Preparation for End-of-Life Decision Making in Mild Alzheimer's Disease

NCT Number: NCT03311711

Protocol Version Date: 15 July 2020

Preparation for End-of-Life Decision Making in Mild Alzheimer's Disease

(Short title: SPIRIT in Mild AD)

National Clinical Trial (NCT) Identified Number: NCT03311711

Principal Investigator: Mi-Kyung Song

Funded by: NIH/NIA, R01AG057714

Version Number: v.14

15 July 2020

Summary of Changes from Previous Version:

Version No.	Date	Affected Section(s)	Summary of Revisions Made	Rationale
V14	7.15.2020	1.1 Synopsis 3 Objectives-Aim 2 4.2 Scientific rational-study design 6.1.1 Study intervention description 6.3 Randomization 6.4 Study intervention compliance 9.2 Sample size 9.4.2 Analysis of primary endpoints 10.1.1.2 Consent process/documentation	Eliminate SPIRIT in-person modality and change the study design change to a 2-group (SPIRIT-remote vs usual care) RCT. Northwestern and Rush Universities will make potential participant referrals.	In consideration of SARS-COV-2 Pandemic CDC guidelines Optimize study recruitment: Grady clinic withdrew participation due to space limitation during pandemic

Table of Contents

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

  National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

  The protocol, informed consent form(s), recruitment materials, and all participant materials have been approved by the Institutional Review Board (IRB) at:

  Emory (Study No.: IRB0099738; approved on 10/24/2017)

  Any amendment to the protocol requires review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved.

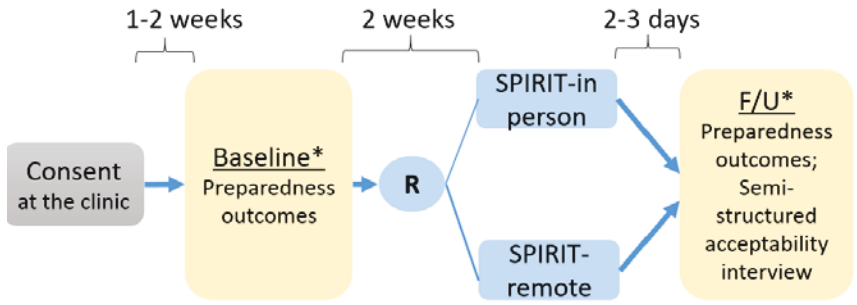
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Preparation for End-of-Life Decision Making in Mild Alzheimer's Disease
Study Description:	The proposed study will adapt and pilot test an efficacious advance care planning intervention, SPIRIT (Sharing Patient's Illness Representations to Increase Trust), with patients with mild Alzheimer's Disease and their surrogates to promote open, honest discussions while such discussions about end-of-life care are possible.
Objectives:	**Aim 1**. Adapt SPIRIT (in person) to target patients with mild AD and their surrogates through a process of modification-pretesting-refinement using stakeholders (patients, family caregivers, and clinicians) and experts, including adapting the delivery mode to interactive web-based videoconferencing (SPIRIT-remote). **Aim 2**. In a 2-group RCT with 120 patient-surrogate dyads, evaluate the feasibility and acceptability of SPIRIT-remote, and the preliminary efficacy compared to usual care (wait-list control) on preparedness outcomes for end-of-life decision making 2-3 days after the intervention. **Secondary Aim a**. Compare the completion of advance directives among the two treatment conditions at 1-year post-intervention. **Secondary Aim b**. Using a qualitative method, in a sample of surrogates, explore their perceptions of SPIRIT at 1-year post-intervention for acceptability and preparation for end-of-life decision making.
Endpoints:	Preparedness for end-of-life decision making: a) Dyad congruence b) Surrogate decision-making confidence c) Surrogate preparedness for end-of-life decision making
Study Population:	Adults with dementia and their surrogates
Phase:	Phase I
Description of Sites/Facilities Enrolling Participants:	Outpatient clinics
Description of Study Intervention:	**SPIRIT** (**S**haring **P**atient's **I**llness **R**epresentation to **I**ncrease **T**rust), a patient and family-centered ACP intervention based on the Representational Approach to Patient Education, is to establish a testable model of how end-of-life care discussions could occur between a patient and his/her chosen surrogate (usually a spouse or adult child). The discussions, which are facilitated by a trained interventionist, are framed around addressing each individual's representations of (beliefs about) the illness and views of life-sustaining measures at the end of life. SPIRIT follows a six-step learning objective over two-sessions, which together take about 60 minutes.
Study Duration:	5 years
Participant Duration:	In Phase I to modify and pretest SPIRIT for mild dementia, about three weeks In Phase II to pilot test the modified SPIRIT, about one year after randomization

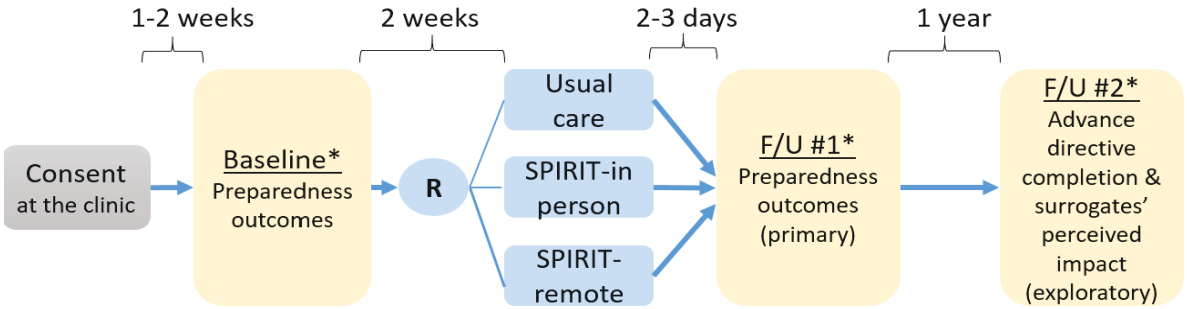
1.2 SCHEMA

Stage IA



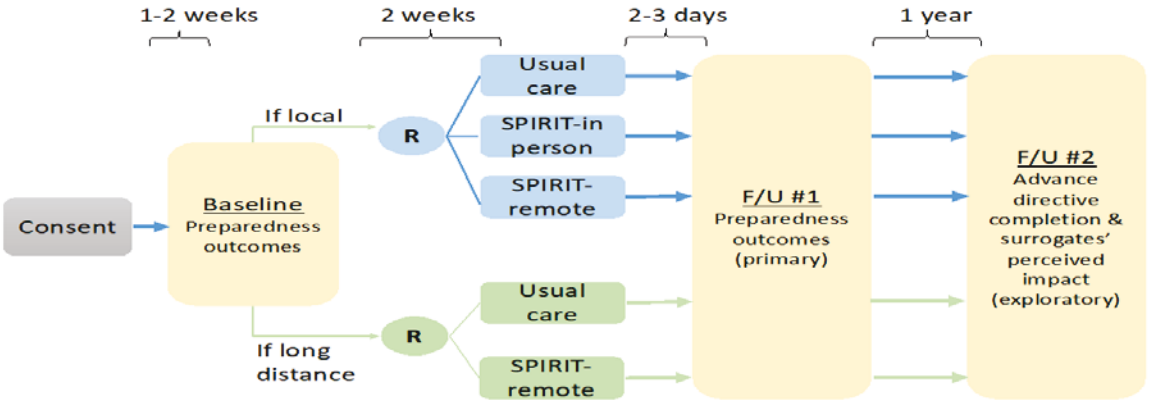
*All data collection from participants will be telephone-based.

Stage IB

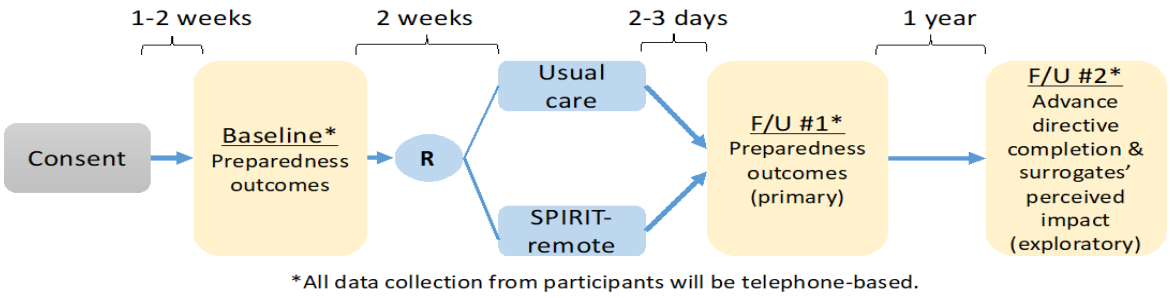


*All data collection from participants will be telephone-based.

With revision (V12)



With revision (V14)



*All data collection from participants will be telephone-based.

2 INTRODUCTION

2.1 STUDY RATIONALE

Alzheimer's disease (AD), the most prevalent class of dementing illness, is a leading cause of death and affects over 5 million individuals in the US.[1] Like most dementing illnesses, AD cannot be effectively prevented and is incurable. Progressive memory loss and impairment of reasoning and judgment are its main symptoms.[2] For this reason, people in the early stages of AD are encouraged to engage in advance care planning (ACP) while they are still competent to appoint a surrogate decision maker and meaningfully participate in ACP discussions with the surrogate.[3,4] Yet only a minority (39%) of older adults with early cognitive impairment complete any form of ACP following the diagnosis.[5]

The most common type of ACP is completing a medical power of attorney or living will, which does not require the patient and/or the family to understand the complexity of the medical decision-making process faced by the surrogate as the patient progresses to advanced disease. The failure to engage in ACP before the window of opportunity closes (i.e., before loss of decision making capacity) has serious adverse consequences with the greatest impact on the surrogate. As a matter of course in AD, family members are left to make decisions regarding care transition, tube feeding, and other life-sustaining treatment without input from the patient and in the absence of a full understanding of the wishes, values and preferences of the patient.[6-8] Unfortunately the culture of technological imperative to deliver aggressive or futile medical care to very frail older adults drives end-of-life decision making especially when there has been no ACP.[9,10] Of direct relevance to this proposed study, the vast majority of family members of patients with AD report not being prepared for these difficult decisions,[11-13] and they report experiencing considerable negative mental health sequelae after they face end-of-life decision making.[12-23] Thus, while ACP is of great relevance to the dignity of the patient, the true emotional burden of care falls to the surrogate.

To make an impact on the state of ACP for patients with AD and their surrogates, we will adapt and pilot test an efficacious ACP intervention, **SPIRIT** (**S**haring **P**atient's **I**llness **R**epresentations to **I**ncrease **T**rust), with patients with mild AD and their surrogates (NIH Stage I behavioral intervention development[24] in PAS-17-027) to promote open, honest discussions while such discussions about end-of-life care are possible. SPIRIT is a brief, scalable patient- and family-centered ACP intervention based on the Representational Approach to Patient Education[25,26] with a goal to promote cognitive and emotional preparation for end-of-life decision making for patients with a serious or life-threatening illness and their surrogates. SPIRIT focuses on having both the patient and the surrogate fully understand end-of-life decision making in anticipation of a loss of decision-making capacity.

Over the past decade, SPIRIT has been iteratively tested in 5 randomized controlled trials (RCTs) to establish feasibility, patient-surrogate acceptability, and efficacy in patient populations, including end-stage renal disease, advanced heart failure, and cardiac surgery.[27-32] Patients and surrogates who received SPIRIT showed significant improvements in key outcomes reflecting preparedness for end-of-life decision making: a) increase in patient and surrogate agreement on end-of-life care goals, b) reduction in patient's conflict about benefits and burdens of life-sustaining treatments, and c) increase in surrogate confidence about the surrogate role, which in turn resulted in decreased post-bereavement psychological distress for surrogates. We designed SPIRIT as a testable model of how end-of-life care discussions could occur between patient and surrogate. The facilitated discussions are structured to address each individual's representations of (i.e., beliefs about) the illness and views of life-sustaining measures at the end of life. The overall goal of this project is to produce an effective and maximally implementable ACP intervention for patients with mild AD and their surrogates. Collaboration with researchers from NIH-funded AD research centers will set the stage for a future implementation study that could lead to

improvements in patient- and family-centered outcomes at end of life.

2.2 BACKGROUND

At the end of life, many patients with dementing illnesses receive burdensome interventions with no clear therapeutic benefits. AD and related dementias (ADRD) are the 6th leading cause of death in the U.S. with no effective treatment.[2,33] Mortality in patients with advanced ADRD is high (median survival=1.3 years[34-36]); most die after acute illnesses, such as pneumonia or a febrile episode rather than from "devastating" complications such as stroke or heart attack.[37] For those with advanced ADRD, intensive or burdensome end-of-life care is common. Nearly 41% undergo at least one intensive intervention (e.g., tube feeding, mechanical ventilation) in the last 3 months of life, which may prolong life but not address quality of life (or quality of dying).[34,35,37,38] A major contributor to high intensity of care at the end of life is that many patients and their family members do not recognize that ADRD is a terminal disease.[37] Since 2000, the use of mechanical ventilation for Medicare beneficiaries with advanced dementia has been doubled without any measurable survival benefit.[39] The great challenge to the medical community is to prepare patients and families for very complicated end-of-life scenarios rife with medical decision making in the context of the patients' progressive loss of cognitive functioning and selfhood.

Most patients with mild AD and their surrogates miss the window of opportunity for meaningful ACP. Merely completing legal documents to indicate one's preferences for medical care does not adequately improve end-of-life care because family members often do not know or agree with the content of the directive, or do not know how to translate vague preferences into specific treatments at end of life[40]; and legally appointed surrogates lack knowledge of patients' wishes and are poorly prepared for emotional turmoil during end-of-life decision making.[21,41] In contrast, a process of developing an advance directive as an embodiment of a patient's wishes based on discussions about ones values and illness representations can result in high quality ACP that improves quality of life during the end of life and, importantly in AD, and reduce stress for surrogates and caregivers. The practice of ACP has evolved to focus on psychological and practical preparation of patients and surrogates for treatment decision-making at the end of life.[28,42-48] For example, for patients, ACP can involve exploring the personal meaning of illness and gaining knowledge about illness progression; for surrogates, ACP can involve gaining an understanding of the patient's values and goals for end-of-life care and of the role and responsibilities of being a surrogate.[28,49] The objective of a patient-centered ACP process is to prepare a surrogate to execute the patient's wishes rather than simply react based on the instructions in an advance directive.

