveness. For the MoCA, Wu and colleagues (2019)

used the Cohen criteria and classified these effect sizes as large (>0.8), moderate (0.5-0.8), and small (<0.5), adopting a threshold value of 0.5 SD.

When different cognitive assessments are used pre- and post-intervention, a change from using the MoCA or the SLUMS to using the MMSE will initially indicate a clinically meaningful *reduction* in cognitive function, and a change from using the MMSE to the MoCA or SLUMS will initially indicate a clinically meaningful *improvement* in cognitive function. Any such *reductions* or *improvements* in cognitive function determined based on change in instrument use will be compared against the actual assessment scores using the literature for reference. For example, a shift from getting a score of 16 using the MoCA to a score of 16 using the MMSE would be verified as a clinically meaningful change from mild to moderate dementia (Saczynski et al 2015, Table 1). To validate any such initial indications of reductions or improvements in cognitive function that are determined based on a change in instrument used, verification of the change in cognitive function will be requested from the referring physician.

Table 1. Cut scores for MoCA and MMSE (Saczynski et al 2015)

MoCA	Cognition Level	MMSE
≤ 30	Normal	≤ 30
≤ 23	MCI	≤ 27
≤ 17	Mild Dementia	≤ 23
≤ 9	Moderate Dementia	≤ 17

For those using the same instrument in both baseline and follow-up, we also will assess the frequency whether there is a clinically meaningful reduction in cognitive function.

The estimand of the primary outcome would be the marginal difference in proportions of individuals that see clinically meaningful reduction in cognitive function.

Data analysis to test the study hypotheses is described below.

Testing of H1 will entail comparing the proportions of clinically meaningful reduction in cognitive function between the intervention group and the control group. Factors that affect the primary outcome will be controlled for by logistic regression analyses, which include the number of health comorbidities, baseline cognitive function, number of psychotropic medications, diagnoses and sites. With the study sample size, assuming that the rate of reduction in cognitive function is 50% we would be able to detect a 22% decrease in the rate of cognitive decline with 80% power and nominal level of 5%.

Testing of H2 will entail comparing the proportions of clinically meaningful improvement in cognitive function between the intervention group and the control group. Factors that affect the primary outcome will be controlled for by logistic regression analyses, which include the number of health comorbidities, baseline cognitive function, number of psychotropic medications, diagnoses and sites.

Testing of H3 and H4 will entail comparing the marginal prevalence of new prescriptions for or increased dosages of psychotropic medications between the intervention group and the control group. Logistic regression would be used to adjust for baseline clinical and demographic characteristics as in H1.

Testing of H5 will entail calculating the marginal percentage of intervention group participants who accepted the referral, the percentage that accepted the referral who enroll in V-CST, the percentage of V-CST sessions attended by enrolled participants, and the percentage of enrolled participants who ceased

attending V-CST between S1 and the last session S14. To adjust for baseline clinical and demographic variables we will use logistic regression.

Because some patients who are randomized to the intervention group may not assent to the V-CST referral, we also will conduct a secondary principal stratification analysis (Frangakis & Rubin, 2022). This analysis would be used to estimate the effect of the intervention among patients who complied with the treatment (i.e., participants assigned to the intervention group who enroll in V-CST) by performing principal stratification analysis to adjust for those participants assigned to the intervention group who did not enroll in V-CST. We will follow the analysis used in Mealli & Imbens (2004) and Hirano et al (2000).

In addition to hypothesis testing, data collected by the V-CST facilitators, including the Geriatric Depression Scale (GDS), Engagement and Independence in Dementia Questionnaire (EID-Q) – Subscales 3-5, and Positive Psychology Outcome Measure (PPOM), will be examined to detect any changes in scores from before to after treatment.

10 DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

In accordance with this IMPACT Funding Opportunity (RFA-IMPACT-20-P02B), the main purpose of delineating outcome measurement is to demonstrate the feasibility of collecting the outcome measures pragmatically during the pilot study. Currently, even though the participating HCSs in Connecticut are university-based clinics using Epic, few data elements are commonly recorded in the EHRs across HCSs, limiting their research value. During this project, we will use the demographic and health data that are available in EHR and other clinical records, including data on the primary study outcome, cognitive impairment, as well as a V-CST log maintained by CaringKind as part of their standard practice.

10.2 Data Management

Data from the HCSs will be gathered through a targeted raw data pull that includes only select information about study participants from the EHRs. First, clinical sites will retrieve patient data from their records based on the study inclusion/exclusion criteria, including demographic information, medications, diagnoses, and cognitive function (MoCA, SLUMS, and/or MMSE).

