Study Protocol and Statistical Analysis Plan

SAGE LEAF: Reducing Burden in Alzheimer's Disease Caregivers through Positive Emotion Regulation and Virtual Support

RCT #NCT05562583

August 26, 2021

STUDY TITLE:

SAGE LEAF: Reducing Burden in Alzheimer's Disease Caregivers through Positive Emotion Regulation and Virtual Support.

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Name: NA
Department: NA

Are you an:
☐ Undergraduate Student
☐ Graduate Student or Medical Student

VERSION DATE:

08/26/21

RELATED STUDIES:

If there any related NU IRB applications that provide context for the activities covered by this IRB submission, please explain and provide the IRB study numbers for those related applications. (For example, if you plan to use samples or data collected by another study, recruit participants from a registry established by a colleague's research activity, or conduct a continuation of a prior study.)

Check any **applicable** boxes in the table below – you will be asked for further detail on these topics later in the protocol form:

Indicate Vulnerable Population(s) to be Enrolled	☐ Children ☐ Cognitively Impaired Adults ☐ Pregnant Women (IF the research activities will affect the pregnancy or the fetus) ☐ Prisoners (or other detained/paroled individuals)
International Research (check this box if you will collect data from individuals located outside the United States)	☐
Research involving external collaborators (some research activities will be carried out by individuals not employed by Northwestern or NU affiliates)	☒ BrightOutcome will be designing and engineering the online intervention.
Research has U.S. Federal government funding via direct award or a sub-award (e.g., NIH, NSF, other federal agencies or departments)	☐

1.0 Purpose and rationale of the study:

Social Augmentation of self-Guided Electronic delivery of the Life Enhancing Activities for Family caregivers (SAGE LEAF) is a socially enhanced, online intervention to reduce stress in caregivers of individuals with Alzheimer's disease. The intervention will be adapted from a prior version of a positive emotion intervention for dementia caregivers, LEAF 2.0 (1R01AG05613-01). **The project will comprise the two phases of 1) user testing and 2) pilot testing.**

The persistent and progressive nature of Alzheimer's disease (AD) has deleterious effects not only for the care recipient, but the caregiver as well; adversely impacting key aspects of psychosocial functioning.[2-3] The protracted burdens of caregiving may lead to an increased risk of developing psychiatric disorders like depression or anxiety,[4] with increased duration and severity of AD symptoms heightening this risk among caregivers.[5] These outcomes have a tandem effect on outcomes for care recipients, where increased caregiving burden and stress results in diminished quality of care and quality of life for the patient.[6]

To address the issue of caregiver burden, researchers are now utilizing new technologies to deliver efficacious and effective resources to caregivers. One such study that we conducted is LEAF (R01NR014435; Life Enhancing Activities for Family caregivers – LEAF), an online positive-emotion intervention delivered through videoconferencing. A randomized control trial of the intervention found that participation lead to significant increases in positive emotion ($d = .58$; $p < .01$) and positive aspects of caregiving ($d = .36$; $p < .01$), as well as decreased symptoms of depression ($d = -.25$; $p = .02$) and anxiety ($d = -.33$; $p < .01$) compared to an emotion-reporting waitlist control group.[7] During this study, participants met one-on-one with a trained facilitator. However, such delivery formats can be costly in terms of the time, effort, and logistics required to meet with participants individually. Hence, it is an imperative to explore new formats of delivery that might be more efficiently distributed, while maintaining a high level of interactivity and engagement.

One such format that has been widely adopted is the *self-guided* online intervention, where participants have access to the content on their own with minimal guidance provided. Previously, we utilized this medium to deliver a positive emotion intervention for individuals with elevated depression symptomatology.[8] But while such interventions reduce barriers for participation, they are beset by high rates of attrition and poor adherence.[910] Parallel research on other self-guided resources, namely Massive Open Online Courses (MOOCs), have found that the construct of *social presence* – or the ability to perceive others in an online environment – can enhance retention and engagement.[11] Social presence may include features like providing welcome messages, displaying participant profiles, and facilitating online discussion amongst participants.[12] Hence, eHealth and mHealth interventions are likely to benefit from the application of these social features.

With these considerations in mind, such social features may be particularly beneficial for caregiver participants; who experience higher levels of social isolation and loneliness compared to their peers.[13-14] Hence, the objective of this proposal is to adapt the existing positive emotion intervention for SAGE LEAF – a socially enhanced, online intervention for Alzheimer's caregivers. If successful, SAGE LEAF may be scaled as an online resource that caregivers could utilize to better cope with the stressors of caregiving.

For the **1) user test**, we will be evaluating the SAGE LEAF platform's usability and usefulness. Non-Alzheimer's dementia caregivers recruited from the Northwestern Cognitive Neurology and Alzheimer's Disease Center (CNADC) (N=20) will participate in an extended user test where they will receive full access to the SAGE LEAF intervention, and provide their feedback through surveys and interviews on the platform's usability and usefulness upon conclusion of the 6-week program. Subsequently, the necessary refinements to the platform will be made based on the feedback received.

