Preparing Spanish-speaking Older Adults for Advance Care Planning and Medical Decision Making

This trial is registered at ClinicalTrials.gov: NCT01990235 for English-speakers, registered on November 4th, 2013.

This document includes the following items:
1. Original protocol and statistical analysis plan (March 2013)
2. Final protocol and statistical analysis plan and summary of changes (September 2017)

Protocol

Original Version

March 2013

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FUNDING

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CLINICALTRIALS.GOV INFORMATION

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INTRODUCTION AND RATIONALE

Millions of older adults will face complex medical decisions over the course of advanced illness,[2] yet most are unprepared.[3,4] Lack of preparation can lead to uninformed choices, receipt of care inconsistent with personal goals, and lack of patient empowerment during clinical encounters,[5-9] especially for individuals with limited health literacy.[10] Conventional preparation, called advance care planning (ACP), has typically focused on having patients pre-specify preferences for life prolonging procedures, such as mechanical ventilation, and to document these choices in an advance directive (AD).[11] Yet, ADs are hard to understand and are often not completed, especially by minorities.[12,13] And, even when ADs are completed, they often fail to affect the care received at the end-of-life, decrease the stress of decision making, or result in what most experts agree is the most important component of ACP – ongoing conversations between patients, their loved ones (surrogates), and clinicians.[5,14-17] To overcome these limitations, we developed a new paradigm of ACP that focuses instead on preparing diverse, older adults to communicate their evolving wishes over time and to make real-time, complex medical decisions over the course of chronic and advanced illness.[11] We propose to test this new paradigm of ACP using a patient-centered, interactive website in a double-blind, randomized, efficacy trial.

PRELIMINARY STUDIES

We have experience conducting RCTs among diverse, older adults at the San Francisco Health Network (SFHN).[18] Dr. Sudore designed and tested an AD written at a 5th grade reading level among 205 chronically ill, diverse, older adults from San Francisco General Hospital (SFGH) with a 6-month follow-up of 85%. The AD was preferred over a standard AD, with significant interactions for limited literacy (e.g., higher preference rates in patients with limited literacy). It also resulted in greater 6-month AD completion rates (15% vs. 7%, p =.03), doubling the rates from baseline. This AD has been adopted as the official AD for SFGH and is being disseminated in California. It will serve as the active control.

We designed and tested an informed consent process for diverse, older adults with limited literacy.[19] We found that many patients do not understand simplified consent information and were unsure how to ask questions. But, informed decisions can be improved by providing both easy-to-read materials and a teach-back method. We will use this interactive consent method for this study.

Multiple steps of the ACP process:[20] We found that most patients go through a series of ACP behavioral steps. Six months after exposure to the easy-to-read AD, 61% of older adults contemplated ACP, 56% discussed ACP with family or friends and 22% with clinicians, and 13% completed an AD. This work shows that measuring a full range of ACP outcomes, in addition to ADs, and associated behavior change steps (contemplation to action) is important and informs our study outcomes. Previously described barriers to ACP, such as not wanting to burden family,[21] are addressed in PREPARE.

Evidence supporting the new ACP paradigm and content of PREPARE:[22] We completed 13 focus groups with 69 diverse, English- and Spanish-speaking older patients (mean age 78 +/- 8,

61% non- White) and surrogates (mean age 57 +/- 10, 91% non-White) from safety-net settings who reported making serious medical decisions. We used semi-structured interviews to ask about what best prepared them for decision making. Qualitative analysis identified 5 overarching themes, beyond ADs, that prepared patients and surrogates for decision making: (1) choose surrogates wisely and verify they know their role, (2) identify goals based on past experiences and personal values, (3) decide whether to grant leeway in surrogate decision making, (4) inform other family and friends of one's wishes to prevent conflict, and (5) ask clinicians questions. These themes have been incorporated as educational domains of PREPARE.

Validity and reliability of the survey to measure ACP engagement: Surveys were designed with input from Co-Is and extensive cognitive interviews to measure discrete ACP actions (i.e., main outcomes: ACP discussions, AD completion,) and ACP behavior change (e.g., contemplation, self-efficacy, readiness). We recruited 50 older adults, aged ≥ 60 years with ≥ 2 illnesses (32% female, 42% non-White). Internal consistency 7-day test-retest reliability, and discriminant validity (scores compared to healthy young adults – 50% female, 75% non-White) was high. Scores did not differ by race/ethnicity or literacy, $p>.05$. We will also use validated surveys on ACP attitudes and methods to classify patients into behavior change categories.[23,24]

Preliminary evidence that PREPARE is beneficial. In a recent pilot,[25] we recruited 43 diverse, older adults from low-income senior centers. All subjects rated PREPARE easy to use (mean 9/10-point scale). Pre to post ACP behavior change scores from our validated surveys (0-124 points) increased from 72 ± 33 SD to 87 ± 22, a 15-point increase and an effect size of 0.5.

Vulnerable populations have unique needs. The aforementioned pilot demonstrated that, unlike our work with Veterans, patients in safety-net settings are less trustful of research and require in-person recruitment. In addition, these patients are often socially isolated and require tailored ACP for persons without surrogates or families. They also lack ready access to health

information and ancillary support such as social workers or nurses necessitating access to ACP outside of the clinical environment. These findings add further evidence for the need to tailor PREPARE for vulnerable populations and to test PREPARE within safety-net settings.

OVERVIEW OF THE TRIAL DESIGN

Study overview:

This study is a randomized, controlled trial that uses blinded outcome ascertainment to determine the efficacy of the ACP PREPARE website to engage ethnically diverse English- and Spanish-speaking older primary care patients in the ACP process.[1] First, we obtained a Health Insurance Portability and Accountability Act waiver to identify individuals who meet our inclusion/exclusion criteria and have upcoming primary care appointments. Administrative data and chart review are used to determine potentially eligible patients.

Then primary care clinicians' permission is obtained to allow the study team to inform their patients about the study. Patients are then recruited, screened for eligibility, and scheduled for a baseline interview before an upcoming primary care appointment. To standardize the timing of exposure to the intervention and primary care follow-up, study participants are scheduled for baseline procedures 1-3 weeks prior to an upcoming primary care appointment.[26]

Next, informed consent is obtained, and those patients who provide consent are randomized to the PREPARE intervention arm (i.e., the PREPARE website with action plan exercises plus an easy-to-read advance directive plus PREPARE materials to take home, which include a website login, and a PREPARE pamphlet, booklet, and DVD) or the control arm (i.e., an easy-to-read advance directive alone). See a full description of the intervention below.

We then conduct blinded outcome ascertainment by performing chart reviews to determine ACP documentation at baseline and at the end of the study. We also conduct blinded outcome ascertainment using patient surveys at 1 week, and 3, 6, and 12 months after the primary care appointment. We are choosing an active control arm (i.e., an easy-to-read advance directive) because we believe provision of an advance directive for chronically and seriously ill older patients should be the standard of care, even if it is not often "usual" care in clinical practice.[8] In addition, the easy-to-read advance directive used in this study has been adopted by the San Francisco Health Network (SFHN) and San Francisco General Hospital (SFGH) and is available in the primary care clinics.

Research Aims and Study Hypotheses:

The aims of this study are to (1) To determine the efficacy of PREPARE to engage diverse, English- and Spanish-speaking older adults with chronic illness in advance care planning (ACP) compared to controls (AD only) and (2) To determine whether PREPARE efficacy varies by race/ethnicity, literacy, clinician-patient language concordance, and patient's desired role in decision making.[1]

Our primary hypothesis is that the PREPARE program plus an easy-to-read advance directive will result in greater documentation of ACP wishes, including advance directives and documentation of ACP discussions in the medical record, than an easy-to-read advance directive alone in elderly populations with chronic illness.

Our secondary hypotheses are that, compared to an advance directive alone, PREPARE will result in more engagement in behavior change processes concerning ACP, including increased self-efficacy and readiness, as well as greater engagement in a full range of ACP actions, including discussions with surrogate decision makers and other trusted family and friends.