The research sites Yale and UConn will share data directly with UMass via Sharepoint, and will include data on V-CST enrollment, attendance, attrition, fidelity to the treatment administration manual, adverse events, and three measures standardly collected before and after participation in V-CST, the Geriatric Depression Scale, Engagement and Independence in Dementia Questionnaire - Subscales 3-5, and the Positive Psychology Outcome Measure. CaringKind will provide patient data to the referring HCS physician per standard of care. Once data is securely transferred to UMass, all study data will be stored in Microsoft Teams which is a HIPAA compliant password protected server only accessible to the UMass research team.

Confidentiality of participant records will be maintained by HCSs uploading all data to a secured server in a Sharepoint file. Access to the Sharepoint file will be limited to the PI and study coordinator at UMass, who will clean and deidentify data and assigning a unique study identifier for each participant. The UMass team will maintain a de-identified and PHI enrollment internally for communication between the research sites to ensure HIPAA compliance and protection against loss of confidentiality. UMass will be the primary location for all data management, maintenance, and distribution. All data will then be transferred from Sharepoint into MS teams to be maintained and clean accessible to only the UMass team. Sharepoint will only be used to transfer data and will not be the primary storage platform. MS teams is a HIPAA compliant and password protected platform maintained and stored on a UMass IT server. The de-

identified data will be transferred it to the study biostatistician at Brown University in an encrypted email. Using the deidentified data provided by UMass, Dr. Roee Gutman, study biostatistician, will conduct data analysis, interpret results, and report findings to the PI also through encrypted email messaging.

Since the beginning of initiation of this protocol at University of Maryland, Baltimore, Dr. Lepore has transition to a new appointment at University of Massachusetts. With sponsor approval, this project and protocol implementation will continue with Dr. Lepore at UMass. During the regulatory and administrative transition of the project to UMass, Dr. Carpenter at UMB will oversee the data storage and maintenance at UMB. After a data transfer agreement is in place, Dr. Carpenter will securely transfer via Sharepoint. All UMB servers will be scrubbed of all data for this project and will not store any data.

10.3 Quality Assurance

10.3.1 Training

Training for the CST facilitators is provided by St Louis University in affiliation with their Geriatric Workforce Enhancement Program supported by the Health Resources and Services Administration (HRSA) of the U.S. Department of Health and Human Services (HHS). All V-CST facilitators have completed this training for their scope of practice and CaringKind qualifications. Qualifications for V-CST facilitators are reviewed and approved by their employer CaringKind.

All research staff will review the study protocol and study documents prior to study initiation with the PI and study coordinator and sign a protocol training log.

10.3.2 Quality Control Committee

The PI, study coordinator, and biostatistician will serve as the study Quality Control Committee. The Quality Control Committee will review two types of reports.

1. The following reports from the V-CST facilitators will be examined:
    - V-CST Enrollment Reports, which indicate the number of intervention group members that received referral for V-CST who ultimately enrolled in V-CST
    - Adherence Reports indicating whether each participant attends each session,
    - CST protocol adherence checklists from each session, and
    - AE reports.
2. Additionally, the following report from the study coordinator will be examined:
    - Data Collection Issue Reports.

The Quality Control Committee will review the reports every two weeks during the enrollment, therapy delivery, and data collection phases of the trial, and in the unlikely case of AEs will review the AE reports within 5 business days of the reported AE. All AE that are serious or unexpected, and unanticipated problems will be reported immediately upon the facilitators or referring physicians being notified of the event. Based on the committee's review of the reports, opportunities to improve the quality of the trial design will be identified. Pending the committee's determination, official trial protocol adjustments will be made, or follow-up questions will be addressed as appropriate to the expert consultants from one or more of the IMPACT Collaboratory cores, from the HCSs, or from primary stakeholders (people with dementia) through the IMPACT Collaboratory Stakeholder Engagement Team.

10.3.3 Metrics

Of the patients who receive a V-CST referral from their HCS, the percentage who enroll in V-CST will be the primary enrollment metric. This metric will be calculated for each site to assess any site-level differences, and for sub-populations of patients to assess any individual level differences including by race, gender, and ethnicity.

Attendance at V-CST groups will be tracked to assess individual adherence at the individual level. The individual level metric will be the percentage of the 14 V-CST sessions that each intervention group member attends. The distribution of this metric across sub-populations of patients also will be calculated to assess differences by race, gender, and ethnicity.

Attrition from V-CST, indicated by the percentage of enrolled participants who stop attending V-CST between S1 and S14 also will be calculated.