Per usual care, clinicians advise people with early cognitive impairment and their families to complete an advance directive at the time of diagnosis. Typically, this involves providing the patient and family a brief information about how to prepare advance directives. Research has shown that only a minority of older adults with mild cognitive impairment or mild AD complete an advance directive after the initial diagnosis (39%), and if advance directives are not completed during the early stages of cognitive impairment, it is unlikely that this will happen as the patient progresses into an advanced stage.[5] There are numerous AD support groups around the nation. These support groups may be one location to focus attention on ACP and financial planning (and thus are often led by a lawyer rather than a clinician) and provide important legal and technical information and social support. However, a meta-analysis of interventions with dementia caregivers suggests that those types of support groups do not effectively accomplish the goals of ACP described above.[50]

There are several reasons that patients with mild AD do not engage in ACP discussions or complete an advance directive. Remaining functional independence in patients with mild AD may mask troubling declines in cognitive symptoms (e.g., memory lapses, impaired ability to plan complex activities).[51] As a result, the patient and family members may not appreciate the need or urgency for preparing for future medical care, including end-of-life care.[52] Patients and/or their families may be unwilling to believe that the patient will progress to an advanced stage, unaware of the progressive nature and terminality of AD, adopt a passive coping stance (e.g., future is fated

and cannot change), want to delay until a dire medical event presents itself (e.g., critical illness), or underappreciate the end-of-life decision making burden on family members.[3,52-55] A typical scenario is that decision making about intensive, invasive, and expensive medical interventions is left to unprepared surrogates and/or clinicians who are likely unaware of the patient's preferences.[19,56,57]

Lack of preparedness for end-of-life decision making has serious negative consequences on patients, surrogates, and society at large. Studies, including our work,[11,58] have demonstrated surrogates to be overly confident about their ability to act as a surrogate. We have shown that many surrogates lack an understanding of the patient's preferences (assessed by comparing patient preferences and surrogate understanding of those preferences), yet report a high level of confidence in understanding patients' wishes and high confidence that they will be able to execute their role as a surrogate.[58] There are many deleterious consequences to an actual lack of preparedness for end-of-life decision making and these have been well documented, including high levels of intrapersonal and family conflict brought on by having to make life or death decisions (e.g., whether to withhold or withdraw mechanical ventilation, or other life-sustaining measures that are deemed futile); regrets over missed opportunities to benefit from palliative care or hospice; excessive distress for family members during decision making due to interfamily conflict and anguish, time pressure to make important decisions, lack of knowledge about options; and psychosocial sequelae for family members (e.g., depression, anxiety, and post-traumatic stress disorder) and complicated bereavement after the patient's death.[11,17,21,59-68]

Numerous studies, including those of dementia patients, indicate that families experience greater difficulty in decision making when they are uncertain about the patient's wishes, when they feel unprepared for their role because they have never discussed it, and when they are called on to make decisions in a short period of time.[12-19] Dementia family members with a greater sense of burden for decision making are more likely to consent to life-sustaining treatment.[20] There is a high rate of psychiatric illness among family decision makers; in one study of ICU family members, nearly 40% of those who experienced a loved one's death during the previous 3 to 12 months had at least one psychiatric illness meeting DSM-IV criteria, such as anxiety disorder or major depression.[68] Even at 6-12 months after the patient's death, studies show that family members experience intrusive thoughts of regret, guilt or search for evidence that they made the right decision.[16,17,21-23]

SPIRIT, a patient- and family-centered ACP, has documented beneficial effects on a range of psychosocial outcomes for patients and their surrogates. The goal of SPIRIT is to promote cognitive and emotional preparation for end-of-life decision making for patients with a serious or life-threatening illness and their surrogates. SPIRIT is based on the Representational Approach to Patient Education.[25,26] This approach melds two theories: Leventhal's common sense model [69] and the conceptual change model.[70] The common sense model proposes that individuals have representations of their illness or health problems. Representations are based on an individual's experiences, cultural traditions, or media, and may not be medically accurate. It is critical to understand a patient's representations because they filter new learning: representations serve as the cognitive framework that affects whether or not individuals accept or reject new information,[25] and whether knowledge leads to behavior change.[71,72] The conceptual change model proposes that the likelihood of learning increases when the individual has an opportunity to reflect and comment on current ideas, when the individual is dissatisfied with current ideas or recognizes their limitations, and when alternative information is seen as beneficial.[25,26,70,73] Learning and change can occur through integrating new information into existing representations to fill gaps in understanding, by clarifying existing representations to reduce confusion, or through replacing existing ideas with new information.[73,74] The scientific premise for this study is that the Representational Approach to Patient Education requires an interventionist to elicit the patient's existing illness representations before providing new information.[25,26] Then, the interventionist, the patient, and his/her surrogate have an opportunity to recognize gaps or confusions, and the interventionist can give new information that is specific and relevant, increasing the likelihood that it will be acted upon.

SPIRIT is a two-session, 60-minute, structured psychoeducational intervention, targeting both patient and surrogate. SPIRIT was developed by our team and extensively evaluated in patients with end-stage renal disease,

advanced heart failure, and cardiac surgical patients and their surrogates.[27-32] Using an interventionist manual, the interventionist follows six steps: 1) assess illness presentation, 2) identify gaps and concerns, 3) create conditions for conceptual change, 4) introduce replacement information, 5) summarize, and 6) set goals and plan.[75] SPIRIT first establishes an understanding of the cognitive, emotional and spiritual aspects of the patient's representation of (ideas about) his/her illness. This understanding enables the interventionist to provide individualized medical information and to assist the patient in examining his/her own values related to life-sustaining treatment at the end of life. In this way, the patient can more readily express his/her treatment preferences to the surrogate. SPIRIT also enables the surrogate to understand the patient's illness experiences and values and to be prepared for the responsibility and emotional turmoil that can arise during decision making at the end of life. Each element of SPIRIT is designed to enhance the quality and authenticity of exchanges between patient and surrogate about experiences surrounding illness and values. During the process, the patient discovers his/her own representations about illness and examines thresholds and/or conditions for withholding or (dis)continuing life support measures. The surrogate also validates similarities or differences with the patient in regard to life support measures and examines his/her own ability to follow the patient's wishes. This process is critical to preparation for end-of-life decision making.[30,75] To deliver SPIRIT sessions, interventionists are trained in communication skills and end-of-life planning.

Preliminary data on the efficacy of SPIRIT: Over a decade, we have iteratively tested SPIRIT in 5 RCTs to establish feasibility, patient-surrogate acceptability, and efficacy in: patients undergoing major cardiac surgery who were "otherwise healthy," seriously ill patients with end-stage renal disease (ESRD), and elderly patients with advanced heart failure who had a left ventricular assisted device implanted.[27-32] Over the course of these studies, SPIRIT has been modified to target the particular patient population, to tailor content while maintaining theoretical core elements responsible for patient and surrogate outcomes, language complexity (current literacy level at Flesch-Kincaid grade=7), and the number of sessions (1-2 sessions). SPIRIT has been adapted to be culturally tailored for African Americans with ESRD.[75] All studies were in outpatient care settings (both academic and community settings). Importantly, in the study with patients undergoing major cardiac surgery, we demonstrated that a SPIRIT session prior to major surgery did not increase participants' anxiety in spite of clinicians' concerns and efforts to avoid such discussions.[27] We have tested strategies for recruitment, retention, data collection, SPIRIT training, fidelity, and measurement. Recruitment rates have consistently been >80% with very low dropout (<4%) even in an RCT requiring long-term follow up (12 months).

In a full-scale multicenter RCT of patients with ESRD and their surrogates (R01NR011464), we tested the efficacy of SPIRIT compared to usual care (wait-list control) in preparation for end-of-life decision-making. At 2, 6, and 12 months, outcomes were dyad congruence, patient decisional conflict, and surrogate decision-making confidence (preparedness outcomes).[30] We also tested whether SPIRIT reduced post-bereavement distress for surrogates (at 2 weeks, 3 and 6 months post patient's death). Dyads (N=210) of seriously ill dialysis patients and their surrogates from 20 free-standing dialysis facilities (mean age 62, 57% women, 67% African Americans) were randomized to SPIRIT or usual care. ITT analysis showed that, adjusting for time and baseline values, dyad congruence on goals of care (*OR*=1.89 [95% *CI*, 1.1 to 3.3]; *p*=.029) and surrogate decision-making confidence (β=0.13 [*CI*, 0.01 to 0.24]; *p*=.027) were significantly better in the SPIRIT group. Patient decisional conflict was significantly lower in SPIRIT at 12 months (β=-0.19 [*CI*, -0.33 to -0.04]; *p*=.011).

Mortality rates between the groups were similar. Among 45 bereaved surrogates, adjusting for time and baseline values, those in SPIRIT had less anxiety (β=-1.13 [*CI*, -2.23 to -0.03]; *p*=.044), depression (β=-2.54 [*CI*, -4.34 to -0.74]; *p*=.006), and post-traumatic distress (β=-5.75 [*CI*, -10.9 to -0.64]; *p*=.027) than did controls. Our qualitative thematic analysis of post-bereavement interviews with surrogates (**Box 1**) helps explain how SPIRIT reduced surrogates' post-bereavement distress.[14]

Box 1. Perceived impact of SPIRIT: Themes

SPIRIT…

a) was an eye-opening experience regarding the patient's illness, prognosis, and end-of-life care
b) strengthened relationships between patient and surrogate
c) helped surrogates feel prepared during the time leading up to end-of-life decision-making
d) helped surrogates have peace of mind during and after actual end-of-life decision-making

In the context of mild AD, we will focus on short-term preparedness outcomes, rather than end-of-life outcomes, including post-bereavement distress for surrogates, because such efforts are not feasible in this 5-year study due to the protracted nature of AD trajectories (i.e., death is not imminent). Instead, we will evaluate whether SPIRIT results in an embodiment of the patient's wishes (i.e., advance directives) by 1 year post intervention as an exploratory aim. In another exploratory aim, we will interview a sample of surrogates at 1 year to assess the perceived impact of the intervention conditions.

SPIRIT will be feasible for patients with mild AD and their surrogates but first needs to be modified and pilot-tested. While there is considerable heterogeneity in functional performance in the early stages of cognitive impairment due to AD,[33,80,81] numerous studies have shown the feasibility of consenting patients with mild AD (defined as a Montreal Cognitive Assessment [MoCA] score 12-17 or a Mini-Mental State Examination [MMSE] score 18-23;) for research and the feasibility of survey completion.[3,83] Further, Moye et al.[84] demonstrated that most adults with mild dementia can participate in decision making as defined by legal standards for competency. In addition, several studies that examined the level of cognitive impairment and capacity to complete advance directives suggest that an MMSE score of 18-20 is a consistent threshold required for ACP.[85-88] SPIRIT is focused on exploring patient and surrogate beliefs and values, and does not demand ability to process factually intensive information nor does it rely heavily on short-term memory. Thus, SPIRIT is feasible for those with mild AD. The first step of the proposed study is to carefully modify SPIRIT to make it suitable for patients with mild AD, their surrogates, and clinicians while maintaining the integrity of the intervention to achieve the desired patient and surrogate outcomes (i.e., the theoretical core elements),[24,89] and then pilot test it (NIH Stage I behavioral intervention development[24]).

At this time our plan is to accomplish the goals of SPIRIT in one session (as in the original version of SPIRIT) rather than two (which was used in recent RCTs) because patients typically do not return to the clinic for their next medical visit before 6 months. The content of SPIRIT, such as likely situations requiring surrogate decision making and end-of-life treatment, will be tailored to the AD context. Also, we will modify the delivery of content to incorporate techniques such as reducing information load by proceeding in manageable segments or chunks, offering repetition of material, opportunity for rehearsal, and using targeted questioning to verify adequate comprehension prior to eliciting preferences for goals of care.[90-92] The feasibility of using these so-called "enhanced consent techniques" for people with early cognitive impairment has been demonstrated[83] and will be applied to the adapted intervention.

Another important modification will be to develop and test *SPIRIT-remote*, a face-to-face delivery of SPIRIT through web-based videoconferencing to facilitate wider future implementation. Videophone technology has been shown to capture critical, nonverbal communication necessary for psychoeducational interventions and is as effective as in-person delivery, with an additional benefit of reaching people in urban and rural areas with transportation challenges.[93-95] Dr. Hepburn (Co-I) transformed an evidence-based intervention originally delivered face-to-face in-person (Savvy) to be a web-based intervention (Tele-Savvy),[96] now being tested for efficacy at 4 NIA-supported AD Centers (R01 AG054079; Lead PI, Hepburn). Two of the Site PIs (Drs. Morhardt & Shah) are Co-Is on our proposed study. We will leverage the established collaboration between clinicians and scientists across these centers and the infrastructure created for the Tele-Savvy project.

Role of and ethical consideration of a one-time intervention in ACP. Hirschman et al.[97] found that as patients' cognitive impairment progresses to an advanced stage, family members used the 'best interest standard' (decision making based on what a reasonable person would do) more often than 'substituted judgement' (decision making based on what my loved one would have wanted), raising ethical questions about whose preferences are reflected in decisions. Furthermore, the primary reason for using the best interest standard was that there had been no previous discussion about the patient's preferences.[98] This highlights the value of SPIRIT because it allows patients and their families to discuss future wishes and preferences.

SPIRIT can serve as a foundation to help family members navigate the decision-making journey as a patient

progresses to an advanced stage. It can facilitate open discussion about the trajectory of dementia, offer a deeper understanding about the patient's values, goals of care, and possible future treatment choices. It can help family members understand their role in decision making. While there are interventions (e.g., decision aids) targeting surrogates of nursing home residents with advanced dementia[59,101-104] to provide surrogates with decision support at the end of life, most surrogates would still have to formulate treatment decisions without intimate knowledge of the patient's wishes or understanding of their role in substituted decision making. A recent systemic review of interventions for proxy decision making by family members of people with dementia found that no decision aids significantly reduced family members' decision burden.[59]

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

The SPIRIT intervention has proven to be safe and efficacious. The proposed trial involves very minimal or low risk. Patient and surrogate participants may experience an emotional reaction (e.g., anxiety) or fatigue during the intervention or data collection. However, in our previous studies,[17-20] intervention dyads were less apprehensive and more satisfied with the quality of communication than control dyads. It is expected that psychological burden caused by the SPIRIT intervention will be less than or equal to that of usual care.

2.3.2 KNOWN POTENTIAL BENEFITS

Findings from our previous studies indicate benefits of the SPIRIT interventions for participants in the intervention group, including meeting needs to plan for future medical care and sharing values and beliefs. In addition, in our recent study, surrogates in the intervention group perceived the intervention to be highly beneficial during end-of-life decision making for their loved ones and surrogates showed significantly lower post-bereavement distress symptom scores.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

As described above, it is expected that psychological burden caused by the SPIRIT intervention will be less than or equal to that of usual care. Previous studies have demonstrated the potential benefits of SPIRIT.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Aim 1		
Adapt SPIRIT (in person) to target patients with mild AD and their surrogates through a process of modification-pretesting-refinement using stakeholders (patients, family caregivers, and clinicians) and experts, including adapting the delivery mode to interactive web-based videoconferencing (SPIRIT-remote).	No testable endpoints.	We will modify SPIRIT (in person) for people with mild AD and their surrogates and pretest it to assess acceptability.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Aim 2		
In a 2-group RCT with 120 patient-surrogate dyads, evaluate the feasibility and acceptability of SPIRIT-remote and the preliminary efficacy compared to usual care (wait-list control) on preparedness outcomes for end-of-life decision making 2-3 days after the intervention	preparedness for EOL decision making: 1. Dyad congruence 2. Surrogate decision-making confidence (scale) 3. Surrogate preparedness scale	The primary goal of SPIRIT is to prepare the patient and surrogate for end-of-life decision making. The preparedness outcomes will indicate whether or to what extent SPIRIT accomplished the goal.
Exploratory		
Compare patient preparedness and patient and surrogate acceptability post-intervention and the completion of advance directives among the two treatment conditions at 1-year post-intervention	Patient preparedness scale, Patient acceptability and surrogate acceptability at 2-3 post-intervention Completion of an advance directive (binary)	
Using a qualitative method, in a sample of surrogates, explore their perceptions of the impact of SPIRIT at 1-year post-intervention.	No testable endpoints	We will interview a sample of surrogates at 1 year to assess the perceived impact of the intervention conditions.

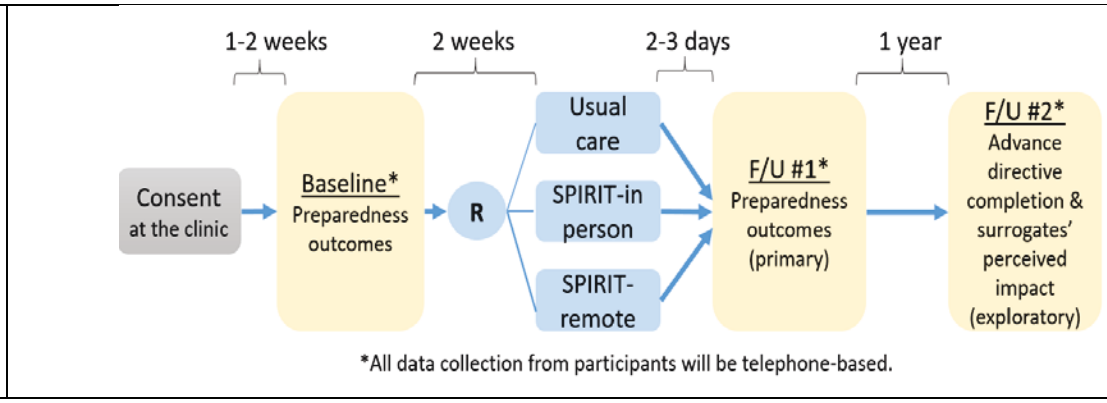
4 STUDY DESIGN

4.1 OVERALL DESIGN

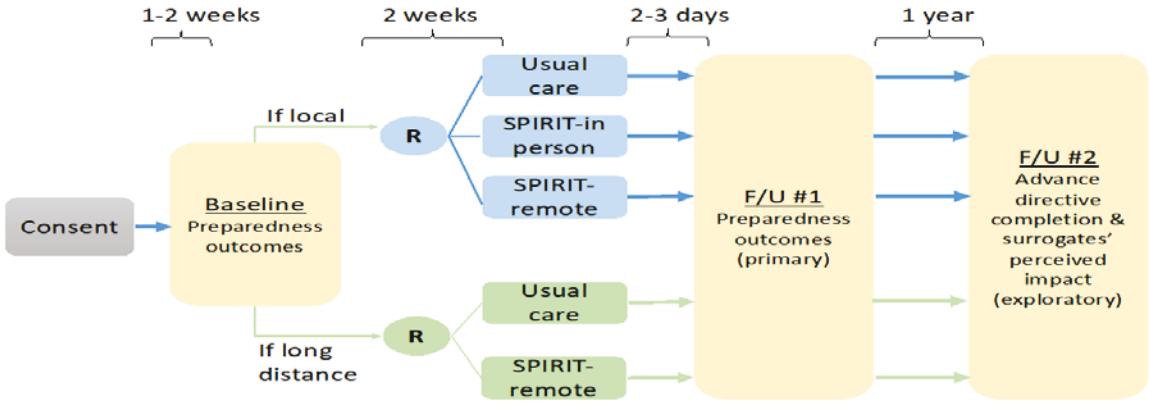
This research is a two-staged project to 1) modify SPIRIT for mild AD, and then 2) formally test its feasibility and efficacy, including a longer-term impact on surrogates, with 120 patient-surrogate dyads (240 individuals).