Secondary outcomes will be ascertained using validated surveys.[23,27,28] We also hypothesize that PREPARE will result in improved satisfaction with patient-doctor communication and informed medical decision making and that PREPARE efficacy may vary across moderator variables such as patient health literacy, clinician-patient language concordance, and patients' desired role in decision making.

STUDY SETTING

Recruitment for this randomized trial is occurring in 4 separate primary care clinics associated with the San Francisco Health Network (SFHN) and the San Francisco General Hospital (SFGH) in San Francisco, California. These 4 clinics are housed in 3 separate physical locations in San Francisco. SFGH is an urban, public hospital that, with the SFHN, serves racially and ethnically diverse, low-income and indigent patients; 30% of patients are Spanish-speaking.[18]

PARTICIPANTS AND ELIGIBILITY AND EXCLUSION CRITERIA

There are no inclusion or exclusion criteria based on gender, race or ethnicity. We assess eligibility in person. Older adults are included in this study if they self-report speaking English or Spanish "well" or "very well"; are 55 years of age or older; have ≥ 2 chronic illnesses determined by chart review; have seen a primary care clinician (physician, nurse practitioner, or physician assistant) at SFHN/SFGH-affiliated primary care clinics ≥ 2 times in the past year (an indication of established primary care); and have had ≥ 2 additional outpatient or inpatient visits in the past year (an indication of severity of illness). Their primary care clinician must also give us permission to contact them to tell them about the study.

Inclusion and Exclusion Criteria

We are recruiting patients ≥ 55 years of age (rather than ≥ 65) because adults in safety net settings experience accelerated aging, functional decline, and sequelae of chronic disease, necessitating decision making and ACP at a younger age than patients with higher socioeconomic status.[29,30] The goal is to start ACP early to change the trajectory of decision making and care over the course of illness. Our inclusion criteria of ≥ 2 primary care visits and ≥ 2 additional visits in the past year ensures patients have established primary care and access care frequently. This will enhance recruitment and follow-up.

Patients will be excluded if their clinician is a principal investigator, co-investigator or clinician-member of the Patient-Clinician Advisory Board. They will also be excluded if they have medical record documentation of being deaf, blind, having dementia, or being psychotic or are deemed by their clinician to be too mentally or physically ill to participate. Through in-person or phone screening by study staff, patients are also excluded if they self-report vision too poor to read a newspaper, lack of a phone (needed for follow-up interviews and scheduling), or plans to be out of the country for ≥ 3 months; if they screen positive for moderate-to-severe cognitive impairment using the validated Short Portable Mental Status Questionnaire followed by the Mini-Cog,[31-33] or self-report or are determined by study staff to be blind, deaf, intoxicated or actively psychotic. Because ACP is an iterative process and people may change their preferences over time,[11,34] subjects with prior ACP experiences (e.g., an advance directive) are not excluded.

Inclusion Criteria	55 years of age or older
	Obtains care in the primary care clinics at in the San Francisco Health Network (SFHN).
	Has been seen at least twice in the last year by a primary care provider (a marker of established primary care) and had at least two additional visits to SFHN in the past year (a marker of illness)
Exclusion Criteria	Clinician is the PI, Co-I or member of the Patient-Clinician Advisory Board
	Dementia by ICD-9/ICD-10 codes, clinician assessment, chart review or self-report
	Blindness or poor vision by ICD-9/ICD-10 codes, clinician assessment, chart review, self-report of blindness or the inability to read print on a newspaper[35]
	Deafness by ICD-9/ICD-10 codes, clinician assessment, self-report, chart review or research staff assessment
	Cognitive impairment as assessed by research staff of any deficits on the validated Short Portable Mental Status Questionnaire (SPMSQ)[36] and the mini-Cog[31,37]
	Delirium or psychosis as assessed by a clinician or research staff
	Does not report speaking English or Spanish “well” or “very well”
	No phone for additional study contacts and follow-up interviews
	Patients who report they will be out of town during their scheduled follow-up interview dates outside of a window of 3 months.
	Patients who cannot answer consent teach-back questions after three attempts

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RECRUITMENT METHODS

Data Extraction:

To facilitate recruitment, we obtained a Health Insurance Portability and Accountability Act waiver to access patients' names, age, primary language, phone numbers, addresses, medical record numbers, as well as dates of outpatient primary care clinic appointments in the past year and up to 3 months in the future, other appointments and hospitalizations and emergency room visits in the past year, and the name of patients' outpatient primary care providers. From these data, we obtain a list of potentially eligible patient participants and send a secure email to their primary care providers asking for permission for our study team to tell their patients about the study through a recruitment opt-out study letter, followed by phone or in-person recruitment. Weekly administrative data pulls from the electronic health record identify patients with upcoming primary care appointments and are used to target patient recruitment efforts.

Clinician Permission to Contact Patients:

Upon completion of the administrative data pulls, providers from all recruitment sites are sent a letter/e-mail informing them about the research study and asking them to review a list of their patients, to refer patient(s) on their patient list who would be appropriate for the study, and to obtain permission to contact their patients to tell them more about the study. Clinicians are also informed that if the study team receives their approval, their eligible participants will receive a letter describing the research study and offering them the opportunity to decline to be contacted by research personnel and/or will be contacted in clinic. Additionally, clinicians are informed that if they do not respond one week after the 3rd attempt to contact them by the study team (including by email, phone, and/or in-person), we will assume assent to contact their patients and a letter describing the study will be sent to patients on behalf of the study team. We obtain permission from all of the Service Chiefs before their clinicians are contacted.

Recruitment Methods and Materials:

Study-related fliers written at a 5th-grade reading level in English and Spanish are posted in approved areas in SFHN/SFGH-affiliated primary care clinics. Because many patients may be too ill to come to frequent clinic appointments and to be interviewed or hear about the study in busy clinic waiting rooms, we include several recruitment strategies. Therefore, in addition, opt-out letters written at a 5th grade reading level in English and Spanish are mailed and describe the research study as well as provide a telephone number to opt-out. If a clinician gives us explicit permission to contact their patients, we will inform patients that their individual doctor gave us permission to contact them. If the clinician merely assents by not responding to multiple attempts to reach them by study staff, patients will be sent non-personalized letters from the study team. Although patients can opt out at any time, those who do not call study staff to decline participation within 1 week of the mailings are deemed eligible to be contacted to describe the study, assess willingness to participate and assess study eligibility. To standardize the timing between intervention exposure and primary care follow-up, we schedule patients for the baseline interview and exposure to PREPARE or the control intervention 1 to 3 weeks prior to their upcoming primary care appointment. Weekly administrative data pulls from the electronic health record identify patients with upcoming primary care appointments and are used to target patient recruitment efforts. Potential participants are then contacted in the clinic.

Patients who consent and enroll are paid $25 for a screening interview and $25 for a baseline interview as well as given a $10 taxi voucher to come back to follow-up interviews in person if they desire. Participants are also reimbursed $25 for each of the 1-week, 3, 6, and 12-month interviews.

Diverse, vulnerable populations are often difficult to recruit for research studies. We employ several strategies to enhance our recruitment. First, we attempt to hire individuals who have

experience with diverse populations and individuals who are bilingual (native Spanish-speaking) and bicultural. Furthermore, we conduct extensive sensitivity training with all research staff and require staff to use approved study scripts when speaking to patients. These study scripts and all study materials used for recruitment are vetted, updated and approved by both our patient advisory and clinical advisory boards. All materials and study scripts are written at a 5th grade reading level and are provided to patients in their preferred language (i.e., English or Spanish).

CONSENT PROCEDURES

We use a modified consent process that several co-authors designed for vulnerable populations.[19,26] Consent forms written at the 5th grade reading level are provided and read to participants in English or Spanish. This review is then followed by standardized "teach-to-goal" questions to ensure understanding. If potential participants cannot correctly complete the teach-back process after 3 attempts, the patient is deemed ineligible.

The consent form has been approved by the UCSF and SFGH Institutional Review Boards, the patient/clinical advisory board, and the Data and Safety Monitoring Board (DSMB). The consent form states the following for the purpose of the study: "Why is this study being done? Sometimes patients and their families have to make hard medical decisions. We want to design and test an easy-to-understand handout to help. This handout will help people think about their values, or what is most important to them in their life. It will also help prepare patients to make medical decisions." We use the word "handout" because, in pilot testing, both groups are given handout materials and written advance directives. For randomization we explain, "We will ask you to look over a handout and answer some questions about your experience with making medical decisions. There will be two groups that will be given different handouts. You will have a 50/50 chance of being in either group."