The number of AEs will be assessed at the individual level, and the distribution of the number of AEs that each participant experiences will be calculated. Additionally, this metric, the number of AEs experienced by each participant, will be summed across all V-CST participants and among sub-populations of patients, including by race, gender, and ethnicity.

The completeness of outcomes data will be measured at the individual participant level to assess the quality of outcomes data with each instrument (i.e., MMSE, MoCA, SLUMS). The percentage of items with missing data will be calculated per V-CST participant as the primary quality control metric to be used for outcome measures. This metric also will be calculated for sub-populations of patients to determine individual level differences including by race, gender, and ethnicity.

10.3.4 Protocol Deviations

Following each V-CST session, in standard practice the V-CST facilitators complete a brief protocol adherence checklist indicating which components of the V-CST protocol were completed. Protocol adherence checklists will be reviewed by the Quality Control Committee when meeting every two weeks during the intervention delivery phases of the trial, and more frequently in the case of AEs.

10.3.5 Monitoring

Intervention protocol compliance will be monitored by the Quality Control Committee reviewing protocol adherence checklists when meeting every two weeks during the intervention delivery phases of the trial.

11 PARTICIPANT RIGHTS AND CONFIDENTIALITY

Participant rights will be upheld, and participants will be aware that confidentiality regarding their participation is limited due to V-CST being a group therapy in which other individuals participating are aware of the participation of others based on active visual and audio engagement during the course of therapy.

11.1 Institutional Review Board (IRB) Review

This protocol and any subsequent modifications will be reviewed and approved by Advarra, the IRB responsible for oversight of the study. This study will utilize a single IRB (Advarra), and all local IRB will cede to Advarra through a reliance agreement established prior to study start.

11.2 Informed Consent Forms

A request for a waiver of informed consent has been requested and approved for this pilot trial. This waiver is deemed justified for the combination of reasons listed below:

Enrollment into the study is considered at the time of randomization as there is no research consent process for this protocol. Intervention group participants will be asked to provide clinical assent for CST referral. The HCS provider will obtain informed clinical assent using a CST informational sheet derived from the CST site standard of care education materials on CST. Risks and benefits of CST, as well as alternative treatments are described in the clinical assent process per standard of care.

Justification for a waiver of informed consent is based on this study involving no more than minimal risk, the protocol cannot be practicably carried out without the requested waiver, and the waiver will not adversely affect the rights and welfare of subjects. This study qualifies as minimal risk based on CST being a low-risk intervention and is being administered as standard of care. Part of the aims of this protocol is to evaluate the feasibility and acceptability of the referral process to establish CST intervention options for PLWD as standard of care. Because it is during the referral process that consent processes would begin, study subjects cannot be consented as that would change the referral process that will be evaluated, and furthermore, the goals of a pragmatic trial such as this one will pilot requires limiting the interference of research activities on standard clinical practice and relying on more organic observational approaches to data capture as possible.

Additionally, the waiver will not adversely affect the rights and welfare of the subjects as the protocol will ensure that referring physicians obtain clinical assent for referral and participants will be engaged voluntarily. As CST is a very low risk non-pharmacological treatment with well-established benefits not readily available in this population, we do not anticipate participants would object to the aims of this protocol to establish CST treatment options; furthermore, in an initial pilot of V-CST, people with dementia who participated commonly reported positive emotional experiences and boosts to their self-esteem, and commonly described the experience of participating as enjoyable (Lepore et al., 2021). We will be collecting identifiable information due to the limited ability of the HCS ability to de-identify and burdensome on the staff to request de-identified data only.

Finally, we will inform patients of their participation in the study and provide results of the data analysis after study completion. After the intervention and follow-up time points are completed, we will distribute a letter directly to the participants from their HCS regarding the trial.

11.3 Participant Confidentiality

Because V-CST is a group therapy in which multiple participants (up to eight) have direct visual and audio contact with each other, and with the V-CST facilitators, confidentiality of the intervention group is limited. Furthermore, consistent with standard referral practices, the participating HCSs will provide the community-based service provider with the names and contact information of PLWD when making referrals for V-CST, and the community-based service providers will use protected health information (PHI; e.g., names, phone numbers, email addresses)) when enrolling PLWD in V-CST and over the course of treatment. Additionally, to ensure the trial is pragmatic by limiting data management tasks by the referring HCSs, the research will use PHI to track patients over time and across sites. In alignment with the use of PHI, a full waiver of Health Insurance Portability and Accountability Act (HIPAA) authorization is requested for both the recruitment and overall study tasks. The waiver is justified for the following reasons:

- Use or disclosure involves no more than minimal risk to the privacy of individuals because of the presence of an adequate plan to protect health information identifiers from improper use or

disclosure, specifically, maintaining all PHI in a secure Sharepoint file server that is maintained by UMass information technology (IT) department.