Design Overview:

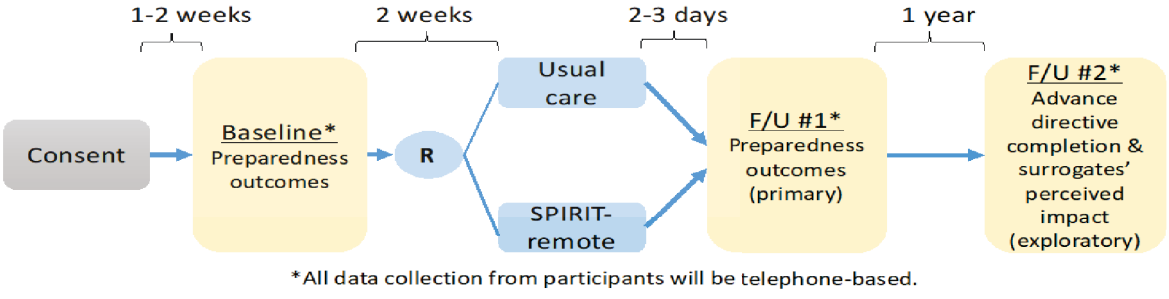
Stage 1A	**SPIRIT adaptation, pretesting, and refinement, completed by Year 2, Quarter 2**
	Initial adaptation of SPIRIT for early dementia by the investigative team
	→Formative review by a panel of clinicians and content experts
	→Analyzing review results and refining SPIRIT
	→Developing SPIRIT-remote (SPIRIT delivered via videoconference)
	→Pretesting of SPIRIT-in person, SPIRIT-remote, and refinement
	→Analyzing patient and surrogate input and final refinement
Stage 1B	**Evaluation of feasibility/acceptability and efficacy, completed during the remaining years**



With revision (V12)



With Revision (V14)



4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

As in our previous studies of SPIRIT, we chose individual randomization because intervention spillover to the control condition is very unlikely. The intervention will be delivered by a trained interventionist, not a care provider, in a private room at the clinic (or another private location for the convenience of the dyad) or via videoconferencing at home (after the COVID-19 outbreak, all SPIRIT sessions will be delivered via videoconferencing), and thus it is nearly impossible for care providers to obtain the knowledge and skill related to SPIRIT to change their ACP practice. Furthermore, once diagnosed with early stage AD, follow-up visits typically occur every six months unless there is a noticeable cognitive decline, and thus it is unlikely that participants in the SPIRIT group could share information with those in the control condition thereby influencing outcomes. In fact, all of our previous studies used individual randomization and successfully demonstrated the efficacy of SPIRIT. We considered a clinic-level cluster RCT in which a care provider delivers SPIRIT, but rejected this option because at Stage I intervention development it is important to determine if the intervention has been modified without compromised potency. In addition, a cluster RCT is too ambitious in the context of pilot testing since it would require many study sites. We chose race (white vs non-white) as a stratification factor to ensure equal allocation of race to each treatment condition to control for race as a confounding variable.[14].

The most challenging aspects of designing this intervention trial are: a) determining an optimal follow-up time point and data collection mode to minimize the potential influence of patients' cognitive impairment on the outcome assessment, and b) maintaining blinding of data collectors. The first follow-up time point (Ideally 2-3 days post intervention however, consideration is given to difficulty of scheduling dyads and extension may result) is to evaluate the impact of SPIRIT on preparedness outcomes while minimizing the potential influence of the patient's impaired ability to recall what was discussed during the SPIRIT session (i.e., the patient needs to recall what he/she clarified as goals-of-care preferences). We considered measuring the outcomes immediately following the intervention, but this would preclude blinding the data collector because of the modality difference. The second follow-up time (12 months post intervention) was chosen to help maximize the number of patients whose conditions progress to an advanced stage within the study period so that we can explore how surrogates experience having or not having an in-depth ACP discussion before the window of opportunity has closed. Although not ideal for people with mild AD, telephone-based data collection was chosen to assure blinding of data collectors and to reduce participants' travel burden. We have used phone-based data collection extensively in our previous studies with seriously ill patients and their surrogates using the procedures described above (see Post-Intervention Assessment).

As in our previous studies, we chose usual care as a comparison condition rather than an attention placebo control. In addition to the fact that there is no methodological standard for attention placebo controls in trials of psychosocial interventions,[116] in the context of preparing for future medical care and end-of-life decision making, an attention placebo (information and discussion irrelevant to the context) would not meet the participants' expectations or motivation to participate in the study, and could cause a high refusal rate, dissatisfaction, and disproportional dropouts.[116] We will offer SPIRIT-remote to control dyads at the completion of the 1 year follow-up if the patient has not progressed to moderate AD. The same protocol was used in our previous efficacy trial with 12-month follow-ups, and a wait-list control did not result in disproportional dropouts (SPIRIT [5.5%] vs usual care [2.0%]).[30]

Revised study design (V12):
In the effort to meet the target sample size, we expand study recruitment activities to 1) Georgia Memory Net sites (Augusta, Macon, Albany, and Columbus) in addition to Atlanta (Grady memory clinic serves as a memory assessment clinic for GA Memory Net), 2) Atlanta Regional Commission (ARC)/a federally designated Area Agency on Aging (AAA) serving older adults in 10 counties (Cherokee, Clayton, Cobb, DeKalb, Douglas, Fayette, Fulton, Gwinnet, Henry, and Rockdale), and 3) Alzheimer's Association's early stage program (e.g., early stage support groups, monthly lunch groups/Carpe Diem, High Museum tour groups, early memory loss support group series) and referrals to GA Memory Net that covers 33 counties.

Revised study design (V14):
Due to the coronavirus pandemic and social distancing recommendations from CDC, it is necessary to eliminate SPIRIT in-person modality to minimize in-person physical contacts with study participants. This makes the study a 2-group (SPIRIT-remote and usual care) RCT.

4.3 JUSTIFICATION FOR INTERVENTION

The SPIRIT intervention is a one-time advanced care planning intervention that has been rigorously tested and has demonstrated its efficacy. The details about the intervention, including the rationale, are described above (2.2 Background).

4.4 END OF STUDY DEFINITION

Because the study includes two phases, the end of the study for participants will be the completion of the one-year follow-up.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Patient eligibility criteria:

a) Mild to moderate dementia based on one of the followings:
    a. a MoCA score ≥ 13, or MMSE score ≥ 18 (If other compatible cognitive tests are used at the clinic, the name of the test and score should be documented clearly);
b) able to understand and speak English; and
c) a UBACC score ≥ 11 or (a score of 9 or 10 with consultation of PI)
   For Stage 1B, a UBACC score ≥ 11.

There will be no age limitation, but nearly all patient participants will be 60 years old or older.

In the case where no medical record is available to determine whether the patient has dementia, the Short Form of the Informant Questionnaire on Cognitive Decline in the Elderly (Short IQCODE) score from the family caregiver interview must be 3.3 or higher. Study staff will also ask caregivers about the comorbid conditions of the person with Dementia.

Surrogate eligibility criteria:

a) 18 years or older (to serve as a surrogate decision-maker, the individual must be an adult);
b) be chosen by the patient;
c) have access to a computer and internet connectivity in a private setting, e.g., either the patient's or the surrogate's home and being able to use email (to receive URL links to a secure videoconferencing software, e.g., Zoom); and
d) able to understand and speak English.

5.2 EXCLUSION CRITERIA

Patient exclusion criteria:

a) lack of an available surrogate
b) speech impairment
c) uncompensated hearing deficits, and

Surrogate exclusion criterion:

a) Those who cannot complete questionnaires due to physical or cognitive limitations will be excluded.

5.3 LIFESTYLE CONSIDERATIONS

Not applicable

5.4 SCREEN FAILURES

The study participation requires both patient and surrogate as a dyad. It is possible that the patient provides written consent to participate in the study first with the assumption that his/her surrogate would be willing to participate (note that patients cannot complete the baseline without willing surrogates), and then the surrogate actually declines to participate.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Recruitment and Consent procedures:
Stage 1A (pre-testing)

Potential patient participants will be those who are currently receiving care from Emory's Brain Health Center located at the Executive Park (2 miles from the School of Nursing). The Brain Health Center encompasses more than 20 clinics which serve a range of neurologic, psychiatric and cognitive conditions. The clinics are staffed by doctors, nurse practitioners, registered nurses, and clinical social workers. Patients who are appropriate for this study may interface with one or more of the clinics to receive services for a diagnosis of dementia.

A study invitation letter signed by the Brain Health Center doctors, nurse practitioners, and PI will be mailed to patients with a recent MoCA score ≥ 13. This letter will explain briefly about the study and include the research staff contact information and an opt-out postcard. After 2 weeks, a research staff member will call potential patient participants who have not returned the opt-out postcard to explain the study further and schedule a brief meeting at the clinic during their upcoming return clinic visit. On the day of the return clinic visit, the research staff will review the patient's medical record to confirm the patient's eligibility (a through c) and approach the patient to obtain verbal consent to administer the UBACC to screen the patient for decision-making capacity. With a patient whose UBACC score is equal to or higher than 11 (or score of 9 or 10 with consultation of PI), the recruiter will determine whether the person accompanying the patient is an appropriate surrogate decision-maker using the Surrogate Selection Guide. Written consent will be obtained from each member of the dyad. Location for consent meeting will typically be an Emory clinic although we will allow for some flexibility in order to meet the demands of patients and surrogates alike.

Stage 1B (formal pilot testing)

Participants will be recruited from: Emory's Brain Health Center, Emory Geriatrics Clinics (Tucker, St. Josephs, and Domiciliary program), Grady's Marcus Stroke and Neuroscience Center, Grady Primary Care, Grady Geriatrics, Assisted Living facilities, Atlanta Adult Day Care facilities, GA Memory Net sites in Augusta, Albany, Macon, and Columbus, Alzheimer's Association early stage program, and Atlanta Regional Commission. Additionally, the current subcontract sites, Rush University and Northwestern University, will assist in recruitment by providing

potential participants who are deemed eligible and have agreed to be contacted by the research personnel at Emory. Patients at the Alzheimer's Disease Research Center at Rush and Northwestern Universities have already provided a blank consent at enrollment for being contacted by researchers.

In addition to the possible recruitment strategy listed under Stage 1A, another strategy for recruitment will be to review the medical records of **patients seen at the above clinics**. Patient medical records will be reviewed to determine eligibility (a through c of inclusion criteria). Study staff will identify patients deemed eligible, and at the patient's next appointment, the patient's care provider will gain permission for the study staff to explain the study. As stated above, study staff will then obtain verbal consent to administer the UBACC to screen the patient for decision-making capacity. With a patient who has met the UBACC criterion, the recruiter will determine whether the person accompanying the patient is an appropriate surrogate decision-maker using the Surrogate Selection Guide. Written consent will be obtained from each member of the dyad. If the surrogate decision-maker is not present at the time of the visit, study staff will offer consent to the patient and then obtain the name and phone number of the surrogate. Study staff will then call the surrogate within 2 days of the consent visit to assess the surrogate's willingness to participate.

We may also periodically receive lists of eligible patients from providers who have introduced the study to the patient at the time of a visit. In that case, we will follow up by phone with the surrogate and arrange a time to offer consent to the dyad at the clinic or over the phone. At the time of return clinic visit, study staff will review medical records to determine eligibility (a through c of inclusion criteria, and d of exclusion criteria). If eligible, study staff will follow the above procedures regarding UBACC screening, confirming the surrogate decision maker, and consenting each member of the dyad.

To recruit participants through Emory's domiciliary program, a study invitation letter signed by the domiciliary program director and PI will be mailed to patients/family caregivers. As done in Stage 1A, this letter will explain briefly about the study and include the research staff contact information and an opt-out postcard. After 2 weeks, a research staff member will review the medical records of domiciliary program patients/families who have not returned the opt-out postcard to screen for eligibility (i.e., dementia diagnosis and MoCA score). If they have met the criteria, the research staff member will call potential patient and/or family caregiver participants to explain the study further and schedule a screening and informed consent meeting at the assisted living facility.

To recruit participants at the assisted living and independent living facilities who are not currently enrolled in the domiciliary program, study staff members may receive recommendations from facility employees. In these cases, study staff will follow the same procedure listed for Emory domiciliary patients (i.e. mailing a letter with an opt- out card and contacting those who do not return the opt out card). We may also receive direct referrals from facility staff who will introduce the study and gain permission from residents and their families to be contacted by a study team member. Study staff members will additionally advertise the study in facility newsletters and/or attend family events at the community to introduce the study to residents and their family members. Study brochures will be made available at these events. Individuals who express interest at these events will be asked to provide contact information. A study staff member will follow up with the interested party and determine eligibility for the study through a screening and informed consent meeting.

To recruit participants from GA Memory Net sites, the Community Services Educator (CSE) at the site will first identify patients who have been diagnosed with dementia and meet the MoCA criterion. When the potentially eligible patient and caregiver make a second visit to the memory assessment center (per GA Memory Net protocol), the CSE will briefly introduce the study to the patient and caregiver (using a script) and ask permission to release their names and contact information (including mailing address) if they are interested in learning more about the study from the research staff. Study brochures will also be made available at the site. Upon the receipt of names and contact information, the research staff will mail a copy of consent form before contacting. A

research staff member will call the dyad to explain the study further, determine the remaining eligibility criteria (e.g., UBACC) and proceed informed consent if eligible.

To recruit participants from Northwestern University and Rush University Alzheimer's Disease Research Center, the co-investigators, Dr. Shah at Rush and Dr. Morhardt at Northwestern, will identify patients who are deemed eligible for the study. Their research staff will phone the potential patient participants (and their family caregivers/potential surrogate participants) to introduce the study and gain permission to share contact information with Emory research staff. Upon receiving referrals, Emory research staff will contact these potential participants by phone or email to determine interest and eligibility, explain the study in detail and obtain verbal consent using Verbal Informed Consent/HIPAA authorization format.

To recruit participants from other recruitment avenues (adult day care programs, Alzheimer's Association early stage program), study staff may send an invitation letter with the program's permission. This invitation letter will follow the same procedures listed for Emory domiciliary patients (i.e. mailing a letter with an opt-out card and contacting those who do not return an opt-out card). Direct referrals may also be received from facility staff members as appropriate. Study staff may additionally coordinate IRB approved study advertisements to be placed in the facility (including newsletters). If appropriate and with permission from the program, study staff will introduce the study at the program's events. Individuals who express interest through these methods will be asked to provide contact information, and study staff members will subsequently follow-up with those individuals. We will also disseminate advertisements through program newsletters (in paper or electronic form).

In the case of Atlanta Regional Commission/AAA), the county case manager, who typically knows the patient's dementia severity and availability of family caregiver, will identify patients/caregivers who are likely to meet the study eligibility criteria. When the case manager is in contact with the caregiver, he/she will briefly introduce the study to the patient and caregiver (using a script) and ask permission to release their names and contact information (including mailing address) if they are interested in learning more about the study from the research staff. Study brochures will also be made available at the site. Upon the receipt of names and contact information, the research staff will mail a copy of consent form before contacting. A research staff member will call the dyad to explain the study further, determine the remaining eligibility criteria (e.g., UBACC) and proceed informed consent if eligible.

