Official Title: Improving Prospective Memory Via Telehealth

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1.0 Background

Up to 70% of persons with multiple sclerosis (PwMS) have cognitive impairment[1]. These difficulties can present early in the disease[2] and can negatively influence their everyday functioning[3]. One cognitive domain that is understudied in MS but can have significant functioning implications is prospective memory (PM) or "remembering to remember." Two broad components are involved in PM: prospectively remembering that a task needs to be done and the retrospectively remembering the content of the task[4]. PM tasks can be categorized as being either event-based (e.g., "When the coffee machine chimes that the coffee is ready, I need to take my medication) or time-based (e.g., "At 1 pm, I have to go to my doctor's appointment). PM tasks can occur once (e.g., going to get a one-time lab draw) or on a regular basis (e.g., taking a daily disease modifying therapy (DMT)). Other cognitive domains affected in MS can influence PM abilities. For instance, deficits in new learning, which is common in MS, can have a negative impact on PM[1].

While PM is not routinely assessed in traditional neuropsychological assessments[4], there is evidence in the literature that PwMS experience reductions in this domain. Compared to healthy adults, PwMS have demonstrated significantly worse PM abilities[5-8], particularly on time-based PM tasks[6,9,10]. These impairments have also been connected to real-world difficulties in PwMS. For instance, PM deficits in MS have been associated with unemployment[11] and difficulty completing everyday functional activities[9], including adherence to DMTs[12] and attendance of MS-related appointments[13]. In addition, both objective and subjective PM have emerged as significant components of self-management behaviors[14], which is important for handling the challenges associated with MS.

Although there have been a number of cognitive-focused interventions in MS[15], there has been limited work on improving PM in this population. Two experimental studies demonstrated that selective reminding[16] and implementation intentions[8] can improve performance on PM tasks. The latter technique, which involves 1) identifying the conditions where a task would be done and 2) visualizing doing so[8], has been successful in other populations[17]. PM was also an exploratory outcome on a self-generation learning intervention, with contextual memory as the primary outcome[18].

Theoretically, improving a PwMS' PM could have significant functional implications, such as improved adherence to DMTs and appointment attendance. However, while there have been successful PM interventions in other clinical populations, to date there has not been a specific PM intervention for PwMS that has been tested in a clinical trial[4]. In addition, evaluating a PM intervention in a telehealth format may increase access to cognitive rehabilitation services. Besides PwMS dealing with barriers to receiving healthcare services, such as mobility and accessibility[19], COVID-19 has had a negative impact on referrals for cognitive remediation as well as other cognition-related services for PwMS[20].

2.0 Rationale and Specific Aims

Rationale:

While PM deficits have been documented in MS[5-10] and they have been associated with functional implications in this population[9,11-14], there has yet to be a clinical trial focused on remediating PM difficulties among PwMS. Cognitive remediation is one of the most common treatments for cognitive dysfunction in MS: a recent survey of Consortium of MS Centers (CMSC) members found that nearly 61% refer their patients for this service, which is a significant increase from 2010[20,21]. In addition, examining the feasibility and preliminary efficacy of this intervention in a telehealth format, which could increase who is able to access cognitive rehabilitation, may potentially have significant implications on patient care.

This study aims to evaluate the feasibility of a PM intervention for PwMS, focusing on two types of strategies: visual imagery and implementation intentions. These strategies have been shown to be beneficial for improving PM in other populations[17,22-24]. Furthermore, they have been included in other cognitive-focused interventions for PwMS with success. For instance, visual imagery is a significant component of the modified Story Memory Technique intervention, which targets new learning and memory[25-27]. However, visual imagery has yet to be examined in PwMS for improving PM-related tasks (e.g., remembering to attend appointments or take medications) and there has yet to be an MS-specific intervention that utilizes both visual imagery and implementation intentions.

Aims:

Aim 1: Evaluate the feasibility of the telehealth PM intervention.

A randomized pilot trial will be conducted to evaluate the feasibility of the intervention, with participants randomized to either the visual imagery and implementation intentions training (n = 18) or education control group (n = 18).
Outcomes: Recruitment, enrollment, and retention numbers during the course of the study; participant-rated expectancy and credibility of the treatment program after the first session; adherence to sessions; and participant-related treatment satisfaction at post-treatment.
Hypothesis: The majority of participants (≥75%) will complete at least two-thirds of the program and will report moderate-to-high (≥7 out of 10) treatment satisfaction, expectancy, and credibility.

Aim 2: Establish the preliminary efficacy of the telehealth PM intervention.