Next, we will conduct a (N=30) single-arm pre-post 2**) pilot test / feasibility study** of SAGE LEAF for AD caregivers. Participants will receive access to the SAGE LEAF platform and complete the positive emotion skills intervention over 6 weeks. We will evaluate the number and percentage of participants retained at the post assessment as well as the means and ranges for the proportion of intervention content completed (i.e., number of pages viewed out of the total possible pages across all skills and lessons in the intervention) and participants' acceptability ratings (i.e., participants' ratings of whether they would recommend SAGE LEAF to other AD caregivers).

2.0 Enrollment Criteria (who can be in your study and who would not be eligible to participate in your study):

1) **User Test Inclusion criteria:**

- Age 18 and over
- Speaks and reads English
- Identifies as the primary family caregiver of a person with non-Alzheimer's dementia.
- Have access to high-speed internet.

2) **Pilot Test Inclusion criteria:**

- Age 18 and over
- Speaks and reads English
- Identifies as the primary family caregiver of a person with Alzheimer's disease.
- Have access to high-speed internet.

Exclusion criteria: none

3.0 Sample Size:

We will recruit a total of 50 participants: 1) 20 participants for the user test and 2) 30 participants for the pilot test. These sample sizes are commensurate with the exploratory nature of this preliminary research.

4.0 Recruitment and Screening Methods:

For the 1) user tests, we aim to recruit non-Alzheimer's dementia caregivers from Northwestern Memorial Hospital's Cognitive Neurology and Alzheimer's Disease Center (CNADC), and for the 2) pilot testing, we aim to recruit AD caregivers from CNADC.

For both phases, potential participants will be sent an email containing study details and a link to an online screener survey. Participants who are eligible will see a message that says a member of the study team will reach out to schedule a phone call. Participant flow:

Online-Pre-Screener -> Screener Phone Call with Study Staff -> Consent / Baseline (T1)

Online Pre-Screener Link

This link leads to a REDCap pre-screener questionnaire that helps determine eligibility. **A copy of the pre-screener questionnaire has been attached with this submission**. These questions verify whether an individual has met the study criteria to participate. If an individual does not meet the criteria, they will see a message after completing the pre-screener that thanks for them their time, but notifies them that unfortunately, they are ineligible to participate. If an individual is eligible, they will be informed that a member of the study team will reach out to schedule the screener phone call.

Data collected from the pre-screener link will be stored on a secure, HIPAA-compliant, and password-protected server at the Feinberg School of Medicine. We will flag identifiers on the REDCap platform, so that these variables will be excluded from any data exports. For example, we will flag First Name, Last Name, phone number, and email address. Outside of REDCap, identifying information will never be linked with the data from the pre-screener. Only de-identified data will be exported from REDCap and saved on the password-protected FSM server. Only IRB-approved individuals will be able to access the data on REDCap. This de-identified data will be aggregated and used only for the purposes of gauging recruitment trends.

Phone Screen (~30 minutes)

Subsequently, study staff will contact eligible participants to explain the requirements of the study and seek informed consent. Study staff contact information will be provided to participants so that they can call or email if they have any questions about their participation. Participants will also be reminded that they may opt out of the study or decline to answer any of the questions:

A copy of the phone screen script has been uploaded to the Supporting Documents section of the IRB application. The pre-screener information from eligible individuals will feed into the REDCap database and dashboard, where the Project Director (PD) can view eligible individuals to schedule phone calls. The PD or a member of the study team will then reach out to the individual to schedule a ~30 minute phone call to reiterate what the study entails, including time commitment, timing, survey, feedback interview, and overall

summary of the SAGE LEAF course – while emphasizing that the focus of the study will be on feedback about the social features of the intervention. This allows the individual to ask questions, discuss any concerns, and confirm whether or not they want to be in the study. Consenting individuals will then be provided access to the SAGE LEAF platform through a sign-up email prompting them to set up their password.

After the phone screen, if the participant is determined to be eligible, they will be sent an email to the online consent form through REDCap. Participants will be instructed to contact study staff if they have any questions about the study.

Consent, Baseline Assessment (T1)
Consent will be time-stamped and participants will be able to save, download, and/or print a copy of the consent form for their records. Participants will consent electronically by entering the date and by typing their full name into the form, which will represent their electronic signature. Participants will be considered "consented" only if they provide both items (date and electronic signature). Participants may also email the project director to request a copy of the consent form at any time.

Consent scenarios:

- If a user test participant consents "Yes," they will be sent a welcome email containing instructions for setting up their password on the SAGE LEAF platform. If a pilot test participant consents "Yes," they will automatically continue on to complete the baseline assessment. Upon completion they will be sent the welcome email containing instructions for setting up their password on the SAGE LEAF platform.
- If an individual does not respond to the consent form, our study team will follow-up with a reminder up to 3 times by phone or email using information provided on the screener.
- If an individual responds "No" and declines to participate, they will see a message thanking them for their time.

5.0 Research Locations:

All research will be based at Northwestern University's (NU) Feinberg School of Medicine through the Department of Medical Social Sciences (MSS) as the lead research site. NU holds the IRB of record. However, the development of the SAGE platform will be managed by Bright Outcome (https://www.brightoutcome.com/), a company experienced in designing online platforms for patient reported outcomes research. Bright Outcome has a proven track record of collaboration and delivery of technology products/services to investigators at the Feinberg School of Medicine.

6.0 Multi-site Research (research that involves external collaborating institutions and individuals):

SAGE LEAF is a single-site study.