Because adult day care programs and other community organizations are social services, they typically may not keep health records. In the cases where a dementia diagnosis cannot be confirmed from reliable sources, study staff will administer screening questions and a valid questionnaire, "Short Form of the Informant Questionnaire on Cognitive Decline in the Elderly (Short IQCODE)"), to the family caregiver to determine whether a patient's cognitive impairment is likely dementia or due to other neurodegenerative condition. The initial screening questions will consist of the following questions:

- Has your loved one been evaluated for memory problems at the doctor's office?
    - If yes, what was the formal diagnosis at that time?
    - Do you have any test results related to the diagnosis?
- Does your loved one take any cognition- enhancing drugs, such as Aricept, Exelon, Reminyl, Namenda, or Provigil?
- Has your loved one had a stroke before this memory problem?

If a caregiver reports their loved one as having dementia based on the screening question and IQCODE (a score 3.3 or higher), study staff will schedule a meeting to determine full eligibility of their loved one and consent.

For all recruitment sites, the location for consent meeting can be flexible to meet the demands of participants.

Retention strategies:
Stage 1A (pre-testing)
Subject participation will last about three weeks. Each member of the dyad will receive a $30 gift card at completion of the post-intervention follow-up (Ideally 2-3 days after the intervention session).

Stage 1B (formal pilot testing)
To Maximize Participant Retention, strategies found effective in retaining dyads over 12 months (dropouts, 3.8%) in our efficacy trial[30] will be used: (a) obtain backup contact information, (b) make confirmation phone calls 2 days prior to each appointment, (c) make scripted monthly check-in calls, (d) send holiday and special occasion cards, (e) assign the same data collector whenever possible, (f) compensate each member of the dyad as a token of appreciation ($20 at baseline, $25 at post-intervention assessment) and surrogates who complete the 1-year follow-up interview ($30 at 12 months); and (g) use a cell phone matched to the participant's wireless network provider whenever possible (so that their minutes do not run out).

6 STUDY INTERVENTION(S)

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

SPIRIT Intervention prior to modification:
In its current form, all sessions of SPIRIT are conducted in a private room in a clinic and follow the structured SPIRIT Interview Guide. The goals of SPIRIT are to assist patients to clarify their end-of-life preferences and to help surrogates understand the patient's wishes and prepare for the surrogate role. Currently SPIRIT has two face-to-face sessions with patient and surrogate together. During the first session (~45 min.), an interventionist assesses the patient's and surrogate's cognitive, emotional, and spiritual/religious representations of the patient's illness, progression, and end-of-life care. This allows the interventionist to provide individualized information about topics, such as the effectiveness of life-sustaining treatment for people with progressive chronic illness (to be adapted for AD), and assist the patient to examine his/her values about life-sustaining treatment at the end of life. The interventionist also helps the surrogate prepare for end-of-life decision-making and for the emotional burden of decision-making by actively involving the surrogate in the discussion. If the surrogate is someone out of the order of the hierarchical compensatory model[105] (e.g., a sibling is chosen instead of a spouse or child), the interventionist explores potential family conflicts and encourages the dyad to talk with other family members and complete a medical power of attorney. A Goals-of-Care tool is completed at the end of the session to indicate the patient's preferences. A brief second session (~15 min.) is conducted about 2 weeks later to address remaining or new concerns and questions raised after the first session. The patient's Goals-of-Care tool is reviewed and assessed for the need for clarification or correction. The interventionist documents the patient's end-of-life preferences and the surrogate's name and relationship to the patient in the medical record.

Planned adaptations of SPIRIT

Modification type	Nature of modification
Format/modality	• Virtual face-to-face via web-based videoconferencing for SPIRIT-remote
Setting	• Home for SPIRIT-remote
Content	• Condensing two sessions to one (combining Steps 5 & 6)

	• Tailoring illness trajectory discussion to AD • Tailoring the likely situations requiring EOL decision making and types of EOL treatment relevant to AD
Delivery process	• Integrating "enhanced consent techniques"
Training & evaluation	• Integrating "enhanced consent techniques" • Adding use of videoconferencing for SPIRIT-remote

Guided by Stirman's framework for adaptations of evidence-based interventions,[106] we have identified modifications that are needed to target patients with mild AD. Drs. Song and Ward will draft the initial content adaptations and integrate the enhanced consent techniques into the SPIRIT Interview Guide and will work iteratively with Drs. Hepburn, Morhardt, and Shah to complete the initial modifications. The Treatment Fidelity Assessment Tool[107] will also be modified accordingly.

SPIRIT-remote. We will adapt SPIRIT to a videoconference format so that patients and surrogates can receive the intervention in their home. We anticipate SPIRIT delivery via videoconferencing will require minimal training of the interventionist and instructions for participants. The equipment needed for videoconferencing includes a computer, a webcam, a headset, a microphone (if not already built in the computer), and the Internet. We will use Zoom®, a videoconferencing platform supported in Window, Mac, Linux, and other virtual desktop environments. Zoom also includes a recording module that is consistent with HIPAA security requirements. A videoconferencing workstation will be set up in a private room in the School of Nursing, where the interventionist will conduct sessions.

If a dyad is assigned to the SPIRIT-remote group, a research assistant trained to handle technical aspects of Zoom will schedule a phone call to take the surrogate through the steps of using email to follow URL links that open Zoom. He/she will also guide the surrogate through practice in using basic videoconference operations, e.g., accepting an incoming conference invitation, viewing shared documents, muting/unmuting the microphone or camera, and ending the call. For dyads with a computer without video capabilities, a loaner web cam (and headset and microphone as needed) will be shipped as soon as the group assignment is known. This research assistant will initiate the Zoom call for SPIRIT-remote sessions and silently observe sessions to troubleshoot difficulties the dyad or interventionist might encounter. These procedures have been used effectively in the Tele-Savvy pilot and current R01 project. The interventionist will confirm a follow-up call for outcome assessment to occur in the next 2-3 days ideally.

Usual Care at the Emory ADC. At the time of the diagnosis of a dementing illness, an advanced practice nurse provides written information on advance directives to a patient and his/her family caregiver and reviews this information and encourages them to complete an advanced directive. This typically takes about 10 minutes. Patients and their family members may be referred to attorneys who can assist them in completing an advance directive. If completed, the presence of an advanced directive is documented in the electronic medical record and a copy of the advance directive is scanned to the electronic chart. Patients and families may be referred to a support group program organized by a social worker in which legal and financial issues are discussed in a group setting (by a lawyer). We will review the patient's medical records at the clinic at baseline and quarterly to track activities associated with usual care. To capture any changes in usual care, policy and procedures related to ACP at the clinic will be reviewed every 6 months by a research assistant.

Usual Care in Emory Geriatrics, Grady's Marcus Stroke and Neuroscience Center, Grady Geriatrics and Grady Primary Care. At the time of this writing, there are no standardized procedures in place to address the need for advance care planning. Some care providers may encourage patients and/or family caregivers to complete an advanced directive and provide written information during the patient's clinic visit.

Usual care at Georgia Memory Net by community services educator (CSE). During the second visit of a patient and caregiver at the memory assessment clinic, the CSE asks if the patient has an advance directive, provide written information about advance directives if the patient does not have one, and encourage the patient and caregiver to complete one. This procedure is standardized across the GA Memory Net sites.

Usual care at Rush University's Memory Clinic. Inquiry of completion of legal forms including a living will, POA health care and POA property is done. If incomplete, patients are provided with the forms and may be encouraged to complete before competency comes into question. DNR discussions are typically happening through the PCP, not in our clinic. If someone is truly advanced or at end-stage dementia, discussions about end of life may occur. If a patient or family has more questions, Rush often refers to a social worker for further discussion. A management plan is provided and completion of legal forms is recommended as a part of the management plan.

Usual care at Northwestern University's Memory Clinic.

As applicable (i.e., patients recruited from a clinical care setting), we will review the patient's medical records at the clinic at baseline and quarterly to track activities associated with usual care. For patients without accessible medical records (such as patients receiving care outside of Emory or Grady health systems), study staff will collect medical history from the surrogate decision maker about the patient with dementia. To capture any changes in usual care, policy and procedures related to ACP at the clinic will be reviewed every 6 months by a research assistant.

6.1.2 DOSING AND ADMINISTRATION

Described above (6.1.1).

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

For Stage 1B pilot testing, Dr. Paul (statistician/Co-I) will generate a randomization scheme using stratified (by race, white vs non-white study site, Emory vs Grady), permuted block randomization with block size 6, using a random-number generator. Dyads will be randomized with equal allocation (1:1:1) to SPIRIT-in person, SPIRIT-remote, or usual care.

With Revision 14, randomization will be stratified by race (white vs non-white) within recruitment site (Emory, Rush, and Northwestern), with equal allocation to SPIRIT-in person or usual care.

Due to the nature of the intervention, blinding dyads to their group allocation is impossible, but the research staff assessing outcomes will be blind. Immediately after the completion of the baseline assessment by phone, the data collector will open a sealed envelope to identify group assignment and schedule an intervention session to take place ~2 weeks hence for SPIRIT- in person or –remote (with revision 14, all SPIRIT-remote), as well as a follow-up data collection session in the next 2-3 days.

6.3.1 INTERVENTIONIST TRAINING AND ACCOUNTABILITY

Two interventionists will deliver both SPIRIT modalities. Interventionist minimal qualification is having at least 2 years of clinical experience in caring for people with AD as a nurse (RN or APRN) or social worker. Interventionist training (led by Drs. Song and Hepburn) will consist of a 3½-day competency-based program used in our previous trials using training manuals. Module 1 (1 day) focuses on understanding AD and end-of-life care issues, communication as key to improving end-of-life care, and the Representational Approach (theoretical underpinnings of SPIRIT); Module 2 (1 day) is a skill-based session on delivery of the SPIRIT intervention (e.g., communication behaviors and enhanced consent techniques), including role plays; Module 3 (1/2 day) focuses on videoconferencing procedures and etiquette, features of Zoom, and handling technical problems (adapted from the Tele-Savvy Training manual). A 2-week practice period is then scheduled for integration of skills. Module 4 (1 day) involves skill-demonstration and certification.

6.3.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Not applicable.

6.3.3 PRODUCT STORAGE AND STABILITY

Not applicable.

6.3.4 PREPARATION

Not applicable.

6.4 STUDY INTERVENTION COMPLIANCE

To promote consistency and quality of intervention delivery, the SPIRIT Interview Guide will be used during each session. To monitor fidelity, we will use two data sources. 1) The SPIRIT Interview Guide will direct the interventionist to document performance data after each patient-surrogate dyad encounter; these data will be entered into the Research Electronic Data Capture [REDCap] by the project director. The Guide has a checklist of SPIRIT components, including start and finish times, and brief self-evaluation. 2) As in our previous studies, all intervention sessions will be audio-recorded. Every 2 months, 50% of sessions randomly selected from SPIRIT-remote will be reviewed by the PI (approximately 2 sessions from each group). Using the modified Treatment Fidelity Assessment Tool, the interventionist's adherence to intervention content, process, and duration will be evaluated on a 3-point scale (1=appropriate, 3=skipped). Problems detected including drift from protocol will be discussed with the interventionist and re-training will be provided if adherence is <80% based on the Fidelity Assessment Tool.

6.5 CONCOMITANT THERAPY

Not applicable (all patients receive usual care related to advance care planning). Patient participants will receive usual care only or usual care plus an intervention condition.

6.5.1 RESCUE MEDICINE

Not applicable.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

SPIRIT is a one-time intervention. Any incomplete intervention will be tracked along with the reason.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant from the study for the following reasons:

- If the participant meets an exclusion criterion that precludes further study participation.

The reason for participant discontinuation or withdrawal from the study will be recorded on the study REDCap. Subjects from the clinic randomized to initial SPIRIT who sign the informed consent form but do not receive the study intervention may be replaced. Subjects in the initial SPIRIT who sign the informed consent form and receive the study intervention, and subsequently withdraw from the study will not be replaced.

7.3 LOST TO FOLLOW-UP

A patient or surrogate participant will be considered lost to follow-up if he or she fails to complete the scheduled post-intervention follow-up (for studies in both Stages) and is unable to be contacted by the study site staff until the end of the 12-month follow-up period (for Stage 1B study). Or, a surrogate participant who has been selected for a semi-structured interview will be considered lost to follow-up if he or she fails to complete the scheduled 12-month follow-up and is unable to be contacted by the study site staff.

The following actions must be taken if a participant is determined to be lost to follow-up:

- The research staff will attempt to contact the participant and reschedule the missed appointment for 4 weeks and ascertain if the participant wishes to continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's record in REDCap.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 OUTCOME ASSESSMENTS

In Stage 1A,

Feasibility of recruiting and retaining patients with mild AD and surrogates for SPIRIT-in person and SPIRIT-remote will be assessed by tracking the numbers of dyads who are eligible and who agree to participate, and the reasons for refusal and withdrawals. Feasibility of conducting SPIRIT-in person and SPIRIT-remote will be assessed by tracking the number of dyads who complete their session, the number of incomplete or interrupted sessions, and

the minutes required to complete SPIRIT-in person and SPIRIT-remote. We will also explore whether these variables are associated with patients' MoCA or MMSE scores.

Acceptability. After the outcome assessment, the research assistant will conduct a brief semi-structured interview (10-15 minutes) with each member of the dyad to ask about: the overall experience with SPIRIT; any facets of the intervention that the participant found helpful/not helpful and the reasons; pacing, length, and modality; and suggestions for improvement. This interview will be audio-recorded and transcribed for analysis.

Outcomes

Preparedness for end-of-life decision making (measured at baseline and 2-3 days after the intervention or randomization) Note flexibility may be necessary due to challenges of the population and demands of scheduling both patients and surrogates:

- **Dyad congruence** will be assessed using the Goals-of-Care Tool,[28,30] which has been modified to include two scenarios relevant to the context of AD. In the first, the patient has progressed to advanced dementia and develops a severe infection and is admitted to a hospital; the medical team believes recovery unlikely and continuing life-sustaining treatment would no longer be beneficial. There are three response options: "The goals of care should focus on delaying my death no matter what, and thus I want to continue life-sustaining treatment", "The goals of care should focus on my comfort and peace, and thus I do not want life-sustaining treatment", and "I am not sure". In the second scenario, the patient has progressed to advanced dementia and develops a severe infection. The nursing home staff is asking whether the patient should be taken to an ED, which will lead to hospitalization with life-sustaining treatments. Patients and surrogates complete this tool independently and their responses are then compared to determine dyad congruence -- either congruent in both scenarios or incongruent. If both members of the dyad endorse "I am not sure", they are considered incongruent.
- **Patient decisional conflict** will be measured using the 13-item Decisional Conflict Scale (DCS), a validated measure in the context of end-of-life decision making[27]; higher scores indicate greater difficulty in weighing benefits and burdens of life-sustaining treatments and decision making (range 1-5; Cronbach's α = 0.8 – .93[27,28,30,121]).
- **Surrogate decision-making confidence** will be measured using the 5-item Decision Making Confidence (DMC) scale (Cronbach's α = 0.81-0.90[28,58]); higher scores reflect greater comfort in performing as a surrogate (0="not confident at all" to 4="very confident"). DMC assesses a surrogate's confidence in: knowing the patient's wishes, ability to make treatment decisions even in a highly stressful situation, ability to seek information about risks and benefits of medical choices, ability to handle unwanted pressure from others, and ability to communicate with providers about the patient's wishes.
- We will also assess **the overall preparedness for end-of-life decision making** using the 26-item investigator-developed measure. The measure assesses the level of preparedness for end-of-life decision making in the cognitive, emotional, and behavioral dimensions on a 4-point scale (4=strongly agree to 1=strongly disagree) with higher scores indicating higher levels of preparedness. Patient and surrogate each will complete this measure separately.

In Stage 1B,

Acceptability. Patient and surrogate acceptability will be assessed using the 10-item ACP Acceptability Questionnaire developed from our previous trial.[24] Participants are asked how strongly they agree or disagree (4 to 1) with statements about their experience with SPIRIT sessions, including duration, interactions with the interventionist, level of comfort and satisfaction. Higher scores indicate greater acceptability. Each patient and surrogate will complete this survey following the preparedness outcome measures after the intervention.