The same randomized pilot trial will be used to compare the intervention (n = 18) to the control (n = 18).
Outcomes: The primary outcome will be objective PM abilities, as measured by the Memory for Intentions Test (MIST)[28,29], which will be used to generate a preliminary effect size estimate for a future trial. A secondary outcome will be subjective PM abilities, as measured by the Perceived Deficits Questionnaire (PDQ) subscale[30].
Hypothesis: Compared to the control group, participants in the treatment group will exhibit an improvement in their PM abilities. In addition, the treatment group will endorse fewer PM difficulties.

3.0 Inclusion/Exclusion Criteria

Inclusion Criteria:

- Clinical diagnosis of MS
- Able to read, write, and speak in English
- Between the ages of 18 and 60
- All genders
- No history of other serious neurologic or psychiatric illness, including drug or alcohol misuse
- No relapses within the past two months
- Access to the Internet and a web camera
- Not enrolled in a cognitive rehabilitation program within the past six months
- Self-reported issues "remembering places they have to be" and "things they have to do"

Exclusion Criteria:

- No diagnosis of MS
- Unable to complete the study protocol due to language barriers
- Younger than 18 or older than 61
- No gender exclusions
- History of other serious neurologic or psychiatric illness, including drug or alcohol misuse
- Had a relapse within the past two months
- No access to the Internet and/or a web camera
- Currently enrolled or enrolled in a cognitive rehabilitation program within the past six months
- No self-reported issues with "remembering places they have to be" or "things they have to do"

4.0 Enrollment/Randomization

The study will be conducted at the Mandell Center for MS (Mandell Center), which provides comprehensive care to persons with MS, thus allowing for easier recruitment of the intended patient population. As of December 31, 2019, 3,134 unique patients have been seen at the Mandell Center (M. Farr, personal communication, January, 23, 2020). Similar to the general MS population[31], our patient population has more women than men (C. St Andre, personal communication, November 16, 2017). Patients range from age 18 to 88 (mean: 50.23 years) and are, on average, moderately disabled, as measured by the Expanded Disability Status Scale (EDSS) (mean: 3.8; range: 0-8.5)[32] (C. St Andre, personal communication, November 16, 2017).

Participants will be primarily recruited through the *Recruitment Pool for Studies at the Mandell Center for Multiple Sclerosis* (IRB# MSH-19-48), an ongoing project where PwMS opt-in to be contacted about research opportunities at the Mandell Center. To date, there are over 400 individuals who have agreed to be contacted about research studies being conducted at the Mandell Center. Potential participants will be contacted via email (with an IRB-approved recruitment letter) or via phone call. Recruitment flyers will also be posted in the Mandell

Center, made available to staff, and distributed to the community. All recruitment materials will list the inclusion criteria and contact information. Prior to enrollment in the study, potential participants will be screened over the phone for the inclusion criteria. As the study is primarily being conducted via telehealth, we plan to have participants have minimal on-site visits.

After completion of the baseline evaluations, participants will be randomized 1:1 into the treatment or control group, stratified by age and gender. A research assistance not involved in the data collection will be responsible for treatment allocation. This study will be single masked: different study personnel will be involved in the assessment and treatment portions of the study.

5.0 Study Procedures

Baseline and Post-Treatment Assessments

All participants (n = 36) will complete a baseline (week 1) and a post-treatment cognitive evaluation (week 6). These assessments will be conducted by Dr. Gromisch, a licensed neuropsychologist and research scientist at the Mandell Center with experience conducting cognitive-focused studies. Both the PM (active) and Education (control) groups will be receiving the same assessment measures at the same time points (see **Figure 1** and **Figure 2**).

Questionnaires:

Demographics will be collected, including age, gender, race/ethnicity, disease duration, MS subtype, level of education, living situation and location, insurance type, and current DMT usage. Adherence to DMTs will be assessed with a single item, ("People often have difficulty taking their medications for one reason or another. How many times have you missed taking your DMT in the past month?")[33]. Items about other functional tasks, such as driving, will be asked. Level of disability will be assessed using the Patient Determined Disease Steps (PDDS)[34-37] and MS symptoms will be measured using the SymptoMScreen[38]. All of these measures are included in the document **TPMI Baseline Questionnaires**.

At baseline and post-treatment, both groups will complete the Perceived Deficits Questionnaire (PDQ)[30], a 20-item self-report measure of cognitive functioning. While we will be primarily looking at subjective PM with the PM subscale, we will also collect participants' reports on the three additional subscales (retrospective memory, attention, and planning/organization). This measure has been uploaded in the document **PDQ for TPMI**.