7.0 International Research (where data collection will occur outside the United States and U.S. territories, including online activities)

N/A

8.0 Procedures Involved:

Please check the boxes for all applicable data collection procedures you plan to use:
☒One-on-one interviews
☒Focus Groups
☒Questionnaires/surveys
☐Analysis of secondary data (medical record data, educational records, government or private sector datasets, etc.)
☐Ethnographic observation
☐Physiological measurements (e.g., EEG, EKG, MRI)
☐Biospecimen collection (saliva samples, blood draws, hair samples, etc.)
☐Mobile applications/data collection devices (e.g., Fitbits, actigraphs, etc.)
☐Behavioral decision making tasks (e.g., puzzles, interactive games, etc.)
☐Physical activities such as walking and other forms of exercise
☐Other procedures (briefly list types of procedures here if not covered by the check-boxes above): _____

Procedures for Phase 1: User Test

Upon providing informed consent and completing the phone screen, consented individuals will then be provided access to the SAGE LEAF platform through a sign-up email prompting them to set up their password.

6 Sessions over 8 weeks: approx. 30 minutes/online module
Week Self-Guided Intervention "Online Lessons"
The SAGE LEAF online lessons consist of 6 modules for the intervention; one module unlocked per week over 6 weeks, but participants will have an 8-week period to complete the 6-module intervention. The intervention content, emotion reporting forms, and assessment questionnaires are all mobile-enabled and, thus, can be completed on desktop, laptop, tablet, or smartphone. In this self-guided intervention, skills will be delivered within 8 weeks. Participants will also have access to social features, which include the discussion board, didactic videos from study staff, virtual awards, etc.

Participants can participate from their home computer, smartphone, or a tablet from a location with wifi. A week will consist of 1-2 days of didactic material and 5-6 days of real-life skills practice and reporting. Participants cannot skip ahead, and can only progress to the next lesson if they have completed the current one, but they can return to old lessons or exercises if they wish to. Participants will receive email or text notifications throughout the study, and will have access to a control panel to configure their preferences. As part of the daily home practice, intervention participants will be asked to complete the daily stress and emotion questions. Other data collected from the Bright Outcome platform will be securely stored on Northwestern servers, accessible only to IRB-approved study staff. These data include number of log-ins, completed home exercises, number of skills completed, data from the daily emotion reporting surveys, number of awards earned, discussion posts, etc.

Time Commitment

The estimated time commitment for participating in the SAGE LEAF Study is up to 9 hours over 8 weeks.

Event	Time Commitment
Screener + Phone Screen + Consent + 2 surveys (up to 1 hour each)	~3 hours
6 SAGE LEAF Sessions	<3 hours
Daily Home Practice / Emotion Check-In	~3 hours
Feedback Survey + Interview	<2 hours
Total Hours Over 8 Weeks	<9 **hours**

Bright Outcome Platform

Bright Outcome "Discussion" Feature

Participants accessing the "Online Lessons" on the platform will have a tab called "Discussion" where they can discuss topics related to the study. These topics will be based on the Skills. For example, there will be a discussion thread called "Gratitude" so that participants can post there about their comments/thoughts on practicing gratitude. The discussion threads will be moderated by a staff member on the research team. The moderator will post weekly prompts to generate discussion, moderate the discussions to stay on-topic, and address and respond to any signs of distress or suicidal ideation. All posts will be tied to a SAGE LEAF Study ID and an avatar. No identifiable information will be posted/shared. Guidelines will include refraining from posting personal/identifiable information such as names and contact information, and refraining from bullying or using harsh/offensive language online. We have prepared a data safety and monitoring plan for the Discussion posts (in addition to a plan for handling a range of distress revealed to us at any point in the study), based on our previous online studies with an online forum such as LEAF, MARIGOLD, and LARKSPUR. (See Section **17.0 Data Monitoring Plan to Ensure Safety of Participants** for more details.)

Profile Page
Participants will have access to a profile page where they will be able to select an avatar and fill out additional profile information (e.g. hobbies, challenges that they are facing as a caregiver, etc.) that they have the option of displaying if they choose to do so. No identifiable information will be posted/shared.

Virtual Awards Feature
Participants accessing the "Online Lessons" on the platform will have a page called "Awards" where they will receive virtual badges for reaching certain goals e.g. logging in daily for 7 days, completing home practice for 4 consecutive days, or completing an online module. They will also be able to view their achievements in relation to others. This data will also be collected on Bright Outcome. Each participant will be able to see their earned badges as an incentive to proceed and engage with the study.

SAGE LEAF Positive Emotion Skills
Please see the table below for an overview of the intervention's skills, goals, and home practice exercises, administered via the Bright Outcome online platform.

The total time involved from the beginning to the end of the study is approximately 8 weeks.

Overview of Intervention sessions, Goals, and Home Practice.