INTERVENTION AND COMPARISON CONDITIONS

PREPARE arm

As previously described, PREPARE is an easy-to-use, patient-centered, interactive website that is available in English or Spanish, is written at a 5th grade reading level, includes voice-overs of all text for the reading-impaired and closed-captioning of all videos for the hearing impaired (www.prepareforyourcare.org).[25,26] The conceptual framework for PREPARE has been previously published and is based based primarily on Social Cognitive Theory, [38,39] with elements from the Health Belief Model,[40] the Theory of Planned Behavior,[41] and Behavior Change Theory.[39,42] In these theories and in behavioral studies, modeling of behaviors helps people change their behavior. Successful behavioral change interventions model skills, enhance self-efficacy, and address perceived barriers,[43,44] especially literacy-appropriate interventions.[18] Modeling behaviors (as in PREPARE) can also improve patients' ability to communicate with clinicians and improve outcomes,[45,46] such as increased question asking behavior and a sense of control during a clinical visit,[46,47] an increased desire to participate in decision making, and even improved affect and functional status.[43,48-50] PREPARE incorporates these successful teaching methods through the modeling of behaviors in videos. Video and interactive websites are more powerful mediums to teach information and change behavior than written materials, especially for those with language/literacy barriers.[51-57] PREPARE includes a training and goal setting component which has been shown to be effective in changing outpatient behaviors, such as exercise.[58]

In the design of the PREPARE website, we included essential, theory-based health education strategies, such as the use of video modeling of ACP behaviors and tailored and interactive content based on patients' values and decision preferences. To ensure PREPARE is easy to read and understand, we use clear health communication principles (e.g., targeting text to the 5th grade reading level) informed by extensive formative research and cognitive interviewing

with the target population (i.e., racially and ethnically diverse older adults with limited health literacy and English proficiency) to ensure PREPARE content is acceptable to individuals from diverse cultural backgrounds.[25] The PREPARE website leads people through a 5-step ACP process that ranges from choosing a surrogate decision maker to asking their clinicians the right questions. While going through the website, PREPARE also helps individuals answer personal values questions about their medical care, and helps them create an action plan to engage in some form of ACP. Patient-generated action plans have been shown to help patients engage in other preventative and disease management activities in the outpatient setting.[59]

After the baseline interview, participants in the PREPARE arm review all 5 steps of the PREPARE website in English or Spanish in our research offices. Participants are asked to review PREPARE on their own and in its entirety. Research assistants are available to answer questions only if needed, but do not go through the website with the participants. At the end of the program, a summary of the patient's medical wishes and action plan are automatically generated from the PREPARE website in written format. This information along with the participant's PREPARE website login information is included in a take-home folder that also contains PREPARE information in pamphlet, booklet, and DVD format. We include PREPARE content in non-website formats because some patients may not have access to the internet at home. PREPARE arm participants are also given an easy-to-read advance directive in English or Spanish to review and consider completing.[18,60] Participants are asked to review the advance directive form for at least 5 minutes and up to 15 minutes in research offices, and then to take the form home to discuss with their potential surrogates and/or their clinicians. The time frame of 5-15 minutes was chosen because our goal is only to introduce the advance directive and allow participants to ask questions. The goal is not to have patients complete the form on the day of the study, before potential discussions with clinicians or surrogates, unless the participant would like to do so.

AD-only arm

Participants in the control arm are only given the easy-to-read advance directive, are asked to review it for at least 5 minutes and up to 15 minutes, and to take the form home to discuss with their potential surrogates and clinicians.

Both arms: Reminder of primary care appointments

One to 3 days before the patient's next scheduled primary care appointment, research staff call the PREPARE arm participants to remind them to bring in their study materials (i.e., action plan and advance directive) and to talk to their clinician about ACP. For the control arm, research staff members only remind patients about their upcoming appointment and do not provide additional encouragement about ACP.

RANDOMIZATION PROCEDURES

A statistician not involved in recruitment or data collection uses a computer-based random number generator to create a randomization scheme using block randomization by health literacy (adequate health literacy versus limited health literacy, as determined by a validated question concerning confidence with medical forms) and race/ethnicity (non-white versus white).[61] Random block sizes of 4, 6, and 8 are used to ensure an equal number of patients with limited health literacy in each group. Randomization information is associated with a unique patient identification number and is kept separate from other patient data. Due to the need to secure interview rooms for the duration of the baseline questionnaire and intervention (i.e., approximately 2 hours for the AD-only arm and 3 hours for the PREPARE arm), randomization occurred prior to scheduling a baseline interview.

BLINDING

Clinicians are blinded to patient group assignment. Although we obtain clinicians' permission to recruit their patients, the interventions are not described, and no clinician education is provided. Participants could not be blinded to the intervention; however, they are told during consent there is a "50/50 chance" of getting one of two different ACP guides, and the non-assigned intervention is not described. Because each group obtains ACP materials, such as the easy-to-read advance directive, blinding is enhanced. The research assistant who administers the intervention cannot be blinded to the study arm, but all follow-up outcome assessments are conducted by different and blinded staff. At the start of all follow-up interviews, participants are reminded not to discuss the study materials they reviewed with assistants recording if they became unblinded. If unblinding occurs, a different blinded assistant conducts all subsequent interviews.

INTERVENTION FIDELITY

All staff members are rigorously trained and are required to read and adhere to a standardized study protocol manual, standardized study scripts, and standardized checklists for each contact and interview with participants. Several training videos have also been developed for staff. Research staff are not allowed to conduct study tasks independently until they have reviewed all written and video training materials and can demonstrate complete mastery of all scripts and checklist items. In addition, a 10% random sample of all interviews is observed by senior research staff to ensure study fidelity.

DATA COLLECTION METHODS

Paper surveys are collected and entered into REDCap. REDCap is managed by the UCSF Academic Research Systems Team and is stored behind strong-string password protected firewalls on UCSF servers, not on individual laptops or desktops. All patients are given a unique, non-identifying patient identification number that is removed from any personally identifying

information (PII) or personal health information (PHI). All PII and PHI are stored in a Microsoft ACCESS database behind strong-string password protected firewalls on UCSF and SFGH servers. All paper files are stored in secure, locked research offices in secure, locked file cabinets.

FOLLOW-UP AND RETENTION:

We conduct follow-up interviews one week and 3, 6, and 12-months after the primary care visit in the clinic, by phone. We utilize several measures to help ensure follow-up. Each follow-up interview takes between 30 to 45 minutes and participants are reimbursed $25.

Method of contact for follow-up surveys:

Upon enrollment, we ask participants to provide alternative phone numbers (e.g., cell or work numbers) and one to three additional phone numbers of close contacts who may know how to contact the patient in the event our study staff is unable to reach them. Many patients in safety net settings are marginally housed, have intermittent phone access, and may change locations and phone numbers during the study period. We also ask participants if they prefer a text message or an email to schedule follow-up visits and will use their preferred mode of communication. If these other modes of communication fail, we send out reminder letters. If needed, we also attempt to contact patients during scheduled clinic visits.

Reminders for the primary care visit:

Participants receive a brief reminder call one to 3 days before their next primary care visit. Participants in the AD-only arm are reminded to come to their scheduled appointment while participants in the PREPARE arm are reminded of their appointment and to bring the PREPARE materials to the visit.

Reminders for study interviews:

For all follow-up interviews, participants in both arms receive reminders of their upcoming study interview by phone or in person.

Ascertaining reasons for loss of follow-up or withdrawal: For participants who want to withdraw, we ask them why in open-ended questions. If they cannot provide an answer, we prompt them from a list of reasons we obtained from prior advance care planning trials, such as the study is too long, they are too busy, the study topic is too upsetting, they are too ill, etc.[62]

MEASURES

Overview

Because ACP ideally is a process that occurs over time, we felt it important to measure a full range of ACP measures including ACP documentation (primary outcome) over time, and several behavior change constructs and several additional ACP actions over a 12-month period (secondary outcomes). The main outcome measures are described in detail below.