At baseline and post-treatment, both groups will be given a Prospective Memory Diary[39] (document name: **Memory-Diary**). During the assessment sessions, Dr. Gromisch and the participant will identify five tasks and the participant will fill out how they carried out the task during the week (i.e., Week 1 following the baseline assessment and Week 6 following the post-treatment assessment). These Prospective Memory Diaries will be mailed back or scanned and emailed back to the research team after they are completed. Participants will be provided with a

pre-stamped return envelope, as well as a secure research email address (msresearch@TrinityHealthOfNE.org) if they prefer to scan and email.

Neuropsychological Assessments:

At the baseline and post-treatment assessments, participants will be completing a battery of neuropsychological measures. These are protected, copyrighted measures that are being purchased under Dr. Gromisch's license and will only be administered, scored, and interpreted by Dr. Gromisch. All of these measures are standard neuropsychological measures frequently used in routine neuropsychological assessments. The measures being given are noted in the attached document **TPMI Measure Checklist**. No diagnoses of cognitive impairment will be made after either assessments, as this study is not part of clinical care.

As these measures cannot be scanned and uploaded due to copyright restrictions and accordance with the American Psychological Association's ethics code, details are provided below on each measure:

Test of Premorbid Functioning (TOPF)[40]: is a measure of premorbid functioning. The participant reads aloud a list of words, which increase in complexity. The participant will only complete this measure at baseline. If a participant completed the TOPF in another study (i.e., MSH-21-09), they will not repeat the TOPF in this study as their scores are expected to remain stable over time.

Memory for Intentions Test (MIST)[28,29]: is an eight-task objective measure of PM. The participant is given eight tasks over the course of the test at differing times, to which they must give a response at either a designated time or after a certain cue. The tasks in the MIST are meant to mimic everyday activities (e.g., recalling what medications they take). The participants are given one additional task with a 24-hour delay, in which they would call a secure research line (860-714-3005) and report how many hours of sleep they received the night before. The MIST will be given at baseline and post-treatment, and the total score will be used to calculate the preliminary effect size. To reduce learning effects, different versions of the MIST will be given at baseline and post-treatment.

Neuropsychological Assessment Battery-Daily Living (NAB-DL) module[41]: is a battery of measures designed to mimic everyday functioning. There are five measures included (Driving Scenes, Bill Payment Daily Living, Daily Living Memory, Map Reading Daily Living, and Judgment Daily Living), which tap into memory, attention, and executive functioning. Participants will complete the NAB-DL module at the baseline and post-treatment assessments. To reduce learning effects, different versions of the NAB-DL will be given at baseline and post-treatment.

Processing Speed Test (PST)[42]: is a digital version of the Symbol Digit Modalities Test designed for persons with MS. The PST taps into processing speed, as well as working memory. It will be administered on a Mandell Center iPad and none of the participant's data are saved electronically (i.e., a score is generated but not saved, so it will be written down in the **TPMI Measure Checklist**). During the test, participants match up numbers to symbols as quickly as

they can over a span of 120 seconds. Each time the PST is given, a randomized version is given to reduce learning effects. Participants will complete the PST at the baseline and post-treatment assessments.

Trail Making Test (TMT)[43]: is a two-part test that measures psychomotor processing speed and executive functioning (i.e., set-shifting). In the first part, the participant draws a line connecting numbers 1-25 as quickly as they can. In the second part, the participant alternates between numbers and letters, going in order as quickly as they can, again connecting the items with a drawn line. Participants will complete the TMT at the baseline and post-treatment assessments. As only one version of the TMT has been normed with the Heaton-Reitan norms, the standard version will be used at both times.

Digit Span[44]: is a measure of verbal attention and working memory. There are three parts. In the first part, a list of numbers are said in increasing order, which the participants repeats back verbatim. In the second part, a list of numbers are said in increasing order, but the participant must repeat them back in reverse order. In the third part, a list of numbers are said in increasing order, but the participant must repeat them back in chronological order. Participants will complete Digit Span at the baseline and post-treatment assessments. As there is only one version in the Wechsler Adult Intellegence Scale-Fourth Edition, the standard version will be used at both times.

Test of Everyday Activity (TECA)[45]: is a timed measure of instrumental activities of daily living for persons living with MS. The participant is given a series of tasks and asked to complete them. These tasks are designed to mimic everyday activities (e.g., finding a number in a phone book and making change). Participants will complete the TECA at baseline only.