Skills	Goals of session	Home Practice
Session 1: Positive Events, Savoring, Gratitude	Recognize positive events and the associated positive emotion; practice ways to amplify the experience of positive events; and learning to practice gratitude.	Noting a positive event each day and writing about it (savoring); starting a daily gratitude journal and daily emotion reports. The gratitude list home practice continues through the rest of the intervention period.
Session 2: Everyday Mindfulness and Mindfulness Meditation	Learn and practice the awareness and nonjudgment components of mindfulness.	Daily informal mindfulness activities, a 10-minute formal breath awareness activity, continuing the gratitude journal and daily emotion reports.
Session 3: Positive Reappraisal	Understanding positive reappraisal and the idea that different forms of positive reappraisal can all lead to increased positive emotion in the face of stress.	Reporting a relatively minor stressor each day, then listing ways in which the event can be positively reappraised. The daily formal mindfulness practice, gratitude journal, and

		the emotion reports continue.
Session 4: Self-Compassion	Participant learns about how to show compassion for the self, especially in the context of a caregiver. Understanding how self-compassion relates to the skills throughout the rest of the SAGE LEAF course.	Listing an act of self-compassion for each day. The 10-minute mindful breathing, gratitude journal, and daily emotion reports continue.
Session 5: Personal Strengths, Attainable Goals	Participant lists his or her personal strengths and notes how they may have used these strengths recently; understanding characteristics of attainable goals and setting some goals for the week.	Listing a strength each day and how it was "expressed" behaviorally, working toward one of the attainable goals, and noting progress each day. The 10-minute mindful breathing, the gratitude journal, and the daily emotion reports continue.
Session 6: Skills Summary	Participants will receive a summary of the SAGE LEAF course as a whole. Participants will identify which skills they enjoyed or did not enjoy and why. They will make a plan to practice the positive emotion skills beyond the SAGE LEAF course.	Course wrap-up. The 10-minute mindful breathing, the gratitude journal, and the daily emotion reports continue.
Catch-Up Week	No new skills introduced. Participants continue with daily emotion reports and catch up on any home practice exercises.	Daily emotion reports continue.
Catch-Up Week	No new skills introduced. Participants continue with daily emotion reports and catch up on any home practice exercises.	Daily emotion reports continue.

Measures

Participants will complete self-report questionnaires at 2 time points over approximately 8 weeks. The assessments will be named by their time point "T", e.g. T1 (baseline) and T2 (approx. 6-8 weeks from baseline). At T3 (8 weeks from baseline), participants will participate in a 45-60 min feedback interview (see attached interview guide) through videoconferencing with a member of the study team. All self-report assessments will be completed from home via tablet, a home computer, or mobile device. All instruments will be uploaded to this application for NU IRB approval. In addition to the self-report measures (listed below), we will also assess the following demographic variables, including age, gender, and race/ethnicity. We will assess the following self-report measures in each assessment:

Table of Measures

	Full Name of Measure	**Administered at:**	**In reference to:**
1	Demographics (see uploaded instruments)	Baseline (T1) only	
2	Technology Survey	Baseline (T1) only	Technology/Usability
3	System Usability Scale (SUS)	T2	Technology/Usability
4	Perceived Usefulness Scale (PSU)	T2	Technology/Usability

5	Technology Acceptance Model (TAM)	T2	Technology/Usability
6	Recommendations & Skill Use	T2	Technology/Usability
7	Zarit Burden Interview	All timepoints	Psychological Adjustment
8	Oberst Caregiving Burden Scale (OCBS)	All timepoints	Psychological Adjustment
9	Positive Aspects of Caregiving Scale	All timepoints	Psychological Adjustment
10	Caregiver reaction assessment	All timepoints	Psychological Adjustment
11	Caregiving Mastery subscale of the Caregiving Appraisal Measure	All timepoints	Psychological Adjustment
12	Loneliness/social isolation	All timepoints	Psychological Adjustment
13	Psychological wellbeing (NIH Toolbox)	All timepoints	Health Behaviors
14	PROMIS measures (anxiety, depression, perceived stress, life satisfaction, self-efficacy, and meaning and purpose)	All timepoints	Psychological Adjustment
15	Cohen's perceived stress scale	All timepoints	Psychological Adjustment
16	Differential Emotions Scale	Daily Throughout Intervention	Psychological Adjustment

Procedures for Phase 2: Pilot Test

Upon providing informed consent and completing the phone screen, consented individuals will then be provided access to the SAGE LEAF platform through a sign-up email prompting them to set up their password.

6 Sessions over 8 weeks: approx. 30 minutes/online module
The format and content of the SAGE LEAF pilot test will be the same as the user test. The same online platform will also be used, with minor refinements made based on feedback from the user tests.

Time Commitment
The estimated time commitment for participating in the SAGE LEAF Study is up to 15 hours over 8 weeks.

Event	Time Commitment
Screener + Phone Screen + Consent + 2 surveys (up to 1 hour each)	~7 hours
6 SAGE LEAF Sessions	<3 hours
Daily Home Practice / Emotion Check-In	~3 hours
Feedback Survey + Interview	<2 hours
Total Hours Over 8 Weeks	<15 **hours**

Measures

Participants will complete self-report questionnaires at 2 time points over approximately 8 weeks. The assessments will be named by their time point "T", e.g. T1 (baseline) and T2 (approx. 6-8 weeks from baseline). At T3 (8 weeks from baseline), participants will participate in a 45-60 min feedback interview (see attached interview guide) through videoconferencing with a member of the study team. All self-report assessments will be completed from home via tablet, a home computer, or mobile device. All instruments will be uploaded to this application for NU IRB approval. In addition to the self-report measures (listed below), we will also assess the following demographic variables, including age, gender, and race/ethnicity. We will assess the following self-report measures in each assessment:

Table of Measures

	Full Name of Measure	**Administered at:**	**In reference to:**
1	Demographics (see uploaded instruments)	Baseline (T1) only	
2	Technology Survey	Baseline (T1) only	Technology/Usability
3	System Usability Scale (SUS)	T2	Technology/Usability
4	Perceived Usefulness Scale (PSU)	T2	Technology/Usability
5	Technology Acceptance Model (TAM)	T2	Technology/Usability
6	Recommendations & Skill Use	T2	Technology/Usability
7	Zarit Burden Interview	All timepoints	Psychological Adjustment
8	Oberst Caregiving Burden Scale (OCBS)	All timepoints	Psychological Adjustment
9	Positive Aspects of Caregiving Scale	All timepoints	Psychological Adjustment
10	Caregiver reaction assessment	All timepoints	Psychological Adjustment
11	Caregiving Mastery subscale of the Caregiving Appraisal Measure	All timepoints	Psychological Adjustment
12	Loneliness/social isolation	All timepoints	Psychological Adjustment
13	Psychological wellbeing (NIH Toolbox)	All timepoints	Health Behaviors
14	PROMIS measures (anxiety, depression, perceived stress, life satisfaction, self-efficacy, and meaning and purpose)	All timepoints	Psychological Adjustment
15	Cohen's perceived stress scale	All timepoints	Psychological Adjustment
16	Differential Emotions Scale	Daily Throughout Intervention	Psychological Adjustment

9.0 Research with Vulnerable Populations

This research does not involve the vulnerable populations indicated.

10.0 Incomplete Disclosure or Deception:

N/A

11.0 Consent Process:

For both phases, online consent will take place through a REDCap electronic consent form. Consent will be time-stamped and participants will be able to save, download, and/or print a copy of the consent form for their records. Participants will consent electronically by entering the date and by typing their full name into the form, which will represent their electronic signature. Participants will be considered "consented" only if they provide both items (date and electronic signature). Participants may also email the project director to request a copy of the consent form at any time.

If a participant chooses to withdraw during the study, their data will be retained up until their point of withdrawal. When a participant withdraws, they will no longer receive future assessments and they will no longer receive daily reminders to log-in to the website. Participants can consent to be contacted for future studies. They can also consent to receive SMS text messages to receive their survey assessments. Please refer to the consent form. Study staff will monitor the REDCap project daily in order to track any new completed consent documents and update study tracker.

12.0 Waiver of Participant Signature on Consent Form:

N/A

13.0 Waivers and Alterations of Consent Information:

N/A

14.0 Financial Compensation:

For both phases of the study, SAGE LEAF participants will receive escalating incentives in the form of e-gift cards: $20 for the completion of both assessments at T1 and T2; $30 for the feedback interview for a total of $50 per participant.

15.0 Audio/Video Recording/Photography

Our sources of research material include the video recordings from the feedback interviews that will be conducted through Zoom videoconferencing. Once the video files

have been transferred and saved to the MSS server (identified only by StudyID), these video files will be transcribed with identifying information removed, and the video files will be permanently deleted.

16.0 Potential Benefits of this Research:

There is no guaranteed benefit from participating in SAGE LEAF, however participants might enjoy the skills taught and continue practicing them beyond the online course e.g. keeping a gratitude journal, completing everyday chores mindfully, or listening to a breath awareness meditation recording. Participants may gain mindfulness skills, regularly capitalize on positive events, or use positive reappraisal to reassess daily stressors. Even after completing the course, participants are encouraged to keep using their favorite skills, whether formally through the website and/or journaling about their experiences, or informally in their everyday lives.

On a broader scale, we predict that the skills taught in SAGE LEAF may help AD caregivers increase their positive affect and lower depression, anxiety, caregiver burden, and perceived stress.

17.0 Potential Risks to Participants:

Minimal Risk; Possible discomfort while interacting with the SAGE LEAF platform
SAGE LEAF is relatively easy to administer and is a low cost intervention compared to existing interventions. A potential risk of discomfort might arise with participants who have less experience using the internet, a tablet/computer, or mobile device. Participants might experience frustration or delayed onboarding if they are less familiar with using computer applications, browsing the internet, or connecting to wireless internet. All participants will receive clear instructions for website/technology use, and guidance on how to use the hardware/software required to participate in the study to ensure lack of online experience is not a barrier to participation.

Minimal Risk; Possible discomfort when responding to questions

The risks of participating in SAGE LEAF are minimal. In past research, we have not observed any participants experiencing serious or lasting distress in response to similar interventions or assessments. The intervention has been user-tested to remove any material/content that might be upsetting or insensitive, to reduce the chances of using those questions in future versions. Therefore, risk of discomfort is extremely low. However, some might experience slight discomfort when asked about their emotions, coping, anxiety, and stressful events, or reflecting upon experienced negative emotions. Participants are notified that they may skip any questions they do not wish to answer.

SAGE LEAF study staff who are interacting with participants or monitoring their responses to study procedures will be alert to indicators of elevated distress or possible suicidality. If a SAGE LEAF study staff member observes a possible sign of significant distress and/or suicidal ideation, they will follow an established safety protocol (attached), working together with designated team members to evaluate the severity of the situation, generate a tailored response, and complete final responding and reporting.