Preparedness for end-of-life decision making (measured at baseline and ideally 2-3 days after the intervention or randomization):

- **Dyad congruence** will be assessed using the Goals-of-Care Tool,[28,30] which has been modified to include two scenarios relevant to the context of AD. In the first, the patient has progressed to advanced dementia and develops a severe infection and is admitted to a hospital; the medical team believes recovery unlikely and continuing life-sustaining treatment would no longer be beneficial. There are three response options: "The goals of care should focus on delaying my death no matter what, and thus I want to continue life-sustaining treatment", "The goals of care should focus on my comfort and peace, and thus I do not want life-sustaining treatment", and "I am not sure". In the second scenario, the patient has progressed to advanced dementia and develops a severe infection. The nursing home staff is asking whether the patient should be taken to an ED, which will lead to hospitalization with life-sustaining treatments. Patients and surrogates complete this tool independently and their responses are then compared to determine dyad congruence -- either congruent in both scenarios or incongruent. If both members of the dyad endorse "I am not sure", they are considered incongruent.
- **Surrogate decision-making confidence** will be measured using the 5-item Decision Making Confidence (DMC) scale (Cronbach's α = 0.81-0.90[28,58]); higher scores reflect greater comfort in performing as a surrogate (0="not confident at all" to 4="very confident"). DMC assesses a surrogate's confidence in: knowing the patient's wishes, ability to make treatment decisions even in a highly stressful situation, ability to seek information about risks and benefits of medical choices, ability to handle unwanted pressure from others, and ability to communicate with providers about the patient's wishes.
- We will also assess **the overall preparedness for end-of-life decision making** using the investigator-developed measure. The measure assesses the level of preparedness for end-of-life decision making in the cognitive, emotional, and behavioral dimensions on a 4-point scale (4=strongly agree to 1=strongly disagree) with higher scores indicating higher levels of preparedness. Patient and surrogate each will complete this measure separately.

Completion of Advance Directives (at 12 months). A research assistant will review the patient's medical record to determine if the patient has completed an advance directive (a medical power of attorney or living will) by 12 months. If there is no documentation, the research assistant will call the surrogate to confirm.

Surrogates' Perceived Impact of SPIRIT (intervention group only). At 12 months, 44-46 surrogates will participate in a semi-structured interview by phone: approximately 26 surrogates of patients who have progressed to an advanced stage (CDR score > 1; 22% progression rate[33,113-115]) and 20% randomly selected surrogates of patients who have not progressed (~18-20 surrogates). A research assistant will review medical records to identify if a patient's dementia has progressed. A trained interviewer/research assistant will conduct the interview using the Perceived Impact Interview Guide, which includes questions about surrogates' experiences with the treatment condition, the perceived impact of the treatment condition on their loved ones and themselves, and what they found most and least helpful and why. This 15-30 minute interview will be audio-recorded and transcribed.

Descriptors and Potential Covariates (collected at baseline). Patients and surrogates will each complete a Sociodemographic Profile which includes demographic information and previous end-of-life decision-making experience. Patients' clinical characteristics, (date of dementia diagnosis, CDR score, MoCA or MMSE scores, and comorbid conditions) will be abstracted from the patient's medical records. For patients whom we do not have access to their medical records, study staff will gather a patient's clinical characteristics from the surrogate. The Medical Profile at Enrollment and the Quarterly Medical Record Review will both require surrogate report when medical records are unavailable.

8.2 SAFETY AND OTHER ASSESSMENTS

SPIRIT is a one-time psychoeducational intervention. The proposed trial involves very minimal or low risk. Patient and surrogate participants may experience an emotional reaction (e.g., anxiety). However, in our previous studies,[17-20] intervention dyads were less apprehensive and more satisfied with the quality of communication than control dyads. It is expected that psychological burden caused by the SPIRIT intervention will be less than or equal to that of usual care.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

SPIRIT is a one-time psychoeducational intervention. The study involves very low risk and the potential risk may include emotional upset during the session, which is not a "medical occurrence". SPIRIT has been extensively tested in previous trials and no safety concerns have ever arisen.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

SPIRIT is an advance care planning intervention to prepare these patients and their surrogates for end-of-life decision making. SPIRIT's safety and beneficial effects (e.g., reducing psychological distress) have been consistently demonstrated. Participants' deaths or hospitalizations, if any, during the trial will occur as part of the illness course and will extremely unlikely be related to the intervention or any study related procedures. However, any participant's death will be reported to IRB through annual progress report and included in the NIH annual progress report.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

Not applicable.

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

Not applicable.

8.3.3.3 EXPECTEDNESS

There are no known expected adverse reactions. SPIRIT has been tested in 5 RCTs with various patient populations with serious chronic conditions and in different U.S. regions and settings. Although possible adverse reactions to the intervention may include emotional distress during the intervention session, no such reactions have been observed in the previous studies. Thus, these reactions are very unlikely to occur. However, intervention sessions will stop if the participant appears to be emotionally distressed, and a break or rescheduling will be offered.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

Not applicable.

8.3.5 ADVERSE EVENT REPORTING

The possible adverse reactions, such as emotional distress during the intervention session, if ever occurs, will be tracked (documented in the study REDCap) and the aggregated numbers will be reported at the upcoming biannual DSMC meeting.

Between the post-intervention (or post-randomization for the usual care group) follow-up and the 12-month follow-up with selected surrogates, there will be no study procedures that are required for participants other than our monthly check-in calls and there will be no data collection involved. Thus, the study team will have no way of knowing if there are any disease-related events (DREs) in the study population. **However, any participant's death, if known, will be reported to IRB through annual progress report and included in the NIH annual progress report.**

8.3.6 SERIOUS ADVERSE EVENT REPORTING

Not applicable.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Not applicable.

8.3.8 EVENTS OF SPECIAL INTEREST

Not applicable.

8.3.9 REPORTING OF PREGNANCY

Not applicable.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

Unanticipated problems are defined by DHHS 45 CFR part 46 as 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 (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved 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.

It will be extremely unlikely in this study that the events of fatigue or emotional distress would meet the all of the criteria above.

8.4.2 UNANTICIPATED PROBLEM REPORTING

If we encounter any adverse event that meets the definition above and that is related to the intervention, the PI will notify the Emory IRB and NINR Program Official and the DSMC within 24 hours of the event being reported to the PI. The expedited report will be followed by a detailed, written SAE report as soon as possible.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Not applicable.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

In Stage 1A, SPIRIT will be tested with the first 10 dyads. Based on the inputs from the first 10 dyads, SPIRIT will be modified and then tested with another 10 dyads. The purpose of this pretesting is to adapt SPIRIT for the target population and test the study procedures. Therefore, there will be no hypotheses to be tested.

In Stage 1B,

- Primary Endpoint(s):
  1) The number of intervention dyads who are congruent on goals of care at post-intervention will be significantly higher than that of control dyads.
  2) Surrogate decision making confidence (DMC) in the intervention group at post intervention will be significantly higher than those of control dyads.
  3) Surrogate preparedness scores in the intervention group at post intervention will be significantly higher than those of control surrogates.

9.2 SAMPLE SIZE DETERMINATION

Our sample size of 40 dyads per group in Stage 1B can detect preliminary efficacy of SPIRIT-in person or SPIRIT-remote (compared to usual care) on two preparedness outcomes based on effect sizes of the SPIRIT intervention in our previous studies.[27-30,32] For dyad congruence, we observed large effect sizes (*OR*=4.4-8.7) at 1 or 2 weeks post intervention,[28,32] which would require only 10-20 dyads/group to achieve over 80% power. For surrogate DMC, a sizable treatment effect was observed at 2 months post intervention,[30] but at short-term (2 weeks), the effect size was negligible (Cohen's *d*=.02).[32] Therefore we plan to carefully investigate trends and obtain an estimate of the effect size for the AD population instead of solely focusing on hypothesis testing.

Revised sample size calculations (with V12): Due to changes in the study design, we revised our sample size calculation. In particular, the new study design will use 2 parallel RCTs: (1) A 3-arm (SPIRIT-in person, SPIRIT-remote and usual care) RCT for dyads residing in Atlanta and vicinities (within ~40 miles from Emory), and (2) a 2-arm (SPIRIT-remote and usual care) RCT if the dyad resides in an area outside of the perimeter. Effect sizes estimates, corresponding to the preparedness outcomes from PI's previous studies, formed the basis for power calculation.[27-30,32] For dyad congruence, we previously observed large effect sizes (*OR*=4.4-8.7) at 1 or 2 weeks

post intervention,[28,32] which would require only 10-20 dyads/group to achieve over 80% power. For surrogate DMC, a sizable treatment effect was observed at 2 months post intervention,[30] but at short-term (2 weeks), the effect size was negligible (Cohen's *d*=.02).[32]

Based on the updated design, we are targeting n=48 dyads for the 3-arm RCT and n=72 dyads for the 2-arm RCT to meet our overall target of N=120 dyads. While we are still adequately powered to detect differences in dyad congruence in the standalone RCTs; However, for the surrogate DMC outcome, our goal will be to estimate the population parameters or effect sizes and investigate trends. In addition, effect sizes from both RCTs will be pooled, whenever appropriate, to improve power.

Revised sample size calculation with V14: In light of the changes in study design, we revised our sample size calculation. Moving forward, the new study design will only use a 2-arm (SPIRIT-remote and usual care) RCT for all dyads included in the study based on 3 sites, both within and outside Georgia. Effect sizes estimates, corresponding to the preparedness outcomes from the previous studies, formed the basis for power calculation.[27-30,32] For dyad congruence, we previously observed large effect sizes (*OR*=4.4-8.7) at 1 or 2 weeks post intervention[28,32]. We found that a total sample size of 72 obtained by sampling subjects from 3 sites with an average of 12 dyads per group (24 total from each site) will achieve adequate (>80%) power to detect the smallest effect size (odds ratio of 4.3). Because the effect size was negligible for surrogate DMC (Cohen's *d*=.02).[32], our goal will be to establish the population parameters. Considering attrition, the target sample size of 120 dyads will achieve sufficient power.

9.3 POPULATIONS FOR ANALYSES

Patient-surrogate dyads will be the primary unit of analysis; all analyses will be intent to treat with all available data from all participants.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Analyses will be intent to treat with all available data from all participants. Preliminary analyses will include summarizing variables with descriptive statistics and graphical displays or frequency tables. Distributional assumptions will be assessed and the data transformed as necessary. Baseline characteristics will be examined to explore possible between-group differences using analysis of variance and chi-square tests as appropriate. We will investigate missing data with pattern analysis for data missing at random or missing not at random, and use maximum likelihood or multiple imputation appropriate for each type to impute missing values. We will conduct sensitivity analyses to encompass different scenarios of assumptions and evaluate consistency or discrepancy among them.

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

SPIRIT effects on the preparedness outcomes: For dyad congruence, a binary outcome (congruent or not congruent), a generalized mixed effects logistic regression model will be used. Specifically, a random intercept model will be used to account for dyad level variation over time while treatment group, time (baseline and post-intervention), and treatment x time interaction will treated as fixed effects. If there is a significant treatment x time interaction ($\alpha<0.05$) (an overall treatment effect), then two contrasts will be tested for individual treatment effectiveness (usual care vs SPIRIT-in person and usual care vs SPIRIT-remote). Adjustments for multiple pairwise comparisons will be made using Tukey's test. Surrogate DMC and preparedness scores, we will use linear mixed

effects regression models, adjusting for potential covariates as appropriate. Since this is not a non-inferiority trial where two or more interventions that have been proven to be superior to usual care are being compared, the contrast, SPIRIT-in person vs SPIRIT-remote, cannot be tested. However, if superiority of the two modalities to usual care is determined, the estimated group differences could be used for selecting a non-inferiority margin or equivalence range[124,125] for future studies.

In light of the changes in study design (V12), we will update the statistical analysis plan. In particular, the preparedness outcomes from the 2-arm and 3-arm RCTs will be analyzed individually to evaluate the effect of the interventions. We will use mixed effects models as mentioned above and use contrasts to compare between the three and two intervention groups respectively. In addition to separate analyses, we will conduct pooled analysis by using analysis of variance methods (ANOVA) and incorporating an indicator variable for study and evaluate the (study x intervention group) interaction effect. We will also explore a meta-analysis approach to obtain a common intervention effect of SPIRIT-remote vs usual-care, from the two studies. If the effect sizes obtained from the individual studies are relatively homogeneous, their individual results may be combined to produce an estimate of the intervention effect. A weighted pooled estimate of effect size can be obtained, using the inverse of each study's variance as the weight. Because the studies are almost identical, we anticipate the variance to be fairly similar in both cases; a fixed effects approach will be used to estimate the variance.

With revision V14: The revised statistical analysis plan will be similar to that described in V12. Our primary aim will be to evaluate the effect of the SPIRIT- remote intervention group versus usual care on the outcomes of interest. We will use generalized linear mixed effect modeling and compare changes in treatment group means or proportions over time using contrasts. Because we only have 3 clusters (sites), fitting a multilevel model would not be feasible. We will instead adjust for site as a fixed effect in our mixed effects model. We will also compare our findings to those from Stage 1A to assess any substantial difference in effect sizes.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

SPIRIT effect on advance directive completion (secondary aim): This analysis will be limited to patients who did not have an advance directive at the time of enrollment. For this binary outcome (completed or not completed) measured post intervention, the probability of completion will be estimated for the three groups using logistic regression. Baseline characteristics that differ across groups will be adjusted. Adjusted group mean proportions of completion will be compared between the groups; adjustments for multiple comparisons will be made using Tukey's test.

Surrogates' perceived impact (secondary aim): As in our previous work,[126] qualitative analysis will use content and thematic techniques.[127] Initial coding involves line by line examination, labeling, and organizing of data into segments, preserving detail in participants' words.[128] To optimize validity, codes and definitions will be reviewed and refined by the research team and applied to subsequent interviews.[129] Related codes will be grouped into categories representing aspects of the surrogates' experiences. Similarities, differences, and trends across cases will be examined.[130] Then, data will be organized into themes. This work will be done by Drs. Song and Morhardt and the project director; discrepancies will be resolved by consensus. To explore differences in themes by AD progression and by treatment condition, we will count the occurrence of themes ("quantitizing")[131,132]; the occurrence of each theme will be counted only once for a participant even if it is mentioned more than once. The data will be graphed to facilitate pattern interpretation.[133]

9.4.4 SAFETY ANALYSES

Not applicable.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

See 9.4.1 General Approach.

9.4.6 PLANNED INTERIM ANALYSES

Not applicable.

9.4.7 SUB-GROUP ANALYSES

In order to evaluate whether the SPIRIT has differential effects according to demographic factors such as age, sex, race/ethnicity we consider the same generalized mixed effects model, mentioned in Section 9.4.1. However, because of the small sample size, our sub-group analyses will be only exploratory. We will fit the same generalized mixed model by additionally including a subject level factor (e.g., race) and its' interaction with the SPIRIT. We will report p-values and importantly, standard errors and confidence intervals by recognizing the fact that we do not have power to detect significant interaction effects for examining all demographic factor combinations.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will be listed by measure and time point.

9.4.9 EXPLORATORY ANALYSES

None.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. Prior to going through the informed consent process with a potential participant, a study team member must receive permission to approach the potential participant. This permission may occur as a verbal consent given to a third party (e.g. medical provider or facility staff member) or as a refrain from returning a pre-paid opt-out post card (after receiving an introductory letter). Study staff will then approach potential participants who have consented to being approached (either in person at the clinic or via telephone). Potential participants who agree to be approached by a study staff member will receive the opportunity to screen and consent to the study (if eligible). Once potential participants have demonstrated that they meet all eligibility criteria through the screening process, they may enroll in the study. The following consent materials are submitted with this protocol.

- Patient Consent Form Phase I (Stage 1A)
- Surrogate Consent Form Phase I (Stage 1A)

- Surrogate Verbal Consent Form Phase I (Stage 1A)
- Patient Consent Form Phase II (Stage 1B)
- Surrogate Consent Form Phase II (Stage 1B)
- Verbal Screening Consent & HIPAA
- Surrogate Verbal Consent Form Phase II (Stage 1B)
- Patient Verbal Consent Form Phase II (Stage 1B)

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Stage 1A (pre-testing)
Potential patient participants will be those who are currently receiving care from Emory's Brain Health Center located at the Executive Park (2 miles from the School of Nursing). The Brain Health Center encompasses more than 20 clinics which serve a range of neurologic, psychiatric and cognitive conditions. The clinics are staffed by doctors, nurse practitioners, registered nurses, and clinical social workers. Patients who are appropriate for this study may interface with one or more of the clinics to receive services for a diagnosis of dementia.