  - See section 2.3 for protection procedures against loss of confidentiality and efforts to protect personal health information from improper use or disclosure.
  - After data analysis is complete, data set will be scrubbed of all identifiers by the UMass research team. Only aggregated data set

- Research could not practicably be conducted without the waiver or alteration. The research is a pilot pragmatic trial, in which the referral sites will provide data on patients who are randomly allocated to the intervention group (to receive V-CST referral) and the control group (no referral). In order to maintain the pragmatic study design, ensure no biased is introduced, and maintain external validity, the researchers will not be able to obtain consent and inform the potential participants of the study procedures, therefore, we need a waiver for HIPAA authorization.
- Research could not practicably be conducted without access to and use of PHI. The use of the PHI is necessary for intervention screening and enrollment, and for linking patient-level data from across sites and over time. Because contacting PLWD using contact information and communicating with PLWD by name are basic tenets of social interaction in the study context, the research could not practicably be conducted without the waiver. Additionally, potential participants will be screened for eligibility to ensure safety of the referral and maintain the integrity of the research design. Finally, PHI will need to access and used to increase the pragmatism of the trial and minimalize changes to SOC practice at referral sites.

The confidentiality of patient information beyond the research team will be maintained i by storing study data in a HIPAA compliant platform. No paper records are anticipated, but all paper records will be kept in a locked file cabinet locally at the HCS sites and CaringKind. All computer entry and networking programs will be done using encrypted secure file transfers and storage.

11.4 Study Discontinuation

The study may be discontinued at any time by the IRB, the NIA, the OHRP, or other government agencies as part of their duties to ensure that research participants are protected.

12 ETHICAL CONSIDERATIONS

The primary ethical consideration guiding this study is the commitment to do no harm. There are no known risks to participation in the proposed trial. Indeed, the minimal risk of participation in CST has been established through implementation of CST in numerous studies and countries, as an international CST implementation research study protocol summarizes: “CST has no documented adverse effects and, therefore, risk to participants will be low” (Spector et al., 2019).

Although delivery of CST in person would pose substantial risk for contagious disease infection, our online delivery approach as virtual CST (V-CST) promotes safety. Participants in the trial are currently provided no treatments as an alternative to V-CST. Furthermore, delivery of V-CST eliminates the need for PLWD to travel, which also reduces safety risks.

Another ethical consideration guiding this study is adherence to principles of inclusion and empowerment whereby people with dementia are supported to have a meaningful voice in the design and conduct of studies that are intended to help them. This study engages people with dementia and a wide range of experts—including intervention implementation experts, and experts in integrating interventions in HCSs, PROMs, technical study design, statistics, research ethics and regulation—in designing the pragmatic trial.

13 COMMITTEES

The Quality Control Committee will meet every two weeks during the enrollment, intervention delivery, and data collection phases of the trial, and will convene more frequently as needed in the case of AEs.

14 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the policies and procedures developed during the project in consultation with primary stakeholders and through expert consultation with the NIA IMPACT Collaboratory. We will follow the IMPACT Publication Guide and the IMPACT Publication and Acknowledgement Policy and any presentation, abstract, or manuscript will be made available for review by the IMPACT Collaboratory prior to submission.

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16 SUPPLEMENTS/APPENDICES

Appendix A

Activity Suggestions per the CST Facilitator Manual

Physical Games
Choice A: Throw a softball around, asking people to say something about themselves as they catch the ball, for example their name, where they come from, their former occupation, etc.

Choice B: Play a physical game, such as skittles or indoor bowling, which involves teamwork. This should be a relaxed activity, incorporating movement, touch and score calculations.

Sounds
Choice A: Play sound effects either from YouTube or CDs that include different categories, such as 'indoor sounds' and 'outdoor sounds' and invite members to match sounds with pictures. Alternatively, play selected songs from the appropriate era and invite members to name the song or singer. If necessary, provide a choice of two or three names on the whiteboard as members listen to the song.

Choice B: Give percussion instruments to each person in the group, and use them to play along to familiar music, such as popular music from an appropriate era.

Childhood
Choice A: Ask members to fill out a printed sheet with their name, father's name, mother's name, schools attended, and so on to form the first page of a memory diary. Invite people to make a plan or drawing of their childhood bedroom or home, or even create a reconstruction of it on a board.

Choice B: As members to demonstrate the use of childhood toys, for example, a spinning top, jacks, etc. Talk about childhood sweets. Bring a selection to try and enjoy.