"Pollyanna"

The risk of proclaiming the importance of positive affect in the stress and coping process is that it may appear to minimize the pain and serious individual and societal consequences associated with major stressful events. We are not advocating a simplistic "don't worry-be happy" approach, nor do we believe that simply increasing positive emotion will prove to be a cure-all for the very real and complex issues facing caregivers. Such a Pollyanna-ish stance could easily degenerate into blaming the caregiver for not thinking the positive thoughts that may prevent depression or other negative consequence of enduring stress. However, we argue that an intervention to increase positive emotions sets the stage for adaptive coping. Ultimately, given the high levels of caregiver burden, depression, and anxiety documented in AD caregivers, we consider increasing positive emotion to be an inherently worthwhile intervention goal.

While our study focuses on positive emotion, we emphasize that SAGE LEAF is not a replacement for therapy, nor is it considered a treatment for depression or anxiety. Participants are encouraged to follow the guidelines of their health care provider and advised that they should <u>not</u> put off starting therapy and/or medication or stop treatments recommended by their health care provider.

Withdrawal of participants

If a participant wishes to withdraw, he/she can communicate this on the phone or via email to the project director. Study staff will also be monitoring communications and potentially withdrawal requests coming through on the study website or study email. The participant will then be promptly withdrawn from the study, their data collected and eventually analyzed only up until the point of withdrawal. No further data will be collected after a participant has been withdrawn. We will document the reason for withdrawing.

18.0 Provisions to Protect Participant Privacy and Data Confidentiality:

Confidentiality in data

The risk of loss of confidentiality is extremely low. Identifiable information will be collected using REDCap which uses industry-standard encryption to protect participants' information while in transit from the moment data is entered to the moment it is stored on HIPAA compliant servers. Data is never fed back to participants or displayed on the participant website. Access to REDCap is granted to key personnel and all study staff

handling personally identifiable information will have taken the CITI Human Subjects Training Course. Participants will be assigned and identified by a unique Study ID on the SAGE LEAF platform, and their information will be stored in encrypted form on Northwestern computers. Any hard-copy documents will be stored in locked cabinets in the Department of Medical Social Sciences and all electronic copies of data, study emails, or records will have double-protection through password-protected access for NU servers and to REDCap. Even if a participant's account is later compromised, submitted information on the website is protected and not released.

The REDCap instance at Northwestern supports the SMS text messages. We are using REDCap's feature to integrate SMS text messaging with Twilio to send the assessments. Access to the phone numbers are password-protected and secure. The same data protections that exist for the REDCap PHI exists for the SMS messaging feature as well. Assessment data will not be stored locally on the phone or any device. If receiving an assessment via text, the message will include a link to a web-based survey (protected and hosted by NUCATS). If issues arise with the SMS feature, we will immediately contact the REDCap administrators at Northwestern University to resolve any issues.

The SAGE LEAF online platform is hosted by Bright Outcome and is protected by end-to-end encryption and password measures. Participants will be able to access the SAGE LEAF intervention on their computer, tablet or mobile phones with an internet connection. Participants will submit their home practice through the website (i.e. gratitude journal) and submit their feedback for the lessons, since participants are encouraged to visit the site every day. IRB-approved NU study staff will be able to access the data collected through the platform through direct export. No data will be stored locally on participants' devices.

Confidentiality in general

Once a participant is enrolled in the study, there is the chance someone might see a participant filling out assessments or reading the positive emotion skills on the platform. To protect participant privacy, we encourage all participants to find a private room with a closed door and to use headphones (if needed) when completing online modules or participating in the feedback interview. We will also encourage participants to be mindful and aware of their location (i.e., in a public or crowded space) when filling out their online assessments. Since the assessments are completed online, this allows for flexibility and participants can answer the questions from the comfort and privacy of their own home on their mobile device/tablet computer/laptop etc.

19.0 Data Monitoring Plan to Ensure the Safety of Participants:

We have developed the following data and safety monitoring plan. Our goal is to collect data on acceptability, adherence, and retention of the intervention through self-report

measures and by tracking website usage and engagement. We aim to do so in a way that protects and ensures participants safety and confidentiality.

The assessments and intervention sessions pose no more than minimal risk to participants. The data and safety-monitoring plan identifies the PI as the primary monitor of risks to human subjects in the form of data and safety related risks. The study's biostatistician is the back-up data custodian to the PI, advising and providing support in data decisions. Any serious adverse events will be promptly reported to the institution's IRB and project officer of the funding source by the study PI. Risks, monitoring procedures, and reporting and action plans are described below for both data and safety related risks.

Data Risks and Monitoring

Data related risks. Data related risks to participants could consist of circumstances where an insufficient amount of data was collected to answer the research questions, or a breach of confidentiality where the safety of identifiable data has been compromised.

Data monitoring procedures. The PI, Dr. Judith Moskowitz will be the primary data custodian for SAGE LEAF. Overall recruitment goals, missing data, and follow-up failures will be monitored by the project manager, and the PI will receive regular updates and maintain constant communication with the project manager, and the rest of the team; at first bi-weekly, then monthly as needed. The biostatistician will also provide ongoing monitoring of study progress and advise with proposed changes and precautions, if necessary (i.e. updates to protocol to meet recruitment goals, etc.). Post-doctoral fellows and co-Investigators who will be assisting with data analysis will be added to the IRB.