Study invitation letters signed by Brain Health Center doctors, nurse practitioners, and PI will be mailed to patients with a recent MoCA score ≥ 13. This letter will explain briefly about the study and include the research staff contact information and an opt-out postcard. After 2 weeks, a research staff member will call potential patient participants who have not returned the opt-out postcard to explain the study further and schedule a brief meeting at the clinic or a convenient location for the dyad. On the day of the meeting, the research staff will review the patient's medical record to confirm the patient's eligibility (a through c) and approach the patient to obtain verbal consent to administer the UBACC to screen the patient for decision-making capacity. With a patient whose UBACC score is equal to or higher than 11 (or 9 or 10 with consultation of PI), the recruiter will determine whether the person accompanying the patient is an appropriate surrogate decision-maker using the Surrogate Selection Guide. Written or verbal consent will be obtained from each member of the dyad.

Stage 1B (formal pilot testing)
Participants will be recruited from: Emory's Brain Health Center, Emory Geriatrics Clinics (Tucker, St. Josephs, and Domiciliary program), Grady's Marcus Stroke and Neuroscience Center, Grady Primary Care, Grady Geriatrics, Assisted Living facilities, Atlanta Adult Day Care facilities, GA Memory Net sites in Augusta, Albany, Macon, and Columbus, Alzheimer's Association early stage program, Atlanta Regional Commission, Northwestern University and Rush University.

In addition to the possible recruitment strategy listed under Stage 1A, another strategy for recruitment will be to review the medical records of **patients seen at the above clinics**. Patient medical records will be reviewed to determine eligibility (a through c of inclusion criteria). Study staff will identify patients deemed eligible, and at the patient's next appointment, the patient's care provider will gain permission for the study staff to explain the study. As stated above, study staff will then obtain verbal consent to administer the UBACC to screen the patient for decision-making capacity. With a patient who has met the UBACC criterion, the recruiter will determine whether the person accompanying the patient is an appropriate surrogate decision-maker using the Surrogate Selection Guide. Written consent will be obtained from each member of the dyad. If the surrogate decision-maker is not present at the time of the visit, study staff will offer consent to the patient and then obtain the name and phone number of the surrogate. Study staff will then call the surrogate within 2 days of the consent visit to assess the surrogate's willingness to participate.

We may also periodically receive lists of eligible patients from providers who have introduced the study to the patient at the time of a visit. In that case, we will follow up by phone with the surrogate and arrange a time to

offer consent to the dyad at the clinic or over the phone. At the time of return clinic visit, study staff will review medical records to determine eligibility (a through c of inclusion criteria, and d of exclusion criteria). If this is not possible due to SARS-COV2, eligibility will be determined using screening methods over the phone. If eligible, study staff will follow the above procedures regarding UBACC screening, confirming the surrogate decision maker, and consenting each member of the dyad.

To recruit participants through Emory's domiciliary program, a study invitation letter signed by the domiciliary program director and PI will be mailed to patients/family caregivers. As done in Stage 1A, this letter will explain briefly about the study and include the research staff contact information and an opt-out postcard. After 2 weeks, a research staff member will review the medical records of domiciliary program patients/families who have not returned the opt-out postcard to screen for eligibility (i.e., dementia diagnosis and MoCA score). If they have met the criteria, the research staff member will call potential patient and/or family caregiver participants to explain the study further and schedule a screening and informed consent meeting at the assisted living facility.

To recruit participants at the assisted living and independent living facilities who are not currently enrolled in the domiciliary program, study staff members may receive recommendations from facility employees. In these cases, study staff will follow the same procedure listed for Emory domiciliary patients (i.e. mailing a letter with an opt- out card and contacting those who do not return the opt out card). We may also receive direct referrals from facility staff who will introduce the study and gain permission from residents and their families to be contacted by a study team member. Study staff members will additionally advertise the study in facility newsletters and/or attend family events at the community to introduce the study to residents and their family members. Study brochures will be made available at these events. Individuals who express interest at these events will be asked to provide contact information. A study staff member will follow up with the interested party and determine eligibility for the study through a screening and informed consent meeting.

To recruit participants from GA Memory Net sites, the Community Services Educator (CSE) at the site will first identify patients who have been diagnosed with dementia and meet the MoCA criterion. When the potentially eligible patient and caregiver make a second visit to the memory assessment center (per GA Memory Net protocol), the CSE will briefly introduce the study to the patient and caregiver (using a script) and ask permission to release their names and contact information (including mailing address) if they are interested in learning more about the study from the research staff. Study brochures will also be made available at the site. Upon the receipt of names and contact information, the research staff will mail a copy of consent form before contacting. A research staff member will call the dyad to explain the study further, determine the remaining eligibility criteria (e.g., UBACC) and proceed informed consent if eligible.

To recruit participants from other recruitment avenues (adult day care programs, Alzheimer's Association early stage program), study staff may send an invitation letter with the program's permission. This invitation letter will follow the same procedures listed for Emory domiciliary patients (i.e. mailing a letter with an opt-out card and contacting those who do not return an opt-out card). Direct referrals may also be received from facility staff members as appropriate. Study staff may additionally coordinate IRB approved study advertisements to be placed in the facility (including newsletters). If appropriate and with permission from the program, study staff will introduce the study at the program's events. Individuals who express interest through these methods will be asked to provide contact information, and study staff members will subsequently follow-up with those individuals. We will also disseminate advertisements through program newsletters (in paper or electronic form).

In the case of Atlanta Regional Commission/AAA), the county case manager, who typically knows the patient's dementia severity and availability of family caregiver, will identify patients/caregivers who are likely to meet the study eligibility criteria. When the case manager is in contact with the caregiver, he/she will briefly introduce the study to the patient and caregiver (using a script) and ask permission to release their names and contact

information (including mailing address) if they are interested in learning more about the study from the research staff. Study brochures will also be made available at the site. Upon the receipt of names and contact information, the research staff will mail a copy of consent form before contacting. A research staff member will call the dyad to explain the study further, determine the remaining eligibility criteria (e.g., UBACC) and proceed informed consent if eligible.

Because adult day care programs and other community organizations are social services, they typically may not keep health records. In the cases where a dementia diagnosis cannot be confirmed from reliable sources, study staff will administer screening questions and a valid questionnaire, "Short Form of the Informant Questionnaire on Cognitive Decline in the Elderly (Short IQCODE)"), to the family caregiver to determine whether a patient's cognitive impairment is likely dementia or due to other neurodegenerative condition. The initial screening questions will consist of the following questions:

- Has your loved one been evaluated for memory problems at the doctor's office?
    - If yes, what was the formal diagnosis at that time?
    - Do you have any test results related to the diagnosis?
- Does your loved one take any cognition- enhancing drugs, such as Aricept, Exelon, Reminyl, Namenda, or Provigil?
- Has your loved one had a stroke before this memory problem?

If a caregiver reports their loved one as having dementia based on the screening question and IQCODE (a score 3.3 or higher), study staff will schedule a meeting to determine full eligibility of their loved one and consent.

To recruit participants from Northwestern University and Rush University Alzheimer's Disease Research Center, the co-investigators, Dr. Shah at Rush and Dr. Morhardt at Northwestern, will identify patients who are deemed eligible for the study. Their research staff will phone the potential patient participants (and their family caregivers/potential surrogate participants) to introduce the study and gain permission to share contact information with Emory research staff. Upon receiving referrals, Emory research staff will contact these potential participants by phone or email to determine interest and eligibility, explain the study in detail and obtain verbal consent using Verbal Informed Consent/HIPAA authorization format.

For all recruitment sites, the location for consent meeting can be flexible to meet the demands of participants.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

It is very unlikely that this study may be suspended or prematurely terminated since the SPIRIT intervention has been extensively tested, including its safety and efficacy. Also, this study aim includes collecting feasibility and acceptability data and no planned interim analysis and stopping rules. Nonetheless, if suspension or termination occurs, written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, participating clinics, and regulatory authorities. If the study is terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study appointment schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor and IRB.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor. The study documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic), for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored in REDCap study database for internal use during the study. At the end of the study, all paper records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be directly entered into and stored in REDCap study database (Stage 1A). During Stage 1B, all data collection from the participants will be completed using paper forms first and then entered into REDCap, followed by data verification. Individual participants and their research data will be identified by a unique study identification number. All information collected during the study will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Emory School of Nursing.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at the Emory School of Nursing. After the study is completed, the de-identified, archived data will be transmitted to and stored in the REDCap study archive for use by other researchers including those outside of the study. When the study is completed, access to study data will be provided through the Emory School of Nursing.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Project Manager**	**Consultant**	**Co-Investigator**
Mi-Kyung Song, PhD, RN Professor Emory University, School of Nursing 1520 Clifton Rd NE, Atlanta, GA 30322 404-727-3134 mi-kyung.song@emory.edu	Maria Bolanos Emory University, School of Nursing 1520 Clifton Rd. NE, Atlanta, GA 30322 404-727-1978	Sandra Ward, PhD, RN, Professor Emerita University of Wisconsin-Madison 608-257-0119 sward@wisc.edu	Kenneth Hepburn, PhD Professor Emory University, School of Nursing khepbur@emory.edu

Co-Investigator/Statistician Sudeshna Paul, PhD Assistant Professor Emory University, School of Nursing sudeshna.paul@emory.edu	**Co-Investigator** Darby Morhardt, PhD, LCSW Associate Professor Northwestern University d-morhardt@northwestern.edu	**Co-Investigator** Raj Shah, MD Associate Professor Family Medicine and Rush Alzheimer's Disease Center Rush University Raj_C_Shah@rush.edu	

10.1.6 SAFETY OVERSIGHT

The SPIRIT in mild AD is a single-site, Stage I intervention development and testing research project involving minimal risk. The PI will be responsible for ensuring participants' safety on a daily basis. The *Data and Safety Monitoring Committee (DSMC)* will act in an advisory capacity to the PI to monitor participant safety, evaluate the progress of the study, to review procedures for maintaining the confidentiality of data, the quality of data collection, management, and analyses.

The PI will convene weekly meetings with staff to review progress, subject accrual, and any anticipated and unanticipated problems. The weekly progress information will be aggregated for reports and presented at bi-monthly or monthly all investigators meetings.

The PI will convene a videoconference with the study investigators monthly. At these meetings the investigators will assess study performance related to subject recruitment (at least 5 dyads per month), review the quality of the data, and discuss any adverse events. The investigators will determine any need for re-training of study staff. We will set up a DSMC responsible for reviewing trial data on an ongoing basis. The DSMC will meet twice annually by teleconference call to review study progress, data quality, and participants safety. The PI will be informed of SAE as soon as they occur and will notify the NIA and DSMC within 24 hours of notification.

The content of the data and safety monitoring report will include:

- Overall study status
- Enrollment (actual vs expected) and participant enrollment status
- Reasons for screen failures and protocol deviations and violations
- Participant demographic and key baseline characteristics
- Summary of incidence of adverse events, serious adverse events, and unanticipated problems
- Data quality, missing data.

See the DSMP and DSMC Charter for more details.

10.1.7 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

All study data will be directly entered into REDCap. The data entry forms in REDCap will be set up such that out-of-range values are not accepted, which will minimize data entry error.

- The PI and Project Director will conduct monitoring quarterly throughout the study. A random review of 10% primary endpoint data and secondary endpoint data will be performed. A monitoring report will be generated at completion of review and will be shared with the study team.
- Independent audits will not be conducted as this trial collects medical history and data related to the AD diagnosis at baseline and AD progression at 12 months.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

All research staff will complete competency-based training for recruitment and data collection activities. The PI and Project Manager will train staff in all study procedures. All project staff will complete university sponsored research integrity training, including modules on the protection of human subjects, HIPAA, and Good Clinical Practice. All roles, responsibilities, and a protocol with scripted subject contacts will be clearly delineated in the study Standard Operating Procedures (SOPs). These SOPs will be easily accessible to the research staff.

Data collectors/recruiters will attend a competency based, one-day training session that the PI and Project Manager will convene. Following a demonstration by the PI or Project Manager on how to recruit participants and obtain informed consent, the recruiters will be expected to perform three satisfactory practice recruitment sessions before actual performance. After demonstrating satisfactory performance of consenting sessions, the recruiters will be authorized to recruit and enroll participants.

Training for data collection will include scripted data collection techniques with special attention to assessing participant fatigue or discomfort during the data collection session. Data collectors will conduct a series of three practice baseline and follow-up data collections using volunteers. After demonstrating satisfactory performance on data collection, they will be authorized to perform data collection activities with enrolled participants. They will also need to demonstrate completeness of data collection activities using REDCap.

The following strategies will be employed for internal quality management of study conduct, data collection, documentation and completion:

- Use of data collection and data entry SOP
- Using paper forms for data collection and then entering data into REDCap
- Use of a second staff member to quality assure data entry between paper and database
- Each data collector signs his/her work
- Audit research staff members' performance (e.g., consenting and data collection) biannually.

We will also employ systematic checking of data quality: The project manager will run quality control checks on the database quarterly during active subject recruitment and data collection; any missing data or data anomalies will be reported to the PI for clarification/resolution.

The PI/Dr. Song will convene weekly meetings with staff to review progress, subject accrual, and any unanticipated problems. The weekly progress information will be aggregated for reports and presented at monthly investigators meetings.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

The School of Nursing at Emory University will maintain close contact with every entity within the study and will monitor study activities. We will use a common study web-portal using the Research Electronic Data Capture

(REDCap) created and managed in Emory SON. We will create and update study participants' data through REDCap. During data entry, automated checks will be performed that will immediately flag problematic data (e.g., missing, out of range, inconsistent), allowing for the research staff member to address any discrepant data promptly thus increasing data quality. Data entered into the web-based form are immediately stored in a study database and tracked through a journaling process where they are accessible for review by the study team. Suspicious data can be flagged through a query management system, and automated alerts provided to the sites. A complete audit trail is stored for each database modification. Any discrepant data identified through analytic manipulations will be communicated to the sites. Once all queries have been resolved and the database has been deemed "clean", it will be officially locked. All permissions to make changes (append, delete, modify or update) to the database by the sites will be removed at that time.

Record keeping and data collection are the responsibilities of the research staff under the supervision of the PI. The investigator is responsible for ensuring the accuracy, completeness, legibility (if hardcopies of worksheets are used), and timeliness of the data reported.

10.1.9.2 STUDY RECORDS RETENTION

All study's written records will be stored in a locked cabinet for 5 years. Study data will be de-identified and shared with future researchers per written request and IRB approval (Resource and Data Sharing Plans).

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 7 working days of identification of the protocol deviation. See Protocol Deviation/Violation Report Form and the related SOP. All deviations will be addressed in study source documents, reported to the Study Coordinator. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:
National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.
This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial has been registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals.

Authorship determination: Authorship confers credit and has important academic, social, and financial implications. Authorship also implies responsibility and accountability for published work. We will follow the recommendations by the International Committee of Medical Journal Editors (ICMJE) to determine authorship (vs.

non-author contributors). http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html

Authorship will be based on the following 4 criteria:

1. Substantial contributions to the conception or design of the work or the acquisition, analysis, or interpretation of data for the work; AND
2. Drafting the work or revision it *critically for important intellectual content* (simply participating in writing or technical editing of the manuscript is insufficient for authorship); AND
3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Those who do not meet all 4 of the above criteria will be acknowledged as non-author contributors.

Data sharing:

We will make the final data from the study, including a codebook, available to researchers after acceptance for publication of the main findings from the final dataset. The final data will be a complete and cleaned data set free of identifiers. We will make the research data available to users with a data-sharing agreement that includes: (1) a commitment to using the data only for research purposes, (2) a commitment to securing the data using appropriate computer technology, (3) a commitment to destroying the data after analyses are completed and not redistributing to third parties, and (4) IRB approval and clear research questions. Data request and sharing procedures, data request forms, and a data-sharing agreement will be accessible through the website of Center for Nursing Excellence in Palliative Care, Nell Hodgson Woodruff School of Nursing. The requester will be able to download final dataset and codebook. Also, care providers or administrators who wish to use the SPIRIT intervention in their practice and care setting can place a request through the Center's website and will be able to download the SPIRIT intervention manual.