Clock Drawing[46]: is a measure of visuospatial ability and executive functioning. The participant is asked to draw a clock, write in all the numbers, and set the time to "10 past 11." In this version, the participant is not given any prompts (e.g., a pre-drawn clock face) and will only be given a blank piece of paper and a drawing instrument (i.e., a pencil). Participants will complete Clock Drawing at baseline only.

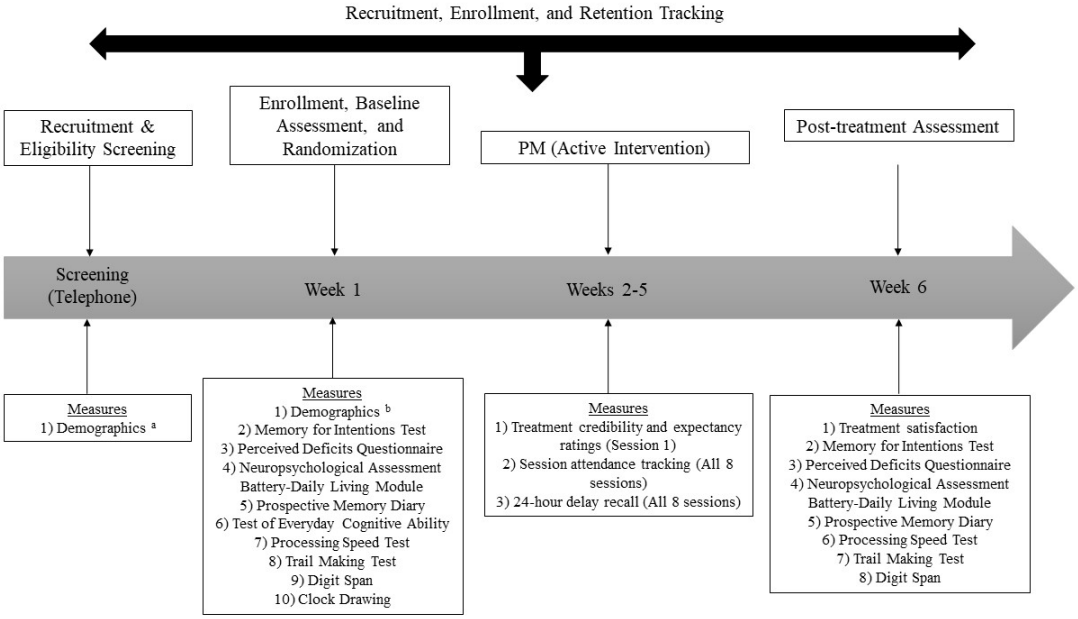

Figure 1: Timeline of feasibility trial for PM (active intervention) group

[a] Demographics related to inclusion criteria: age, diagnosis of MS, English-speaking, no history of other serious neurologic or psychiatric illness, no relapses within the past two months, access to the internet and a web camera, no cognitive remediation within the past six months, and reported difficulty remembering places they have to be and things they have to do

[b] Age, gender, race/ethnicity, disease duration, MS subtype, education, living situation and location, insurance type, DMT usage and adherence, functional difficulties, Patient Determined Disease Steps, SymptoMScreen, and Test of Premorbid Functioning