Primary Outcome

The primary outcome is documentation of ACP wishes in the SFHN/SFGH medical record. ACP documentation for the purposes of this study includes the easy-to-read advance directive or other valid advance directives or living wills, a durable power of attorney for health care document (DPOAHC), a Physicians Orders of Life Sustaining Treatment form, or other documentation of discussions concerning patients' wishes for medical care (i.e., documentation of oral directives by a physician or notes describing patients' goals for medical care by clinicians).

We assess baseline and 12-month ACP documentation rates and the date of documentation to determine the length of time from study enrollment to subsequent documentation. Patients in our study are enrolled, randomized, and exposed to the intervention 1 to 3 weeks prior to a primary care appointment. ACP documentation is timed to the date of intervention exposure as patients may have engaged in ACP prior to seeing their primary care provider. The patient-reported outcomes in the follow-up surveys (1 week, 3, 6, and 12-months), however, are timed to the primary care visit because those questions concern engagement in discussions with clinicians (see secondary outcomes below).

Because legal forms and documented discussions can be used to direct medical care, we created a composite variable of any ACP documentation (forms and/or discussions); we also plan to report the percentage of forms and discussions separately. All medical review data is double coded by 2 independent, blinded research assistants. Discrepancies are adjudicated by the principal investigator (R.L.S.).

Secondary Outcomes

Main Patient-Reported Outcome

The main patient-reported secondary outcome, the validated Advance Care Planning Engagement Survey,[25-27] was chosen to measure the full process of ACP. The Advance Care Planning Engagement Survey measures both ACP Behavior Change Processes, such as knowledge, contemplation, self-efficacy, and readiness on a validated 57-item scale. The ACP Behavior Change Process scale is measured on a 5-point Likert scale and average 5-point scores will be calculated. We will also measure ACP actions on the validated 25-item Action scale, which assesses ACP activities (yes or no) such as identifying a surrogate decision maker, identifying values and goals for medical care, choosing the level of leeway in surrogate decision making, discussing one's wishes with clinicians and surrogates, and documenting one's wishes

in an advance directive. Validity and reliability of the ACP Engagement Survey, as well as the questionnaire's ability to detect change in response to an ACP intervention, have been previously described.[25-27]

Feasibility and Satisfaction

To evaluate whether and how PREPARE will be used in clinical practice and in the community, we also assess acceptability of the PREPARE website compared to an advance directive alone using validated scales of ease-of-use (10-point scale, "On a scale of 1 to 10, with 1 being very hard and 10 being very easy, how easy was it to use this guide?") and satisfaction (comfort: "How comfortable were you viewing this guide?", helpfulness: "How helpful was this guide?", and recommendations: "How likely are you to recommend this guide to others?" assessed on a 5-point Likert scale (not-at-all to extremely) from our prior work.[18] For the PREPARE arm only, and at the end of the 12-month interview and after unblinding, we also ask how likely patients are to recommend the PREPARE intervention to others.[63]

Adverse Event Outcomes

In addition, to ensure that the PREPARE program does not cause undue harm, we also assess both depression[64,65] and anxiety.[66,67] We administer the Patient Health Questionnaire (PHQ)-4 at baseline and at each follow-up interview.[68] The PHQ-4 includes the PHQ-2 for depression and the Generalized Anxiety Disorder (GAD)-2 anxiety screening tool. A score of 3 or greater on a 0 to 6 scale suggests possible depression or anxiety.

Potential Mediating or Moderating Variables & Participant Characteristics

Based on the previously published conceptual framework of PREPARE,[25] we also hypothesize that PREPARE efficacy may vary across several moderator or mediator variables (e.g., health literacy using the validated Short form Test of Functional Health Literacy in Adults s-TOFHLA,

scores 0-36[69] and dichotomized to limited = 0-22 & adequate = 23-36, and patient's desired role in decision making with the medical provider using the validated Decision Control Preferences Scale (i.e., wants to make their own decision versus wants doctors/family to make decisions for them).[70] We also hypothesize that PREPARE efficacy may be affected by several confounding variables (e.g., self-rated health, "How would you rate your health?" (5-point Likert)[71,72] dichotomized as fair-to-poor and good-to-excellent and past experiences with ACP including prior documentation of legal forms and documented discussions. We will also assess a full range of patient-reported characteristics, as these factors may impact patient-clinician communication,[73,74] such as age ("What is your date of birth?"), self-reported gender ("What gender do you consider yourself to be? male, female transgender, other"), finances (able to make ends meet versus not make ends meet), having a potential surrogate decision maker or not, education ("What is the highest educational level you have completed?" less than or equal to high school or greater than high school), internet access in the home (yes or no), and religiosity and spirituality (i.e., "How religious/spiritual do you consider yourself to be?" on 5-point Likert scale from not-at-all to extremely).

STATISTICAL ANALYSIS PLAN

Our primary analyses will compare change in ACP documentation between study arms from baseline to 12 months. Secondary outcomes will include ACP Engagement with respect to 5 ACP Actions (yes/no and a 0-25-point scale) and Behavior Change Process scores (average 5-point Likert scores) from baseline to 1 week, and 3, 6, and 12 months. Variables will be assessed for distributional and outlier values using standard summary statistics. Baseline comparability will be assessed between groups using unpaired t-tests, Chi-square tests or Fisher's exact tests. We will use intention-to-treat analysis using SAS version 9.4 (SAS Institute Inc.) and STATA 15.0 (College Station, TX). All p-values will be 2-tailed and set at .05 for the primary outcome. To compare outcomes between the two arms longitudinally, we will use mixed

effects linear, Poisson, or negative binomial regression for continuous measures and mixed effects logistic regression for dichotomous measures. The mixed effects models will include fixed effects for the primary modeling terms of time (baseline and 12 months for ACP documentation and baseline and 1 week, 3 months, 6 months, and 12 months for ACP Engagement with time modeled using dummy variables to allow for non-linearity); arm (AD-only versus PREPARE); an interaction term of study arm and time; and a random effect for subjects. We will adjust for the randomization blocking factors limited vs. adequate literacy,[75] and any predictor variables that differ between arms. All models also will include random physician intercepts to account for nesting of patients within physicians.

For moderator analysis, we will test for interactions by adding interaction terms to the group by time variable for health literacy (limited versus adequate) controlling for prior ACP documentation and clustering effects by clinician. All other interaction terms are adjusted for health literacy (randomization blocking variable) prior ACP documentation and clustering effects by clinician. Additional interaction terms to be added to the group by time variable include decision control preferences for making decisions (i.e., makes own decisions versus doctor makes decisions), age (i.e., < 65 years versus ≥65 years of age), sex/gender (i.e., self-reported man versus woman), race/ethnicity (i.e., white versus non-white), health status (i.e., good-to-excellent versus fair-to-poor), presence of a potential surrogate (i.e., yes versus no), and internet access at home (i.e., yes versus no). For Spanish-speakers, we will also asses patient-clinician language (concordance vs. discordance). A p-value for interaction <0.05 is considered significant.

Missing data for the primary outcome will be assessed. If there is 10% or more of missing data, we will use a mean imputation approach and all available data will be included in mixed-effects

models. We will assess whether any research staff member became unblinded during follow-up assessment and conduct sensitivity analysis as needed.