10.1.12 CONFLICT OF INTEREST POLICY

Any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NIA has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 PROTOCOL AMENDMENT HISTORY

Version	Date	Section	Description of Change	Brief Rationale
V1	10/17/2017		Original version	
V2	02/27/2018	5.1 Inclusion criteria 5.2 Exclusion criteria 5.5 Strategies for recruitment & retention	Inclusion criteria; modifying the initial steps of subject identification and recruitment based on the study clinic's recommendations	To include all types of dementia; To make the inclusion criteria and recruitment procedures consistent with the care setting.

V3	05/01/2018	1.1 Description of Study Intervention 7.2 Participant Discontinuation/Withdrawal from the Study 10.1.1.1 Consent/assent and Other Informational Documents Provided to participants 10.1.1.2 Consent Procedures and Documentation	Removal of dialysis language from all descriptions of participant population. Adding language to describe verbal consent procedures for participants**.**	Language removed to be consistent with the target patient population. To reduce burden on surrogate caregiver participants by enabling them to consent verbally by phone.
V4	6/19/18	5.1 Inclusion Criteria 5.5 Recruitment and Consent Procedures 10.1.1.2 Consent Procedures and Documentation	Adding language to Inclusion Criteria which reflects the tests used to diagnose dementia and the language used to document diagnosis within the patient medical chart. Removal of (a) due to redundancy with (b).Adding Zoom software. Clarifying that patient recruitment may occur at any clinic within the Brain Health Center network for stages 1A or 1B..	To increase our identification and recruitment of individuals in early stages of dementia.
V5	8.14.18	2.2 Background 5.1 & 5.5 Inclusion Criteria 10.1.1.2 Informed Consent 4.5 Scientific Rationale 6.1.1 Study Intervention Description	Removal of language which stipulates recruitment of AD Dementia patients only. Change screening UBACC floor to ≥ 11 or (score 9 or 10 with PI consultation).	Allow patients to enter study with any type of dementia. Ability to reason through the intervention is necessary even if patient has difficulty

		8.1 Outcome Assessment 6.1 Study Intervention Description	Outcome assessment ideally 2-3 days after SPIRIT session. Location of consent procedures and SPIRIT sessions to allow for non-Emory locations. Study personnel to complete outcome measure post-SPIRIT session.	remembering the details. Timeframe loosened due to schedule challenges related to dyads availability. Incorporate convenience to dyads in selection of private location for consent. Study personnel required to complete outcome measure rather than interventionist.
V6	8.21.18	5.5 Strategies for Recruitment and Retention	Addition of and Grady Health System's Marcus Stroke and Neuroscience Center, Geriatrics and Primary Care Clinics as sites for recruitment and enrollment.	To increase the diversity of our patient population.
V7	11.26.18	1.1 Synopsis, 3.0 Aim 2, 8.1 Outcomes Assessment, 9.1 Statistical Hypotheses, 9.2 Sample size determination, 9.4.2 Analysis of the Primary Endpoints 5.5 Recruitment and Consent Procedures 6.1.1 Usual Care 10.1.1.2 Consent Procedures and Documentation 10.1.8 Quality Assurance and Quality Control	Revisions to primary and secondary outcomes Refining recruitment strategies at 1B sites Description of Usual Care practices at 1B sites Refining consent procedures at 1B clinic sites Data collection on paper	Patient cognitive impairment that can results in a lot of missing data in primary outcomes Recruitment strategies customized to study site Availability of more information about usual care each site Customizing consent procedures to each study site Ensuring quality and accuracy of data

V8	4.24.19	5.1 Inclusion criteria 5.2 Exclusion criteria; 9.4.3 Analysis of the secondary endpoints	Removal of CDR from cognitive assessment description. Instead Inserting verbiage to describe moderate dementia Removal of the advance directive criterion; Specification of population to be analyzed for advance directive completion	To reflect the level of cognitive impairment appropriate for advance care planning discussion To help reach the recruitment target without compromising the scientific goals
V9	5.9.19	5.5 Strategies for Recruitment and Retention	Include Emory domiciliary care program and assisted living facilities as areas for recruitment	To increase access to this research study for people affected by dementia in other community settings
V10	7.31.19	5.5 Strategies for Recruitment and Retention 10.1.1.1 Consent Procedures and Documentation	Expand avenues for recruitment at Assisted Living Facilities Elaborate on consent procedures	To increase recruitment of eligible patients in independent and assisted living facilities (outside of Emory's Domiciliary Program). To mirror updated recruitment procedures

V11	9.3.19	5.5 Strategies for Recruitment and Retention	Expand avenues for recruitment to Adult Day Care Facilities and Emory's Brain Health Center (under 1B) Addition of dementia screening questions and IQ CODE procedures for family caregivers	To Increase recruitment of eligible patients To determine whether cognitive impairment is likely due to a neurodegenerative condition that is irreversible when medical records are not available.
		10.1.1.2 Consent Procedures and Documentation	Elaborate on consent procedures	To mirror updates to the recruitment strategy and process
V12	9.23.19	1.2 Schema 4. Overview of study design	Add an additional pathway for participants from remote areas of recruitment (i.e., local [ATL and vicinities] vs. remote areas)	Maintain study integrity while trying to meet the target sample size
		5.1. Inclusion criteria 5.5 Strategies for Recruitment and Retention 6.1.1 Study intervention description 9.2 Sample size determination 9.4.2 Analysis of the primary endpoints 10.1.1. Informed consent process	Expand avenues for recruitment and tailor the screening process to the avenues Add usual care description for additional avenues Revisit sample size for the design change Adjustment to the data analysis consistent with the design change	To meet the target sample size

		10.1.1.2 Consent Procedures and Documentation	Tailor the consent process to the avenues (e.g., participants from remote areas to be consented over the phone)	
V13	11.18.19	6.1.1 Study Intervention Description 8.1 Outcome assessments	Outline procedures for collecting patient medical characteristics when medical record is not accessible	To accommodate participation from people receiving care outside of Emory or Grady

11 REFERENCES

1. Onken LS, Carroll KM, Shoham V, Cuthbert BN, Riddle M. Reenvisioning Clinical Science: Unifying the Discipline to Improve the Public Health. Clinical Psychological Science 2014;2:22-34.
2. Williams CM, Skinner EH, James AM, Cook JL, McPhail SM, Haines TP. Comparative effectiveness research for the clinician researcher: A framework for making a methodological design choice. Trials 2016;17:406.
3. Button KS, Ioannidis JP, Mokrysz C, Nosek BA, Flint J, Robinson ES, Munafo MR. Power failure: why small sample size undermines the reliability of neuroscience. Nature reviews Neuroscience 2013;14:365-76.
4. Fanelli D, Ioannidis JP. US studies may overestimate effect sizes in softer research. Proeedings of National Academy of Science of the United States of America 2013;110:15031-15036.
5. Hoyert DL, Xu J. Deaths: preliminary data for 2011. National vital statistics reports : from the Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System 2012;61:1-51.
6. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Jr., Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R, Mohs RC, Morris JC, Rossor MN, Scheltens P, Carrillo MC, Thies B, Weintraub S, Phelps CH. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & Dementia : the journal of the Alzheimer's Association 2011;7:263-9.
7. Tay SY, Davison J, Jin NC, Yap PL. Education and Executive Function Mediate Engagement in Advance Care Planning in Early Cognitive Impairment. Journal of the American Medical Directors Association 2015;16:957-62.
8. Cheong K, Fisher P, Goh J, Ng L, Koh HM, Yap P. Advance care planning in people with early cognitive impairment. BMJ Supportive & Palliative Care 2015;5:63-9.
9. Garand L, Dew MA, Lingler JH, DeKosky ST. Incidence and predictors of advance care planning among persons with cognitive impairment. The American journal of Geriatric Psychiatry 2011;19:712-20.
10. Engel SE, Kiely DK, Mitchell SL. Satisfaction with end-of-life care for nursing home residents with advanced dementia. Journal of the American Geriatrics Society 2006;54:1567-72.
11. Biola H, Sloane PD, Williams CS, Daaleman TP, Williams SW, Zimmerman S. Physician communication with family caregivers of long-term care residents at the end of life. Journal of the American Geriatrics Society 2007;55:846-56.

12. Givens JL, Kiely DK, Carey K, Mitchell SL. Healthcare proxies of nursing home residents with advanced dementia: decisions they confront and their satisfaction with decision-making. Journal of the American Geriatrics Society 2009;57:1149-55.
13. Kaufman SR. Intensive care, old age, and the problem of death in America. Gerontologist 1998;38:715-25.
14. Svanholm JR, Nielsen JC, Mortensen PT, Christensen CF, Birkelund R. Normativity under change: Older persons with implantable cardioverter defibrillator. Nursing Ethics 2016;23:328-38.
15. Harrison Dening K, King M, Jones L, Vickestaff V, Sampson EL. Advance Care Planning in Dementia: Do Family Carers Know the Treatment Preferences of People with Early Dementia? PloS one 2016;11:e0159056.
16. Caron CD, Griffith J, Arcand M. End-of-life decision making in dementia: The perspective of family caregivers. Dementia 2005;4:113-136.
17. Fetherstonhaugh D, McAuliffe L, Bauer M, Shanley C. Decision-making on behalf of people living with dementia: how do surrogate decision-makers decide? Journal of Medical Ethics 2016. doi: 10.1136/medethics-2015-103301
18. Song MK, Ward SE, Lin FC, Hamilton JB, Hanson LC, Hladik GA, Fine JP. Racial Differences in Outcomes of an Advance Care Planning Intervention for Dialysis Patients and Their Surrogates. J Palliat Med 2016;19:134-42.
19. Baggs JG, Schmitt MH. End-of-life decisions in adult intensive care: current research base 158 and directions for the future. Nursing Outlook 2000;48:158-64.
20. Hansen L, Archbold PG, Stewart BJ. Role strain and ease in decision-making to withdraw or withhold life support for elderly relatives. Journal of Nurssing Scholarship 2004;36:233-8.
21. Tilden VP, Tolle SW, Nelson CA, Fields J. Family decision-making to withdraw life-sustaining treatments from hospitalized patients. Nursing Research 2001;50:105-15.
22. Jacob DA. Family members' experiences with decision making for incompetent patients in the ICU: a qualitative study. American Journal of Critical Care 1998;7:30-6.
23. Forbes S, Bern-Klug M, Gessert C. End-of-life decision making for nursing home residents with dementia. Journal of Nursing Scholarship 2000;32:251-8.
24. Mezey M, Teresi J, Ramsey G, Mitty E, Bobrowitz T. Decision-making capacity to execute a health care proxy: development and testing of guidelines. Journal of the American Geriatrics Society 2000;48:179-87.
25. Braun UK, Beyth RJ, Ford ME, McCullough LB. Voices of African American, Caucasian, and Hispanic surrogates on the burdens of end-of-life decision making. Journal of General Internal Medicine 2008;23:267-74.
26. Shiozaki M, Hirai K, Dohke R, Morita T, Miyashita M, Sato K, Tsuneto S, Shima Y, Uchitomi Y. Measuring the regret of bereaved family members regarding the decision to admit cancer patients to palliative care units. Psycho-Oncology 2008;17:926-31.
27. Wright AA, Zhang B, Ray A, Mack JW, Trice E, Balboni T, Mitchell SL, Jackson VA, Block SD, Maciejewski PK, Prigerson HG. Associations between end-of-life discussions, patient mental health, medical care near death, and caregiver bereavement adjustment. JAMA 2008;300:1665-73.
28. Donovan HS, Ward S. A representational approach to patient education. Journal of Nursing Scholarship 2001;33:211-6.
29. Donovan HS, Ward SE, Song MK, Heidrich SM, Gunnarsdottir S, Phillips CM. An update on the representational approach to patient education. Journal of Nursing Scholarship 2007;39:259-65.
30. Song MK, Kirchhoff KT, Douglas J, Ward SE, Hammes BJ. A randomized, controlled trial to improve advance care planning among patients undergoing cardiac surgery. Medical Care 2005;43:1049-1053.
31. Song MK, Ward SE, Happ MB, Piraino B, Donovan HS, Shields AM, Connolly MC. Randomized controlled trial of SPIRIT: An effective approach to preparing African American dialysis patients and families for end-of-life. Research in Nursing & Health 2009;32:260-273.
32. Song MK, Donovan HD, Piraino B, Choi J, Bernardini J, Verosky D, Ward SE. Effects of an intervention to improve communication about end-of-life care among African Americans with chronic kidney disease. Applied Nursing Research 2010;23:65-72.

33. Song MK, Ward SE, Fine JP, Hanson LC, Lin FC, Hladik GA, Hamilton JB, Bridgman JC. Advance care planning and end-of-life decision making in dialysis: A randomized controlled trial targeting patients and their surrogates. American Journal of Kidney Diseases 2015;66:813-22.
34. Metzger M, Song MK, Devane-Johnson S. LVAD patients' and surrogates' perspectives on SPIRIT-HF: An advance care planning discussion. Heart & Lung 2016;45:305-10.
35. Metzger M, Song MK, Ward S, Chang PP, Hanson LC, Lin FC. A randomized controlled pilot trial to improve advance care planning for LVAD patients and their surrogates. Heart & Lung 2016;45:186-92.
36. Green C, Zhang S. Predicting the progression of Alzheimer's disease dementia: A multidomain health policy model. Alzheimer's & Dementia 2016;12:776-85.
37. Morrison RS, Siu AL. Survival in end-stage dementia following acute illness. JAMA 2000;284:47-52.
38. Meier DE, Ahronheim JC, Morris J, Baskin-Lyons S, Morrison RS. High short-term mortality in hospitalized patients with advanced dementia: lack of benefit of tube feeding. Archives of Internal Medicine 2001;161:594-9.
39. Mitchell SL, Kiely DK, Hamel MB, Park PS, Morris JN, Fries BE. Estimating prognosis for nursing home residents with advanced dementia. JAMA 2004;291:2734-40.
40. Mitchell SL, Teno JM, Kiely DK, Shaffer ML, Jones RN, Prigerson HG, Volicer L, Givens JL, Hamel MB. The clinical course of advanced dementia. The New England Journal of Mdicine 2009;361:1529-38.
41. D'Agata E, Mitchell SL. Patterns of antimicrobial use among nursing home residents with advanced dementia. Archives of Internal Medicine 2008;168:357-62.
42. Teno JM, Gozalo P, Khandelwal N, Curtis JR, Meltzer D, Engelberg R, Mor V. Association of Increasing Use of Mechanical Ventilation Among Nursing Home Residents With Advanced Dementia and Intensive Care Unit Beds. JAMA Internal Medicine 2016.
43. Ditto PH, Danks JH, Smucker WD, Bookwala J, Coppola KM, Dresser R, Fagerlin A, Gready RM, Houts RM, Lockhart LK, Zyzanski S. Advance directives as acts of communication: A randomized controlled trial. Archives of Internal Medicine 2001;161:421-30.
44. Teno JM, Stevens M, Spernak S, Lynn J. Role of written advance directives in decision making: Insights from qualitative and quantitative data. Journal of General Internal Medicine 1998;13:439-46.
45. Fagerlin A, Schneider CE. Enough. The failure of the living will. Hastings Center Report 2004;34:30-42.
46. Gillick MR. Advance care planning. The New England Journal of Medicine 2004;350:7-8.
47. Perkins HS. Controlling death: the false promise of advance directives. Annals of Internal Medicine 2007;147:51-7.
48. Sudore RL, Fried TR. Redefining the "planning" in advance care planning: preparing for end-of-life decision making. Annals of Internal Medicine 2010;153:256-61.
49. Billings JA. The need for safeguards in advance care planning. Journal of General Internal Medicine 2012;27:595-600.
50. McMahan RD, Knight SJ, Fried TR, Sudore RL. Advance care planning beyond advance directives: perspectives from patients and surrogates. Journal of Pain and Symptom Management 2013;46:355-65.
51. Institute of Medicine. Dying in America: Improving quality and honoring individual preferences near the end of life. Washington, D.C.: The National Academy of Sciences, 2014.
52. Kolarik RC, Arnold RM, Fischer GS, Tulsky JA. Objectives for advance care planning. Journal of Palliative Medicine 2002;5:697-704.
53. Pinquart M, Sorensen S. Helping caregivers of persons with dementia: which interventions work and how large are their effects? International Psychogeriatrics 2006;18:577-95.
54. Parikh PK, Troyer AK, Maione AM, Murphy KJ. The Impact of Memory Change on Daily Life in Normal Aging and Mild Cognitive Impairment. The Gerontologist 2016;56:877-85.
55. Lingler JH, Hirschman KB, Garand L, Dew MA, Becker JT, Schulz R, Dekosky ST. Frequency and correlates of advance planning among cognitively impaired older adults. The American Journal of Geriatric Psychiatry 2008;16:643-9.
56. Dening KH, Jones L, Sampson EL. Advance care planning for people with dementia: a review. International Psychogeriatrics 2011;23:1535-51.
57. Hirschman KB, Kapo JM, Karlawish JH. Identifying the factors that facilitate or hinder advance planning by persons with dementia. Alzheimer Disease and Associated Disorders 2008;22:293-8.