Data risk reporting and action plan. The project manager will oversee the data safety and monitoring plan, data management, and data security. She will work alongside the PI and the Project Director to compile the recruitment numbers during all phases of the study and responsible for assuring completion of required assessments, maintaining databases, and identifying missing data and missing follow-up assessments.

Safety Risks and Monitoring

Safety related risks. Safety related risks could consist of:

1) Emotional discomfort while using the SAGE LEAF platform
2) Emotional discomfort while completing assessments
3) Loss of confidentiality in data
4) Loss of confidentiality in general
5) "Pollyanna" effect and mistaking the intervention as therapy
6) Signs of distress or revealing identifying information on the "Discussion" forum

Safety monitoring procedures. All safety related risks will be monitored routinely throughout the study. (1-2) It will be made clear to participants that they are allowed to skip any exercises or questions that may cause them emotional distress. Participants are provided instructions on how to use the website, log-in, access the course, and are given the contact information of the Project Director, PI, and the designated study email. Guidelines and videos to use the website are provided. Participants can email or call study staff and the study is generally staffed Monday-Friday 9am-5pm except holidays, etc.

Dr. Elizabeth Addington is on the SAGE LEAF study team and she is a clinical psychologist. She is also a Research Professor in the Department of Medical Social Sciences, Feinberg School of Medicine. She will be the main point of contact and the study advisor for questions regarding safety concerns. She will help the team make recommendations and take research precautions to ensure the safety of our participants.

Study staff are monitoring the website weekly and will be trained to respond immediately to participant needs and/or questions on technology and the platform. There is also a FAQ page on the website for frequently asked questions. If a question is not listed/answered on the FAQ page, participants may call or email study staff. Based on our experience conducting prior trials of online self-guided delivery of positive affect skills (e.g. MARIGOLD, LARKSPUR), the study team is well versed in handling/managing instances that might require providing caregivers with additional resources. The PD will be the main point of contact and the study advisor for questions regarding safety concerns. She will help the team make recommendations and take research precautions to ensure the safety of our participants.

(3) The security of confidential information will be monitored regularly. Participants will be informed that their responses will be kept confidential and not used against them in any legal, online modules in a private space and to be mindful of where they complete their online assessments, so as to limit the chance of someone overseeing their answers and to limit exposures of their responses from their computer/tablet/phone screen.

(5-6) In the event that a participant contacts the study directly to report severe distress or suicidality, or reveals this information online in an email or via the website's "Discussion" feature, the project manager or study team member will immediately alert the PI. The PI will review the situation and take immediate, appropriate steps. If the situation is serious, designated research staff will promptly respond to a distressed participant with appropriate information about how to seek help. In previous studies, we have developed monitoring plans for responding to signs of distress in an online forum. Study staff have the ability to archive/delete messages that are inappropriate to keep the discussion board related to discussing topics on SAGE LEAF. Based on our past experience conducting online studies with a discussion feature (e.g. MARIGOLD, LARKSPUR), the risk of these occurrences is minimal and the study team is well versed in handling/managing these instances, if they happen.

Safety risk reporting and action plan. Any participant in need of treatment due to distress will be referred for appropriate services by the project manager. In severe cases, the PI will be informed immediately. The project director will report breach of confidentiality risks incurred by participants to the PI. The PI will be responsible for informing the IRBs and the Project Officer immediately of any life threatening incidents (although this risk is very low and not expected to happen). The PI will take appropriate action to stop the study, release a participant from the study, or modify procedures to reduce and/or eliminate the occurrence of the abovementioned risks occurring at an unacceptable level.

Adverse events. Due to the nature and scope of this study, we do not anticipate any adverse events. However, in the case that an adverse event arises, it will be tracked and the PI informed within 24 hours to assess the situation and follow-up. An adverse event form will be developed detailing the problem, actions taken, supervisor notes, and follow-up steps performed. The form will be immediately sent to appropriate agencies, including the IRB and NIH. Any action recommended by one of the IRBs will be conveyed to the NIH. The PI will be responsible for the monitoring and reporting of any adverse events. The co-investigators will be consulted as appropriate.

All problems having to do with subject safety will be reported by the Principal Investigator to the IRB within ten working days. Specifically, the following will be reported, in writing: 1) all serious adverse events associated with the study procedures, and/or 2) any incidents or problems involving the conduct of the study or participation, including problems with the recruitment and/or consent processes. The Principal Investigator will provide a discussion of any problems noticed during each year in the course of the study to the IRB and NIH on an annual basis.

If, during the course of communicating with study staff (e.g., synchronously on phone or asynchronously via email), a participant indicates severe elevation of distress or possible suicidal ideation, study staff will follow the attached Safety Protocol, which has been developed based on procedures used in their prior studies of positive emotion skills delivered online. Staff who are responsible for communicating directly with participants will be trained on the Safety Protocol by Dr. Moskowitz and/or the PD. Trainees will be responsible for reading the entire Safety Protocol prior to training. Then training will include: a discussion/review of all elements of the Safety Protocol; time for all trainees to discuss any relevant experience and ask questions; and the opportunity to role play using the telephone template responses.