SAMPLE SIZE AND POWER CALCULATIONS

We will measure a full range of ACP behaviors including discussions. However, written advance directive completion of legal forms is a primary outcome and is the most well-studied.[76] Power from longitudinal analyses with repeated measures will be stronger, but to be conservative, we consider power for a single post-intervention time point (e.g., 12 months). A recent meta-analysis of written advance directive documentation studies demonstrated a pooled effect size of 0.50 (95% CI; 0.17 -0.83),[76] as did an RCT of an ACP workbook that included both behavior change constructs and a social work visit,[77] and our prior RCT of an easy-to-read AD at SFGH which showed an increased AD completion rate from 7% to 15%.[18] Because both the intervention and control arm will receive the easy-to-read advance directive, we assume that both arms will have an advance directive completion rate of ≤ 15%. Based on prior studies, we assume PREPARE will result in additional benefit of advance directive completion with a minimum effect size of 0.5 (two-fold increase) above 15%. A sample of 350, (175 per arm), will afford us 92% power (2-tailed alpha of 0.05) to detect a difference of advance directive completion rates of 15% in controls vs. 30% in the PREPARE arm and 80% power to detect a difference of 15% vs. 27%. Power is also expected to be strong for the ACP behavioral change scale outcomes (preliminary data demonstrated a pre-to-post improvement of 0.5 SD).[25] With a conservative assumption that controls will improve by 0.1 to 0.2 SD, we will have 85% to 98% power, respectively, to conclude that the improvement is better in the PREPARE arm. We expect a 15% drop out rate at 12 months based on our prior randomized, controlled trial at SFGH,[18] and will therefore attempt to recruit 402 patients, or 201 in each arm for each language (English and Spanish) for a total recruitment of 804 patients.

Our sample size will also allow adequate power to detect clinically important interactions based on potential moderators (literacy, control preferences, language concordance) for our outcomes. In a prior trial of an easy-to-read advance directive in the same patient population with only 200 patients, we found significant interactions for literacy.[8] Thus, if we consider the power scenario of the control group ACP documentation rate of 15% and the PREPARE group of 28%, and suppose the control group rate is the same (15%) for both levels of the moderating factor, then for a moderating factor split of 1:1, we would have 80% power to detect an interaction. If the PREPARE arm ACP documentation rate is 18% for one level of the factor and 40% for the other, this corresponds to a relative rate of ACP documentation of 2.2 times as high for one level of the factor compared to the other. A 2:1 split of the moderating factor still allows detection of a 2.4-fold increase in the relative rate of documentation. Power to detect interactions will likely be stronger for continuous outcomes (e.g. engagement/behavioral scales).

ETHICS AND ADVISORY COMMITTEES

This study is approved by the University of California, San Francisco (UCSF) (IRB reference #13-10847). This study is guided by a Patient-Clinical Stakeholder Advisory Board that is comprised of patients and patient advocates (including native Spanish-speakers), surrogates, and SFHN/SFGH primary care clinic staff and medical directors. It is also guided by a DSMB consisting of 4 experts in randomized trials, human subjects research and consent, vulnerable populations, palliative care, advance care planning, and biostatistics. Both advisory groups will review and approve all study protocols and related materials. In addition, we continue to meet with both groups every 4-6 months to review the progress of the trial, make suggestions for recruitment, review any potentially adverse events, and ensure that we are following our study protocols in a way that protects vulnerable patient populations.

HUMAN SUBJECTS PROTECTIONS

Protection of the rights and welfare of participants:

All study staff are required to take annual training regarding the rights and protections of research participants. Additionally, weekly study team meetings will ensure that all study staff are following the research protocol and that all study participants are consented according to our study protocol.

Furthermore, our consent process ensures that study participants have a clear understanding of the study and understand that they can choose to not participate in the study at any point in time, and that the care they receive will not be affected by declining to participate in our study. Our consent process involves using a consent form written below a 6th-grade reading level, reading the form to potential subjects verbatim, allowing time for questions and discussion, and then assessing comprehension using teach-to-goal. If questions are not answered correctly, repeated education and reassessment of comprehension are continued until complete comprehension is achieved. If subjects take more than three passes through the comprehension assessment, formal assessment for cognitive impairment will be completed. If patients are found to be cognitively impaired, they are excluded from the study. If they are not cognitively impaired, we will re-do teach back once more, after which the participant will be deemed ineligible for the study if they are unable to demonstrate comprehension of the study.

Additionally, we include UCSF Clinical Research Office contact information on all consent forms as required for all non-biomedical studies.

Steps taken to minimize risks to subjects:

We have developed a modified research consent process that has been shown to be successful in vulnerable patient populations as described above.[19] All study fliers, consent forms, and questionnaires are read to the subjects in their entirety by native English- and Spanish-speaking

research staff. Participants are reminded that they can opt out of the study at any time. All study materials are in an easy-to-read (5th grade reading level, large 14-point font) format. The consent materials and the study interviews are conducted in the language the participant is most comfortable speaking (English or Spanish).

This study will employ research assistants who are fluent in English or Spanish. Only fluent research assistants will be in contact and will communicate with Spanish-speaking participants. We will also ensure that all study materials are accurately translated into Spanish by having them initially translated from English to Spanish by native Spanish- speakers. We will then have them back translated into English to ensure accuracy. Finally, we will have the final translated documents reviewed for accuracy by third party native Spanish- speakers. To help participants follow along during the interview, they may review a large font Participant Version of the survey at baseline and all follow-ups that can be reviewed while the research assistant is asking research questions verbatim. We use 14-point font and color-coded, standardized, large font response options to help with understanding.

Data security:

- Data are stored securely in the encrypted, secure UCSF MyResearch environment
- Data are coded; data key is kept separately and securely
- Data are kept in a locked file cabinet
- Data are kept in a locked office or suite
- Electronic data are protected with a password
- Data are stored on a secure network
- Data are collected/stored using REDCap or REDCap Survey

Measures to ensure confidentiality and protect identifiers from improper disclosure

Risks to subjects are minimal and may include loss of confidentiality and psychological discomfort about discussing end-of-life issues. Subjects are assured that their answers to study questions will not be directly linked to their names. Instead, any identifying information is coded and separated from the data. The identifying information will only be known to the primary investigators but will not be used in data analysis. In addition, signed consent forms are kept in locked file cabinets and kept separate from the data collection instruments. Study subjects are also reminded that the information obtained will not be shared with their providers except in non-identifying aggregate form at the end of the study. We also make clear that the responses to the PREPARE guide are only for research purposes and will not be shared with their clinicians or put in their medical record.

We will store all study materials in locked offices and locked storage cabinets. We will utilize UCSF MyResearch and REDCap to enter and maintain data in a secure environment. The paper files are stored in secure, locked research offices in secure, locked file cabinets.

As some of the questions concerning end-of-life may cause psychological discomfort for some study subjects, subjects are reminded at the beginning of the interview of their right to refuse to answer any and all questions and their right to terminate the interview at any time. We will also reassure subjects that if they choose not to be in the study or choose to terminate the interview, it will not change the medical care that they normally receive from their clinic or their clinician. In addition, we will reiterate that the information shared within the research interview will not be shared with their clinicians or used in medical care. However, subjects can take home a copy of the PREPARE guide with them and bring it back to their clinicians if they wish. Subjects are given the name and number of the primary investigator and may call if they have questions or are concerned about their participation in the study.

Required reportable information:

As these interviews may be completed in people's home and, in the interviews, we are asking patients to describe their experiences and opinions, it is possible that reportable events such as elder abuse, suicidal or homicidal ideation may be detected. If they are detected, they will be handled according to the American Psychological Association code of ethics. If elder abuse is suspected, the participant will be encouraged to take steps to ensure their safety. They will be offered contact information for local supportive services and informed that the concerns will be discussed with the elder abuse hotline for assistance. When there are concerns about self-harm or harm to others, severity of harm will be assessed. Participants will be offered local support services and officials will be notified as necessary.

DATA SAFETY MONITORITY PLAN

Monitoring will focus on recruitment, baseline comparability of treatment groups, protocol adherence, completeness of data, accrual of primary endpoint data, safety, and follow-up rates. This monitoring will provide the basis for monthly review by the study investigators, review by the SFGH Patient-Clinician Advisory Committee, and Data Safety and Monitoring Board (DSMB), and yearly reporting to our IRBs. We will implement methods of verifying entered data and of quality control. All study materials data are kept on secure, password-protected, encrypted servers. All consent materials and any identifying information are kept in locked cabinets within locked offices, on password-protected, encrypted servers, on card-key protected research floors. Dr. Sudore, will be directly responsible for identifying and immediately reporting all adverse events to the IRBs Privacy Officers, and funding agency as appropriate. The SFGH Patient-Clinician Advisory Committee will ensure participant safety in the clinic and will meet up to 4 times per year. The formal DSMB includes 4 experts in randomized trials, human subjects research and consent, vulnerable populations, palliative care, advance care planning, and biostatistics. The DSMB will review and approve the research protocol and plans for data and

safety monitoring; and assess data quality; participant recruitment, accrual and retention; baseline comparability of treatment groups, accrual of primary endpoints; and participant safety (e.g., adverse events, protocol violations). They will also develop stopping rules for the trial. The DSMB will meet up to 4 times per year.