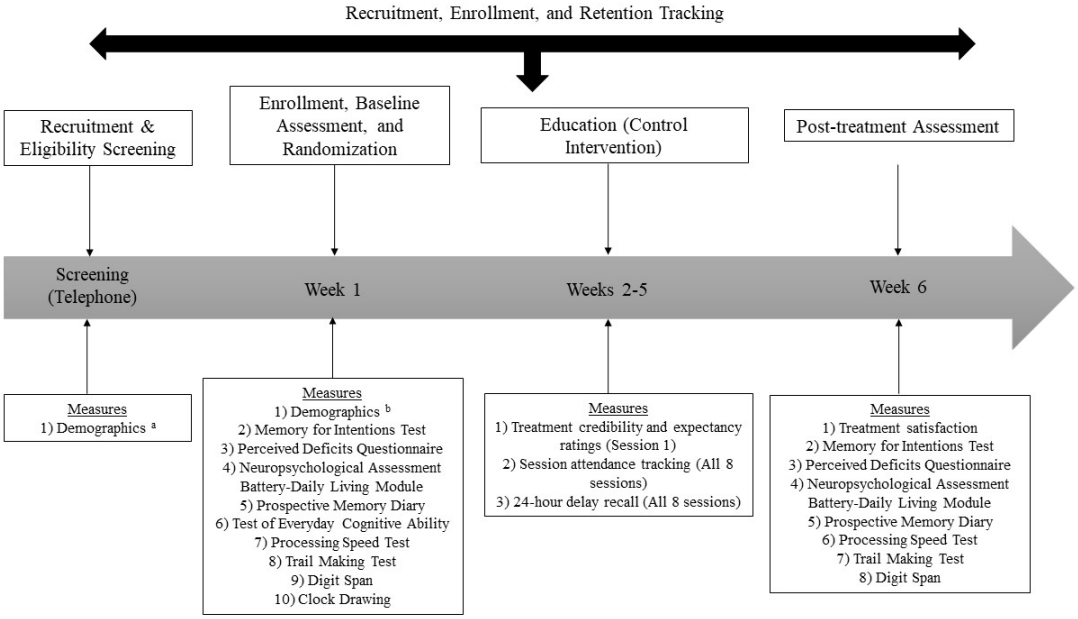

Figure 2: Timeline of feasibility trial for Education (control intervention) group

[a] Demographics related to inclusion criteria: age, diagnosis of MS, English-speaking, no history of other serious neurologic or psychiatric illness, no relapses within the past two months, access to the internet and a web camera, no cognitive remediation within the past six months, and reported difficulty remembering places they have to be and things they have to do

[b] Age, gender, race/ethnicity, disease duration, MS subtype, education, living situation and location, insurance type, DMT usage and adherence, functional difficulties, Patient Determined Disease Steps, SymptoMScreen, and Test of Premorbid Functioning

During the course of the intervention, we will monitor for any changes in medication that may affect cognitive performance (e.g., opioids) as well as other health changes, but no changes in standard medical care will be done.

Feasibility Measures

In order to assess the feasibility of the intervention, we will be measuring 1) recruitment, enrollment, and retention; 2) adherence to the treatment; 3) treatment credibility and expectancy; and 4) treatment satisfaction. Enrollment will be tracked throughout the recruitment and study procedures, including 1) how many people were approached or expressed interest; 2) reasons people declined (including how many did not meet inclusion criteria); and 3) any drop-outs during the course of the trial and the reasons why. Throughout the treatment, we will be tracking participants' attendance of their scheduled sessions. During the first session of both groups (week 2), participants will be asked to rate the credibility and expectancy for improvement from the intervention on a 10-point scale, with 10 indicating the highest level of credibility/expectancy[47]. Satisfaction will be measured post-treatment (week 6) using a scale of 0 (no satisfaction) to 10 (complete satisfaction) in terms of the overall treatment they received. Session adherence, treatment credibility and expectancy, and treatment satisfaction will be recorded on the uploaded document **TPMI Feasibility Measure Collection Sheet**.

Treatment Groups

Participants randomized to the PM intervention (active group) will meet with an interventionist twice a week for four weeks. Interventionists will be research assistants who will be added to the IRB of this study and supervised by Dr. Raskin, an expert in PM, with the materials based on her previous interventions in traumatic brain injury[23]. The first four sessions will focus on visual imagery, while the last four sessions will focus on implementation intentions. Participants will be led through a manualized treatment (**Telehealth Prospective Memory Interventional Manual PM Group**). The interventionists will also be using a standardized list of stimuli (**PM Group Interventionist Packet**). All participants will be receiving the same packet of training materials (**PM Group Patient Packet and Implementation-Planner-PDF**), which will be given to them prior to the start of the telehealth sessions. As the sessions will be held via telehealth, participants will be mailed their training materials during Week 1 after randomization and prior to the start of the intervention. To account for issues with mail, participants will also be sent a digital copy to their email from a secure research email (msresearch@TrinityHealthOfNE.org).

The control group (Education) will meet with a research assistant for the same frequency of sessions and will receive psychoeducation on MS and cognitive functioning. The interventionists will be following a manual (**Telehealth Prospective Memory Intervention Manual Education Group**) and accompanying PowerPoint slides (**TPMI Education_session 1-8**). The Education group will not be receiving any additional materials.

All sessions will be delivered via a video-based telehealth session using a HIPAA-compliant version of Qliqsoft. The interventionists will be using Trinity College lab computers which are password protected and encrypted or due to the current pandemic, interventionists may do the sessions off campus in a secure location (i.e., locked private room with headphones in on password protected computers. After each session, participants will be instructed to call 24 hours later and report how many hours they slept the night before as a probe. Participants will be instructed to call 860-714-3005 which is a dedicated research line at the Mandell Center that only members of the research team will have access to.