58. Jethwa KD, Onalaja O. Advance care planning and palliative medicine in advanced dementia: a literature review. BJ Psychological Bulletin 2015;39:74-8.
59. Cherlin E, Fried T, Prigerson HG, Schulman-Green D, Johnson-Hurzeler R, Bradley EH. Communication between physicians and family caregivers about care at the end of life: when do discussions occur and what is said? Journal of Palliative Medicine 2005;8:1176-85.
60. Houts RM, Smucker WD, Jacobson JA, Ditto PH, Danks JH. Predicting elderly outpatients' life-sustaining treatment preferences over time: The majority rules. Medical Decision Making 2002;22:39-52.
61. Song MK, Ward SE, Lin FC. End-of-life decision-making confidence in surrogates of African-American dialysis patients is overly optimistic. ournal of Palliative Medicine 2012;15:412-7.
62. Lord K, Livingston G, Cooper C. A systematic review of barriers and facilitators to and interventions for proxy decision-making by family carers of people with dementia. International Psychogeriatrics 2015;27:1301-12.
63. Badger JM. Factors That Enable or Complicate End-of-Life Transitions in Critical Care. American Journal of Critical Care 2005;14:513-21.
64. Boyle DK, Miller PA, Forbes-Thompson SA. Communication and end-of-life care in the intensive care unit: patient, family, and clinician outcomes. Critical Care Nursing Quarterly 2005;28:302-16.
65. Swigart V, Lidz C, Butterworth V, Arnold R. Letting go: family willingness to forgo life support. Heart & Lung 1996;25:483-94.
66. Hardin SB, Yusufaly YA. Difficult end-of-life treatment decisions: do other factors trump advance directives? Archives of Internal Medicine 2004;164:1531-3.
67. Abbott KH, Sago JG, Breen CM, Abernethy AP, Tulsky JA. Families looking back: one year after discussion of withdrawal or withholding of life-sustaining support. Critical Care Medicine 2001;29:197-201.
68. Hebert RS, Schulz R, Copeland VC, Arnold RM. Preparing Family Caregivers for Death and Bereavement. Insights from Caregivers of Terminally Ill Patients. Journal of Pain and Symptom Management 2009;37:3-12.
69. Azoulay E, Pochard F, Kentish-Barnes N, Chevret S, Aboab J, Adrie C, Annane D, Bleichner G, Bollaert PE, Darmon M, Fassier T, Galliot R, Garrouste-Orgeas M, Goulenok C, Goldgran-Toledano D, Hayon J, Jourdain M, Kaidomar M, Laplace C, Larche J, Liotier J, Papazian L, Poisson C, Reignier J, Saidi F, Schlemmer B. Risk of post-traumatic stress symptoms in family members of intensive care unit patients. American Journal of Respiratory and Critical Care Medicine 2005;171:987-94.
70. Curtis JR, Engelberg RA, Wenrich MD, Shannon SE, Treece PD, Rubenfeld GD. Missed Opportunities during Family Conferences about End-of-Life Care in the Intensive Care Unit. American Journal of Respiratory and Critical Care Medicine 2005;171:844-9.
71. Siegel MD, Hayes E, Vanderwerker LC, Loseth DB, Prigerson HG. Psychiatric illness in the next of kin of patients who die in the intensive care unit. Critical Care Medicine 2008;36:1722-8.
72. Leventhal H, Nerenz D, Steele DS. Illness representations and coping with health threats. In: Baum A, Singer JE, editors. Handbook of psychology and health. New York: Erlbaum, 1984:221-252.
73. Posner G, Strike K, Hewson P, Gertzog W. Accommodation of a scientific conception: Toward a theory of conceptual change. Science Education 1982;66:211-227.
74. Kleinman A, Eisenberg L, Good B. Culture, illness, and care: clinical lessons from anthropologic and cross-cultural research. Annals of Internal Medicine 1978;88:251-8.
75. Kleinman A, Mendelsohn E. Systems of medical knowledge: a comparative approach. Journal of Medicine and Philosophy 1978;3:314-30.
76. Hewson M. Patient education through teaching for conceptual change. Journal of General Internal Medicine 1993;8:393-8.
77. Hewson P, Hewson M. The role of conceptual conflict in conceptual change and the design of instruction. Instructional Science 1984;13:1-13.
78. Song MK, Ward SE. Making visible a theory-guided advance care planning intervention. J Nurs Scholarsh 2015;47:389-96.

79. Barnes LL, Leurgans S, Aggarwal NT, Shah RC, Arvanitakis Z, James BD, Buchman AS, Bennett DA, Schneider JA. Mixed pathology is more likely in black than white decedents with Alzheimer dementia. Neurology 2015;85:528-34.
80. James BD, Bennett DA, Boyle PA, Leurgans S, Schneider JA. Dementia from Alzheimer disease and mixed pathologies in the oldest old. JAMA 2012;307:1798-800.
81. Schneider JA, Arvanitakis Z, Bang W, Bennett DA. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. Neurology 2007;69:2197-204.
82. Ganguli M, Dodge HH, Shen C, DeKosky ST. Mild cognitive impairment, amnestic type: an epidemiologic study. Neurology 2004;63:115-21.
83. Karlawish JH, Casarett DJ, James BD, Xie SX, Kim SY. The ability of persons with Alzheimer disease (AD) to make a decision about taking an AD treatment. Neurology 2005;64:1514-9.
84. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology 1993;43:2412-4.
85. Mittal D, Palmer BW, Dunn LB, Landes R, Ghormley C, Beck C, Golshan S, Blevins D, Jeste DV. Comparison of two enhanced consent procedures for patients with mild Alzheimer disease or mild cognitive impairment. The American Journal of Geriatric Psychiatry 2007;15:163-7.
86. Moye J, Karel MJ, Azar AR, Gurrera RJ. Capacity to consent to treatment: empirical comparison of three instruments in older adults with and without dementia. The Gerontologist 2004;44:166-75.
87. Fazel S, Hope T, Jacoby R. Effect of cognitive impairment and premorbid intelligence on treatment preferences for life-sustaining medical therapy. The American Journal of Psychiatry 2000;157:1009-11.
88. Gregory R, Roked F, Jones L, Patel A. Is the degree of cognitive impairment in patients with Alzheimer's disease related to their capacity to appoint an enduring power of attorney? Age and Ageing 2007;36:527-31.
89. Fazel S, Hope T, Jacoby R. Assessment of competence to complete advance directives: validation of a patient centred approach. BMJ 1999;318:493-7.
90. Fazel S, Hope T, Jacoby R. Dementia, intelligence, and the competence to complete advance directives. Lancet 1999;354:48.
91. Taub HA, Kline GE, Baker MT. The elderly and informed consent: effects of vocabulary level and corrected feedback. Experimental Aging Research 1981;7:137-46.
92. Grisso T, Appelbaum PS. Mentally ill and non-mentally-ill patients' abilities to understand informed consent disclosures for medication: preliminary data. Law and Human Behavior 1991;15:377-88.
93. Okonkwo O, Griffith HR, Belue K, Lanza S, Zamrini EY, Harrell LE, Brockington JC, Clark D, Raman R, Marson DC. Medical decision-making capacity in patients with mild cognitive impairment. Neurology 2007;69:1528-35.
94. Demiris G, Parker Oliver D, Wittenberg-Lyles E, Washington K, Doorenbos A, Rue T, Berry D. A noninferiority trial of a problem-solving intervention for hospice caregivers: in person versus videophone. Journal of Palliative Medicine 2012;15:653-60.
95. Demiris G, Parker Oliver DR, Courtney K. A Study of the suitability of videophones for psychometric assessment. Behav Inf Technol 2006;25:233-237.
96. Seguranyes G, Costa D, Fuentelsaz-Gallego C, Beneit JV, Carabantes D, Gomez-Moreno C, Palacio-Tauste A, Pauli A, Abella M, Postpartum Telematics Research G. Efficacy of a videoconferencing intervention compared with standard postnatal care at primary care health centres in Catalonia. Midwifery 2014;30:764-71.
97. Griffiths PC, Whitney MK, Kovaleva M, Hepburn K. Development and Implementation of Tele-Savvy for Dementia Caregivers: A Department of Veterans Affairs Clinical Demonstration Project. The Gerontologist 2016;56:145-54.
98. Hirschman KB, Xie SX, Feudtner C, Karlawish JH. How does an Alzheimer's disease patient's role in medical decision making change over time? Journal of Geriatric Psychiatry and Neurology 2004;17:55-60.
99. Hirschman KB, Kapo JM, Karlawish JH. Why doesn't a family member of a person with advanced dementia use a substituted judgment when making a decision for that person? The American Journal of Geriatric Psychiatry 2006;14:659-67.

100. van der Steen JT, van Soest-Poortvliet MC, Hallie-Heierman M, Onwuteaka-Philipsen BD, Deliens L, de Boer ME, Van den Block L, van Uden N, Hertogh CM, de Vet HC. Factors associated with initiation of advance care planning in dementia: a systematic review. Journal of Alzheimer's disease 2014;40:743-57.
101. Vandervoort A, Houttekier D, Van den Block L, van der Steen JT, Vander Stichele R, Deliens L. Advance care planning and physician orders in nursing home residents with dementia: a nationwide retrospective study among professional caregivers and relatives. Journal of Pain and Symptom Management 2014;47:245-56.
102. Hanson LC, Carey TS, Caprio AJ, Lee TJ, Ersek M, Garrett J, Jackman A, Gilliam R, Wessell K, Mitchell SL. Improving decision-making for feeding options in advanced dementia: a randomized, controlled trial. Journal of the American Geriatrics Society 2011;59:2009-16.
103. Austin CA, Mohottige D, Sudore RL, Smith AK, Hanson LC. Tools to Promote Shared Decision Making in Serious Illness: A Systematic Review. JAMA Internal Medicine 2015;175:1213-21.
104. Hanson LC, Zimmerman S, Song MK, Lin F-C, Rosemond C, Carey TS, Mitchell SL. The goals of care intervention for advanced dementia: A cluster randomized trial. JAMA Internal Medicine 2017;177:24-31.
105. Sampson EL, Jones L, Thune-Boyle IC, Kukkastenvehmas R, King M, Leurent B, Tookman A, Blanchard MR. Palliative assessment and advance care planning in severe dementia: an exploratory randomized controlled trial of a complex intervention. Palliative Medicine 2011;25:197-209.
106. Carr D, Khodyakov D. Health care proxies: whom do young old adults choose and why? Journal of Health and Social Behavior 2007;48:180-94.
107. Stirman SW, Miller CJ, Toder K, Calloway A. Development of a framework and coding system for modifications and adaptations of evidence-based interventions. Implementation Science : IS 2013;8:65.
108. Song MK, Happ MB, Sandelowski M. Development of a tool to assess fidelity to a psycho-educational intervention. Journal of Advanced Nursing 2010;66:673-682.
109. Kassam-Adams N, Marsac ML, Kohser KL, Kenardy JA, March S, Winston FK. A new method for assessing content validity in model-based creation and iteration of eHealth interventions. Journal of Medical Internet Research 2015;17:e95.
110. Jeste DV, Palmer BW, Appelbaum PS, Golshan S, Glorioso D, Dunn LB, Kim K, Meeks T, Kraemer HC. A new brief instrument for assessing decisional capacity for clinical research. Archives of General Psychiatry 2007;64:966-74.
111. Seaman JB, Terhorst L, Gentry A, Hunsaker A, Parker LS, Lingler JH. Psychometric Properties of a Decisional Capacity Screening Tool for Individuals Contemplating Participation in Alzheimer's Disease Research. Journal of Alzheimer's Disease 2015;46:1-9.
112. Hsieh HF, Shannon SE. Three approaches to qualitative content analysis. Qualitative Health Research 2005;15:1277-88.
113. Kondracki NL, Wellman NS, Amundson DR. Content analysis: review of methods and their applications in nutrition education. J Nutr Educ Behav 2002;34:224-30.
114. Spackman DE, Kadiyala S, Neumann PJ, Veenstra DL, Sullivan SD. Measuring Alzheimer disease progression with transition probabilities: estimates from NACC-UDS. Current Alzheimer Research 2012;9:1050-8.
115. Tschanz JT, Corcoran CD, Schwartz S, Treiber K, Green RC, Norton MC, Mielke MM, Piercy K, Steinberg M, Rabins PV, Leoutsakos JM, Welsh-Bohmer KA, Breitner JC, Lyketsos CG. Progression of cognitive, functional, and neuropsychiatric symptom domains in a population cohort with Alzheimer dementia: the Cache County Dementia Progression study. The American Journal of Geriatric Psychiatry 2011;19:532-42.
116. Behl P, Stefurak TL, Black SE. Progress in clinical neurosciences: cognitive markers of progression in Alzheimer's disease. The Canadian journal of neurological sciences Le journal canadien des sciences Neurologiques 2005;32:140-51.
117. Popp L, Schneider S. Attention placebo control in randomized controlled trials of psychosocial interventions: theory and practice. Trials 2015;16:150.
118. Weintraub S, Salmon D, Mercaldo N, Ferris S, Graff-Radford NR, Chui H, Cummings J, DeCarli C, Foster NL, Galasko D, Peskind E, Dietrich W, Beekly DL, Kukull WA, Morris JC. The Alzheimer's Disease

Centers' Uniform Data Set (UDS): the neuropsychologic test battery. Alzheimer Disease and Associated Disorders 2009;23:91-101.
119. Song MK, Ward SE. Disconnect between emergency contacts and surrogate decision-makers in the absence of advance directives. Palliative Medicine 2013;27:789-92.
120. Perrin A, Duggan M. Americans' Internet access: 2000-2015. Pew Research Center, 2015.
121. Internet Live Stats. United States Internet users. 2017. http://www.internetlivestats.com/internet-users/us/
122. Song MK, Sereika SM. An evaluation of the Decisional Conflict Scale for measuring the quality of end-of-life decision making. Patient Education and Counseling 2006;61:397-404.
123. Holstein JA, Gubrium JF. The active interview. Thousand Oaks, CA: SAGE, 1995.
124. Song MK, Ward SE, Fine JP, Hanson LC, Lin F-C, Hladik GA, Hamilton JB, Bridgman JC. Advance care planning and end-of-life decision-making in dialysis: A randomized controlled trial targeting patients and their surrogates. American Journal of Kidney Diseases 2015;66:813-22.
125. Mascha EJ, Sessler DI. Equivalence and noninferiority testing in regression models and repeated-measures designs. Anesthesia and Analgesia 2011;112:678-87.
126. Walker E, Nowacki AS. Understanding equivalence and noninferiority testing. Journal of general internal medicine 2011;26:192-6.
127. Song MK, Metzger M, Ward SE. Process and impact of an advance care planning intervention evaluated by bereaved surrogate decision-makers of dialysis patients. Palliative Medicine 2017;177:24-31.
128. Braun V, Clarke V. Using thematic analysis in psychology. Qualitative Research in Psychology 2006;3:77-101.
129. Patton MQ. Qualitative evaluation and research methods. 3rd ed. Thousand Oaks, CA: Sage, 2002.
130. Maxwell JA. Qualitative research design: An inteactive approach. Thousand Oak, CA: SAGE, 2013.
131. Averill JB. Matrix analysis as a complementary analytic strategy in qualitative inquiry. Qualitative Health Research 2002;12:855-66.
132. Sandelowski M. Real qualitative researchers do not count: the use of numbers in qualitative research. Research in Nursing & Health 2001;24:230-40.
133. Tashakkori A, Teddlie C. Handbook of Mixed Methods in Social and Behavioral Sciences Thousand Oaks, CA: Sage Publications Inc, 2003.
134. Dickinson WB. Visual displays for mixed methods findings. In: Tashakkori A, Teddlie C, editors. SAGE handbook of mixed methods in social & behavioral research. 2nd ed. Thousand Oaks, CA: SAGE, 2010:469-504.