CHARTER OF DATA SAFETY MONITORING BOARD

The Data and Safety Monitoring Board (DSMB) will act in an advisory capacity to the National Institute of Aging (NIA) and PCORI to monitor participant safety, data quality and evaluate the progress of the study. Dr. Sudore, University of California, San Francisco is conducting a comparative trial of two advance care planning interventions among English- and Spanish-speakers. The DSMB for this study includes 2 outside clinicians with expertise in randomized control trials(RCTs) and an outside biostatistician. The DSMB will review and approve the research protocol and plans for data and safety monitoring; and assess data quality; participant recruitment, accrual and retention; baseline comparability of treatment groups, accrual of primary endpoints; and participant safety (e.g., adverse events, protocol violations). They will also develop stopping rules for the trial. The DSMB will meet 2 and up to 4 times per year.

DSMB Responsibilities

The DSMB responsibilities are to:

- review the research protocol, informed consent documents and plans for data safety and monitoring;
- advise the NIA on the readiness of the study staff to initiate recruitment;
- evaluate the progress of the trial, including periodic assessments of data quality and timeliness, recruitment, accrual and retention, participant risk versus benefit, performance of the trial sites, and other factors that can affect study outcome;

- consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the trial;
- review study performance, make recommendations and assist in the resolution of problems reported by the Principal Investigator;
- protect the safety of the study participants;
- report to NIA on the safety and progress of the trial;
- make recommendations to the NIA and the Principal Investigator concerning continuation, termination or other modifications of the trial based on the observed beneficial or adverse effects of the treatment under study;
- if appropriate, review interim analyses in accordance with stopping rules, which are clearly defined in advance of data analysis and have the approval of the DSMB;
- ensure the confidentiality of the study data and the results of monitoring; and,
- assist the NIA by commenting on any problems with study conduct, enrollment, sample size and/or data collection.

The DSMB will discharge itself from its duties when the last participant completes the study.

Membership

The DSMB includes experts in or representatives of the fields of:
relevant clinical expertise,
clinical trial methodology, and
biostatistics.

The DSMB members:

- In addition to the NIA program officer members include:
- Dr. David Bekelman, MD, MPH, an internist, psychiatrist, and palliative medicine physician at the University of Colorado School of Medicine and is an expert in health communication and medical decision making
- Dr. Nathan Goldstein, MD, a geriatrician and a national expert in palliative care, communication, and medical decision making at Mt. Sinai School of Medicine,
- Dr. James Wiley, PhD a statistician and Professor in the Institute for Health Policy Studies at the University of California, San Francisco. Dr. Wiley has extensive experience with RCTs and working with safety net populations. Although Dr. Wiley is at UCSF, he does not otherwise work with Dr. Sudore. Membership have no financial, scientific, or other conflict of interest with the trial.

Written documentation attesting to absence of conflict of interest has been obtained.

Dr. Nathan Goldstein, Mount Sinai School of Medicine, has been appointed by NIA to serve as the Chairperson and is responsible for overseeing the meetings, developing the agenda in consultation with the NIA Program Official and the Principal Investigator. The Chair is the contact person for the DSMB. The University of California, San Francisco shall provide the logistical management and support of the DSMB. Dr. Nathan Goldstein is also the safety officer and contact person for serious adverse event reporting. A log of all potential adverse events and protocol violations will be kept and reviewed quarterly by the DSMB. Procedures for notifying the Chair of the DSMB and the NIA Program Official will be discussed and agreed upon at the first meeting.

Board Process

At the first meeting the DSMB will discuss the protocol, suggest modifications, and establish guidelines to study monitoring by the Board. The DSMB Chairperson in consultation with the Principal Investigator and the NIA Program Official will prepare the agenda to address the review of study materials, modifications to the study protocol and informed consent document, initiation of the trial, appointment of a safety officer, as needed, reporting of adverse events, statistical analysis plan including interim analysis and stopping rules, etc.

Meetings of the DSMB will be held 2-4 times per year at the call of the Chairperson and / or NIA Program Official to ensure patient safety and to review stopping rules for the trial. The NIA Program Official or designee will attend most of the meetings. An emergency meeting of the DSMB may be called at any time by the Chair or by the NIA should participant safety questions or other unanticipated problems arise.

Meetings are closed to the public because discussions may address confidential participant data. Meetings are attended by the Principal Investigator and members of his/her staff. Meetings may be convened as conference calls as well as in-person.

Meeting Format

Each meeting must include a recommendation to continue or to terminate the study and whether the DSMB has any concerns about participant safety made by a formal DSMB majority or unanimous vote. Should the DSMB decide to issue a termination recommendation, the full vote of the DSMB is required. In the event of a split vote, majority vote will rule and a minority report should be appended. The DSMB Chair provides the tiebreaking vote in the event of a 50-50 split vote.

A recommendation to terminate the study may be made by the DSMB at any time by majority vote. The Chair should provide such a recommendation to the NIA immediately by telephone and email. After the NIA Director makes a decision about whether to accept or decline the DSMB recommendation to terminate the study, the PI is immediately informed about his decision.

Meeting Materials

DSMB interim report templates will be prepared by the study staff, to be reviewed by the DSMB members at each meeting. The reports will list the study aims, the status of the study, and summarize safety data.

Reports from the DSMB

A formal report containing the recommendations for continuation or modifications of the study will be prepared by the DSMB Chairperson, NIA Program Official or its designee. The draft report will be sent to the DSMB members for review and approval.

Confidentiality

All materials, discussions and proceedings of the DSMB are completely confidential. Members and other participants in DSMB meetings are expected to maintain confidentiality.

PATIENT-CLINICAN STAKEHOLDER ADVISORY COMMITTEE ROLE

This study is guided by a Patient-Clinical Stakeholder Advisory Board that is comprised of patients and patient advocates (including native Spanish-speakers), surrogates, and SFHN/SFGH primary care clinic staff and medical directors. These individuals are paid key personnel on the study and have agreed to meet up to 4 times per year to oversee all aspects of

the study. Native Spanish-speaking staff will be present to translate for our Spanish-speaking patient stakeholders during advisory meetings. All study materials will be translated into Spanish. The advisory committee will be involved in providing ongoing advice about the following important study related activities:

- Recruitment, including study scripts, fliers, methods
- Eligibility and exclusion
- Patient safety and research staff safety
- Clinic workflow and clinical champions
- Informed consent
- Research outcomes
- Presentation of findings
- Dissemination of results

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Protocol

Final Version

September 2017

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CLINICALTRIALS.GOV INFORMATION

This trial is registered at ClinicalTrials.gov: NCT01990235 for English-speakers, registered on November 4th, 2013 and NCT02072941 for Spanish-speakers, registered on February 4th, 2014.