Food
Choice A: Using a combination of groceries and fresh food that has been priced, give people a budget and a scenario to plan, for example, a dinner or two. Categorize the above groceries into foods for different mealtimes, special occasions, savory/sweet. Choose a type of food and bring in a range from different cultures/contexts to taste and discuss.

Choice B: Taste foods which act as memory triggers or have personal meaning. Brainstorm food categories on the whiteboard. List as many as possible in each category. Complete names of food items, such as chicken…parmesan, French…fries.

Current Affairs
Choice A: Discuss issues from a section of recent national and local newspapers and picture magazines. Have multiple copies of interesting articles, so everyone has the same piece to look at. Ensure that the group helps select topics that appeal to their interests for discussion.

Choice B: Use questions on cue cards to stimulate conversation on news, views, attitudes, dreams and aspirations. For example, ask, “What do you think of today’s fashion?”, “Have politics and politicians changed.”

Faces/scenes
Choice A: Prepare multiple copies of pictures of famous faces or of local scenes so that everyone can look at the same picture. Give people one picture, asking what their thoughts are when they look at that picture. Gradually introduce one or more additional pictures, allowing people to familiarize themselves with each one. Then ask for people’s opinions, such as, “Who is the most attractive?”, “Who is the oldest, or youngest?”

Choice B: Use the same types of prepared cards and questions as in Activity A or consider showing pictures of faces which are not famous. Ask for people’s opinions, such as “Who do you think is older/younger?”, “What does their expression tell you about what they are thinking?’

Word Association
Choice A: Ask group members to supply the missing word in a number of phrases. These could be about quantities, famous people, famous places, or proverbs.

Choice B: Present the first few words of a song and ask the group to sing a few lines.

Being Creative
In this session, do a creative activity, such as:
Cooking
Making a seasonal collage
Clay modeling
Gardening
Provide paper and pencils/pens and ask group members to draw each other, and then guess who the drawing is of.

Categorizing Objects
Choice A: Ask people to think of words beginning with a certain letter in a particular category.
Write letters and categories on separate cards and use the cards to prompt the game. Alternatively, simply write the category on the board and invite people to think of as many examples as possible.

Choice B: Place approximately 20 objects or pictures of objects on a table. Ask people to group the objects in different ways, such as by use, color, or initial letter.

Orientation
Choice A: Depending upon where group members come from, show a map of the country or local area. Draw the outline of a map and ask people to come up with places and ask them to mark where they think they should be on the map. Then discuss how long it might take to get from one place to another, different transport routes, etc. If drawing a local street, have people draw out where particular landmarks are, such as the post office, the Church, and the supermarket. Many cities/towns have then and now photographs that document changes during the 21st century. Use these to stimulate discussion if most members know the area.

Choice B: Discuss whether people have moved from area to area, and if so, where from and to. If members have traveled abroad, use a map of the world to identify the different places. Discuss how long journeys take, how far apart places are, transport links, and landmarks.

Using Money
Choice A: Prepare pictures of common objects with prices marked on the back. Ask people to guess the price of items. Add up prices or match the price tag with the object.

Choice B: Show examples of both old and new coins and bills, encouraging people to discuss and compare them. Discuss changes in prices and values using questions, such as, “How much did people used to earn?” and “What can you get for $5 now?”

Number Games
Choice A: Play games involving the recognition and use of numbers like bingo, dominos, or sudoku. One can use a magnetic dartboard and keep score.

Choice B: Play “snap” with playing cards. Go around the group, with each person taking the next card off of a pack of cards and guessing whether it will be higher or lower than the previous card. Guess how many items are in a container. Count them to check whose guess is the closest.

Word Games
Choice A: Play a word identification game, which involves recognition and use of letters and words. Draw a number or dashes for each letter of a word and ask the group to guess the letters. Incorrect letters contribute, one by one, to the drawing of a hangman and losing the game. The group is required to guess the word – if needed, give a category clue. Create a set of cards each with a different word on it. Get the group to pick a card and try to explain or enact the word without actually using the word itself. Encourage the group to guess what the word is.

Choice B: Prepare a large-sized crossword or word search puzzle on paper at a difficulty level geared to the group.

Team Quiz
Play team games. Divide the group into two teams, ask them to choose a team name and then play a trivia quiz, or another game the group have enjoyed previously. Give prizes to everyone in the group. Games such as “True or False” and “Fact or myth” are popular as they focus more on group discussion and opinion. Bring back materials created in previous sessions and display for all to see. Have a special group with drinks and refreshments. Discuss people’s views on the group.