20.0 Long-term Data and Specimen Storage and Sharing:

Dr. Moskowitz, PI, is involved in the development of the online intervention, analysis, data interpretation and manuscript write-up. She will have secure access to the data housed at NU. No other Northwestern personnel will have access to the data unless he/she is listed on the IRB as study personnel. Dr. Moskowitz and her NU collaborators will also use

statistical programming on FSM desktops/computers and store analysis documents on FSM servers.

Data, manuscript drafts, forms and other study-related documents will be stored on secure FSM servers through the Department of Medical Social Sciences (MSS). For the information that must be identifiable for the purposes of the study (i.e. name, phone number, email address for facilitator/participant contact), this information will have added layers of protection (via password access to the file). Participants will be coded and identified by a unique participant ID.

Data input, processing, tracking and storage will happen at Northwestern University. Dr. Moskowitz has oversight over each part of the process. Path to storage: Bright Outcome platform REDCap platform → Northwestern HIPAA-compliant server (storage and analysis) on the FSMFILES MSS Departmental Server.

Identifiable data will only be shared internally amongst researchers listed on the IRB. Only IRB-approved individuals will have access to data through encrypted networks like the FSMFILES network or have permission to download datasets directly from REDCap (i.e. the PI, the biostatistician, the project director, IRB-approved study staff). De-identified data might be shared with collaborators for the purposes of data analysis, secondary data analysis, manuscript-writing, using Northwestern Box. We will take precautionary measures to protect the confidentiality of our participants.

21.0 Qualifications of Research Team to Conduct the Research:

Northwestern University (NU), whose component schools and clinical affiliates form the foundation of this proposal, supports and promotes a vibrant and ever-growing community of clinical and translational scientists that is passionately committed to improving human health. Northwestern is one of the premier undergraduate and graduate universities in the world. It is ranked 12th among US national universities by *US News &World Report*, and is ranked in the top 30 world-wide. NU has notable strengths in medicine, public health, chemistry, nanotechnology, life sciences, engineering, communications, law and business/management. Northwestern's sponsored research awards grew to $620 million in fiscal year 2015, the largest amount in the University's history and a 4 percent increase over 2014's $593.9 million. NU is located in Evanston and Chicago, Illinois. The University has a long history of leadership in interdisciplinary research programs and centers. More than 90 school-based centers and 26 University centers support interdisciplinary research that spans a wide spectrum of areas. Investigators with a Northwestern affiliation have access to the Galter Health Sciences Library at Northwestern University's Feinberg School of Medicine and all other Northwestern University libraries, including the Pritzker Research Library at Children's Memorial Hospital.

The proposed project will be based in FSM's **Department of Medical Social Sciences (MSS)**. MSS was established in 2009, with Dr. David Cella as founding and current chair, and provides a unique scientific home for applied researchers, integrating biomedical and social science approaches to improvement of health and health care delivery in diverse populations across the lifespan. Research themes include health measurement, quality of life measures, developmental mechanisms of health and disease and statistical tools to support clinical research with strength in application to specific disease processes such as cancer, neurologic disease, and early onset psychopathology. MSS is a catalyst for scientific integration across biomedical and social / life sciences campuses. MSS research cuts across traditional disciplinary boundaries, with collaborative ties with a broad range of research institutes and clinical departments across the University.

Within MSS, there is adequate office space and computer work stations for all planned staff and secure data storage (paper and electronic) designated for the proposed study. MSS has its own internal Information Technology group that manages all hardware, software, and support needs for the department. Department computers are generally on a three year replacement cycle and use whatever technology is current at the time of replacement. The computers use either Windows or MacOS operating systems and run individual firewalls, antivirus, backups, and disk encryption that are centrally managed. Servers, while managed by the department IT group, are hosted at the University Data Centers that are shared by all departments. Servers provide web services, database services, file storage, and print services. These are secured behind Data Center firewalls with specific ports open for each specific service. Network access is limited to authorized University IDs. Physical access is limited to specific IT personnel using three factor authentication including biometrics. Files are backed up daily and databases are backed up every two hours. The department currently utilizes 24 servers in a combination of physical machine and virtual machine configurations. Protected health information and personally identifiable information that are stored on MSS database servers and on MSS file servers are layered with various physical and electronic access protections and policies to ensure HIPAA compliance. There are approximately 120 laptop and desktop computers utilized by department faculty and staff for day to day computing needs, along with over 50 laptops dedicated to specific studies.

In addition, we will be working with **Bright Outcome,** a healthcare technology company that has built successful collaborations with other investigators at MSS. They have worked with other clients such as the Centers for Disease Control and Prevention, the National Institute of Mental Health, the National Institute of Nursing Research, and the National Cancer Institute.

22.0 Statistical Analysis:

Statistical Analyses

We will calculate the medians and interquartile range (IQR) for primary measures that assessed the (1) usability, (2) usefulness, (3) feasibility, and (4) acceptability of the SAGE LEAF platform. In addition, we will calculate supplementary user metrics based on data collected by the platform (e.g., percentage of home practice activities completed and percentage of videos watched) that reflect various aspects of engagement. We calculated the means and SDs for the Social Presence Scale and applied them as a correlate with measures of usability, usefulness, feasibility, and acceptability. For measures related to preliminary outcomes, we will perform paired, 1-tailed t tests on the data collected during the baseline and postintervention assessments to examine changes in means. Analyses will be conducted using Excel (Microsoft Corporation) and R Studio (Posit).