INTRODUCTION AND RATIONALE

Background

The population is aging,[1,2] and the prevalence of chronic disease is increasing, especially among underserved and vulnerable populations (i.e., economically disadvantaged, racial and ethnic minorities, the uninsured, etc.).[3] A critical aspect of chronic and serious disease management is advance care planning (ACP), a process whereby patients plan for their future medical care. Traditionally, advance directives have been the main focus of ACP, but unfortunately, most are written with complex, legal language.[4] This lack of attention to limited health literacy and limited English proficiency may explain why advance directives are often not completed and may explain, in part, why less than 20% of racially and ethnically diverse, older adults engage in advance care planning (ACP) by the end-of-life.[5-8]

Furthermore, for ethnic minorities, a population rapidly increasing in the U.S., medical decisions are often complicated by a lack of trust and perceived racism.[9-11] Ethnic minorities are also more likely to prefer aggressive treatment, mistrust advance directives, and have non-autonomous views on decision making (i.e., prefer that family and doctors make medical decisions for

them).[9,12-16] Hispanics/Latinos account for 15% of the U.S. population, a proportion projected to grow to 30% by 2050.[1,2] Spanish-speaking patients face significant communication barriers, and literacy- and language-appropriate ACP tools that address unique aspects of Latino culture (e.g., *familismo* or a strong commitment and orientation to the family) are lacking.[10] In addition, the mean reading level in the U.S. is only at the 8th grade level, and for adults over 65 years of age it is only at the 5th grade level.[17,18] Patients with limited literacy often lack self-efficacy to communicate their wishes or ask questions,[19] and the combination of limited literacy and limited English-proficiency results in low satisfaction with doctor-patient communication and decision making.[20-22] However, studies show that patients can be motivated to take action in response to culturally- and linguistically-appropriate information they trust and can understand.[8,23]

To address these gaps in advance care planning and shortcomings of advance directives, we developed a novel, comprehensive paradigm of ACP focused on preparing patients to identify their wishes, communicate with surrogate decision makers and clinicians, and make complex, decisions over the course of chronic and serious illness.[24] This approach recognizes patients' wishes change based on changing clinical contexts and that advance directives are but one tool to be used to inform in-the-moment decision making.[25,26] To address the gaps in advance care planning for racially and ethnically diverse older adults, and based on the new comprehensive ACP paradigm, we created the interactive, patient-centered PREPARE website (prepareforyourcare.org) in English and Spanish that is culturally, linguistically, and literacy-appropriate. PREPARE has been shown in pilot studies among English-speakers to help older adults engage in the ACP process, but it has yet to be tested in a randomized trial with both English- and Spanish-speaking older adults.[27] Both the new ACP paradigm and the PREPARE intervention have been described in detail elsewhere.[27,28] In addition, a description of a related trial of the efficacy of PREPARE among U.S. Veterans describes the theoretical framework underlying the PREPARE website.[28]

PRELIMINARY STUDIES

We have experience conducting RCTs among diverse, older adults at the San Francisco Health Network (SFHN) primary care clinics.[8] Dr. Sudore designed and tested an AD written at a 5th grade reading level among 205 chronically ill, diverse, older adults from Zuckerberg San Francisco General Hospital (ZSFG) with a 6-month follow-up of 85%. The AD was preferred over a standard AD, with significant interactions for limited literacy (e.g., higher preference rates in patients with limited literacy). It also resulted in greater 6-month AD completion rates (15% vs. 7%, p =.03), doubling the rates from baseline. This AD has been adopted as the official AD for ZSFG and is being disseminated in California. It will serve as the active control.

We designed and tested an informed consent process for diverse, older adults with limited literacy.[29] We found that many patients do not understand simplified consent information and were unsure how to ask questions. But, informed decisions can be improved by providing both easy-to-read materials and a teach-back method. We will use this interactive consent method for this study.

Multiple steps of the ACP process:[30] We found that most patients go through a series of ACP behavioral steps. Six months after exposure to the easy-to-read AD, 61% of older adults contemplated ACP, 56% discussed ACP with family or friends and 22% with clinicians, and 13% completed an AD. This work shows that measuring a full range of ACP outcomes, in addition to ADs, and associated behavior change steps (contemplation to action) is important and informs our study outcomes. Previously described barriers to ACP, such as not wanting to burden family,[31] are addressed in PREPARE.

Evidence supporting the new ACP paradigm and content of PREPARE:[32] We completed 13 focus groups with 69 diverse, English- and Spanish-speaking older patients (mean age 78 +/- 8, 61% non- White) and surrogates (mean age 57 +/- 10, 91% non-White) from safety-net settings

who reported making serious medical decisions. We used semi-structured interviews to ask about what best prepared them for decision making. Qualitative analysis identified 5 overarching themes, beyond ADs, that prepared patients and surrogates for decision making: (1) choose surrogates wisely and verify they know their role, (2) identify goals based on past experiences and personal values, (3) decide whether to grant leeway in surrogate decision making, (4) inform other family and friends of one's wishes to prevent conflict, and (5) ask clinicians questions. These themes have been incorporated as educational domains of PREPARE.

Validity and reliability of the survey to measure ACP engagement: Surveys were designed with input from Co-Is and extensive cognitive interviews to measure discrete ACP actions (i.e., main outcomes: ACP discussions, AD completion,) and ACP behavior change (e.g., contemplation, self-efficacy, readiness). We recruited 50 older adults, aged ≥ 60 years with ≥ 2 illnesses (32% female, 42% non-White). Internal consistency 7-day test-retest reliability, and discriminant validity (scores compared to healthy young adults – 50% female, 75% non-White) was high. Scores did not differ by race/ethnicity or literacy, $p>.05$. We will also use validated surveys on ACP attitudes and methods to classify patients into behavior change categories.[33,34]

Preliminary evidence that PREPARE is beneficial. In a recent pilot,[27] we recruited 43 diverse, older adults from low-income senior centers. All subjects rated PREPARE easy to use (mean 9/10-point scale). Pre to post ACP behavior change scores from our validated surveys (0-124 points) increased from 72 ± 33 SD to 87 ± 22, a 15-point increase and an effect size of 0.5.

Vulnerable populations have unique needs. The aforementioned pilot demonstrated that, unlike our work with Veterans, patients in safety-net settings are less trustful of research and require in-person recruitment. In addition, these patients are often socially isolated and require tailored ACP for persons without surrogates or families. They also lack ready access to health information and ancillary support such as social workers or nurses necessitating access to ACP

outside of the clinical environment. These findings add further evidence for the need to tailor PREPARE for vulnerable populations and to test PREPARE within safety-net settings.

PREPARE has been shown to increase ACP Documentation and Engagement among Veterans. A prior trial of PREPARE was conducted among 414 Veterans.[35] The mean age of the cohort was 71.1 (7.8) years, 91% were men, 57% were white, 20% had limited literacy, 29% reported fair-to-poor health status, and 51% had evidence of prior ACP documentation. The follow-up time point was 6 months and there was a 90% retention rate. There were no differences in demographic characteristics between study arms. In this VA population, advance care planning documentation 6 months after enrollment was higher in the PREPARE arm vs the AD-alone arm (adjusted 35%vs 25%; odds ratio, 1.61 [95%CI, 1.03-2.51]; P = .04). PREPARE also resulted in higher self-reported ACP engagement at each follow-up, including higher process and action scores; P <.001 at each follow-up). These findings add further evidence of the validity of PREPARE. However, PREPARE has never been tested among diverse, English- and Spanish-speaking older adults in a safety-net setting.

OVERVIEW OF THE TRIAL DESIGN

Study overview:

This study is a randomized, controlled trial that uses blinded outcome ascertainment to determine the efficacy of the ACP PREPARE website to engage ethnically diverse English- and Spanish-speaking older primary care patients in the ACP process.[36] First, we obtained a Health Insurance Portability and Accountability Act waiver to identify individuals who meet our inclusion/exclusion criteria and have upcoming primary care appointments. Administrative data and chart review are used to determine potentially eligible patients (Figure, Study Flow Chart).

Then primary care clinicians' permission is obtained to allow the study team to inform their patients about the study. Patients are then recruited, screened for eligibility and scheduled for a baseline interview before an upcoming primary care appointment. To standardize the timing of exposure to the intervention and primary care follow-up, study participants are scheduled for baseline procedures 1-3 weeks prior to an upcoming primary care appointment.[28]

Next, informed consent is obtained, and those patients who provide consent are randomized to the PREPARE intervention arm (i.e., the PREPARE website with action plan exercises plus an easy-to-read advance directive plus PREPARE materials to take home, which include a website login, and a PREPARE pamphlet, booklet, and DVD) or the control arm (i.e., an easy-to-read advance directive alone). See Study Flow Figure and a full description of the intervention below.

We then conduct blinded outcome ascertainment by performing chart reviews to determine ACP documentation at baseline and at the end of the study. We also conduct blinded outcome ascertainment using patient surveys at 1 week, and 3, 6, and 12 months after the primary care appointment. We are choosing an active control arm (i.e., an easy-to-read advance directive) because we believe provision of an advance directive for chronically and seriously ill older patients should be the standard of care, even if it is not often "usual" care in clinical practice.[8] In addition, the easy-to-read advance directive used in this study has been adopted by the San Francisco Health Network (SFHN) and Zuckerberg San Francisco General Hospital (ZSFG) and is available in the primary care clinics.