Consistent with previous studies conducted at the Mandell Center, a list of clinical resources, including behavioral health and neuropsychological services, will be made available to participants whose responses are suggestive of possible depression. This will also be available to any participant who expresses concern about their mood, level of anxiety, or cognition. The list of clinical resources will be provided at the end of the research appointment, and will explain how participants can get a referral to services through their provider. Community resources will also be noted on this handout.

6.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

The Principal Investigator (PI) and the Institutional Review Board (IRB) have the authority to stop or suspend the study or require modifications.

This protocol presents a slight increase over minimal risk to the participants and Unanticipated Problems Involving Risks to Participants or Others (UPIRPOs), including adverse events, are not anticipated. In the unlikely event that such events occur, Reportable Events (which are events that are serious or life-threatening and unanticipated (or anticipated but occurring with a greater frequency than expected) and possibly, probably, or definitely related) or UPIRPOs that may require a temporary or permanent interruption of study activities will be reported immediately (if possible), followed by a written report within 5 calendar days of the PI becoming aware of the event to the IRB (using the appropriate forms from the website) and any appropriate funding and regulatory agencies. The investigator will apprise fellow investigators and study personnel of all UPIRPOs and adverse events that occur during the conduct of this research project via email as they are reviewed by the principal investigator.

The PI will be responsible for monitoring the data, assuring protocol compliance, and conducting safety reviews on a quarterly frequency. During the review process, the PI will

evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment.

7.0 Study Withdrawal/Discontinuation

A participant may withdraw from the study at anytime through written or verbal communication with a member of the research team. If a study participant stops participating in the study, the person will be notified that his/her participation in the study will be discontinued. Once notified of withdrawal or discontinuation, the participant will be immediately removed from the study and no further research appointments will occur.

8.0 Statistical Considerations

For this project, we will be enrolling 36 participants (18 per arm). Fifteen participants has been previously identified as a sufficient sample size per treatment arm to calculate the sample size of a 90% powered main trial with a medium standardized difference[48]. An additional six individuals (three per treatment arm) will be included to account for a 20% attrition rate during the course of the trial. This sample size is adequate to detect a large effect size with 76% power and 5% significance on a one-tailed independent t-test.

A flow diagram will be used to document recruitment, enrollment, and retention. Descriptive statistics will be used for adherence to treatment, and independent t-tests or Mann-Whitney U tests will be run for treatment credibility, expectancy, and satisfaction. For the preliminary efficacy calculations, an intent-to-treat approach will be used, with the expectation maximization (EM) approach to be used if justified by missing values analysis[49]. Cohen's *d* effect size will be computed for the group difference and will be used to inform a definitive clinical trial.

9.0 Privacy/Confidentiality Issues

There is a slight increase over minimal risk associated with this study. The measures being used to assess cognition are ones used by neuropsychologists as part of routine assessments, and the intervention materials mirror those used in cognitive rehabilitation or psychoeducation as part of clinical care. Minor inconvenience may occur during the completion of the assessments and intervention, which may be viewed as potentially frustrating, uncomfortable or distressing and time-consuming. If participants become distressed when discussing their cognition and its effects on their lives, they will be given the time in a private space to process their feelings. They will also have the option to discontinue answering any questions or the intervention. They will also be given alist of clinical resources if the participant expresses concern about their mood, level of anxiety, or cognition. These resources will be provided at the end of the research appointment, and will explain how participants can get a referral to services through their provider. Community resources will also be noted on this handout.

Only authorized persons will have access to the information gathered in this study. Patient names or other identifiers such as social security number, initials, birth date, etc., will not be used to identify electronic records. Identifiable information will only be used for contacting participants for follow-up appointments, compensation, and verification of information in the medical records. A code number will be used to code the questionnaires. The code number will not be based on any information that could be used to identify the participant (for example, social security number, initials, birth date, etc.). Data that are published will in no way identify the individual participants or disclose their identities.

10.0 Follow-up and Record Retention

The study is anticipated to take one year to complete. During the study, all paper files will be stored in a locked file cabinet in the Research Department of the Mandell Center Computers at both the Mandell Center and Trinity College with research data will be password protected and encrypted to ensure confidentiality of participant records. All computers are password protected and encrypted. The PI will be ultimately responsible for the security of the information. After the study is closed and all data analysis is complete, records will be destroyed according to policies regarding length of time that research documents need to be retained after protocol completion.

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