Research Aims and Study Hypotheses:

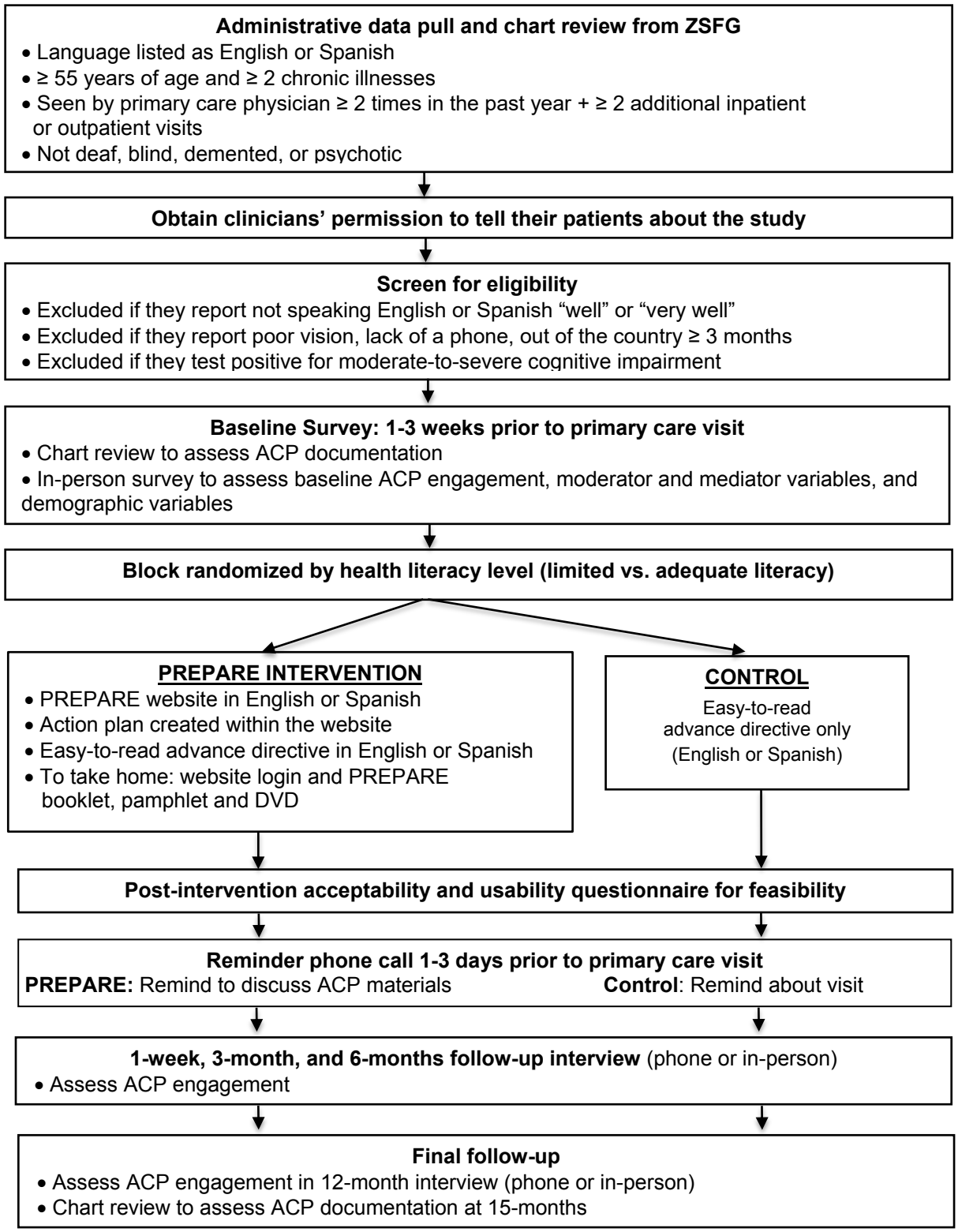
The aims of this study are to (1) To determine the efficacy of PREPARE to engage diverse, English- and Spanish-speaking older adults with chronic illness in advance care planning (ACP) compared to controls (AD only) and (2) To determine whether PREPARE efficacy varies by

race/ethnicity, literacy, clinician-patient language concordance, and patient's desired role in decision making.[36]

Our primary hypothesis is that the PREPARE program plus an easy-to-read advance directive will result in greater documentation of ACP wishes, including advance directives and documentation of ACP discussions in the medical record, than an easy-to-read advance directive alone in elderly populations with chronic illness.

Our secondary hypotheses are that, compared to an advance directive alone, PREPARE will result in more engagement in behavior change processes concerning ACP, including increased self-efficacy and readiness, as well as greater engagement in a full range of ACP actions, including discussions with surrogate decision makers and other trusted family and friends. Secondary outcomes will be ascertained using validated surveys.[33,37,38] We also hypothesize that PREPARE will result in improved satisfaction with patient-doctor communication and informed medical decision making and that PREPARE efficacy may vary across moderator variables such as patient health literacy, clinician-patient language concordance, and patients' desired role in decision making.

Figure 1: PREPARE Study Flow Diagram



STUDY SETTING

Recruitment for this randomized trial is occurring in 4 separate primary care clinics associated with the San Francisco Health Network (SFHN) and the Zuckerberg San Francisco General Hospital (ZSFG) in San Francisco, California. These 4 clinics are housed in 3 separate physical locations in San Francisco. ZSFG is an urban, public hospital that, with the SFHN, serves racially and ethnically diverse, low-income and indigent patients; 30% of patients are Spanish-speaking.[8]

PARTICIPANTS AND ELIGIBILITY AND EXCLUSION CRITERIA

There are no inclusion or exclusion criteria based on gender, race or ethnicity. We assess eligibility in person or over the phone. Older adults are included in this study if they self-report speaking English or Spanish “well” or “very well”; are 55 years of age or older; have ≥ 2 chronic illnesses determined by chart review; have seen a primary care clinician (physician, nurse practitioner, or physician assistant) at ZSFG/SFHN-affiliated primary care clinics ≥ 2 times in the past year (an indication of established primary care); and have had ≥ 2 additional outpatient or inpatient visits in the past year (an indication of severity of illness). Their primary care clinician must also give us permission to contact them to tell them about the study.

We are recruiting patients ≥ 55 years of age (rather than ≥ 65) because adults in safety net settings experience accelerated aging, functional decline, and sequelae of chronic disease, necessitating decision making and ACP at a younger age than patients with higher socioeconomic status.[39,40] The goal is to start ACP early to change the trajectory of decision making and care over the course of illness. Our inclusion criteria of ≥ 2 primary care visits and ≥ 2 additional visits in the past year ensures patients have established primary care and access care frequently. This will enhance recruitment and follow-up.

Patients will be excluded if their clinician is a principal investigator, co-investigator or clinician-member of the Patient-Clinician Advisory Board or they had been enrolled in a previous pilot study of the PREPARE website or been exposed to the PREPARE study materials. They will also be excluded if they have medical record documentation of being deaf, blind, having dementia, or being psychotic or are deemed by their clinician to be too mentally or physically ill to participate. Participants will also be excluded if they have evidence of active drug or alcohol abuse within the past 3 months determined by clinician assessment, self-report, chart review or research staff assessment. Through in-person or phone screening by study staff, patients are also excluded if they self-report vision too poor to read a newspaper, lack of a phone (needed for follow-up interviews and scheduling), or plans to be out of the country for ≥ 3 months; if they screen positive for moderate-to-severe cognitive impairment using the validated Short Portable Mental Status Questionnaire followed by the Mini-Cog,[41-43] or self-report or are determined by study staff to be blind, deaf, intoxicated or actively psychotic. Because ACP is an iterative process and people may change their preferences over time,[24,44] subjects with prior ACP experiences (e.g., an advance directive) are not excluded.

To minimize the risk of unblinding by fellow research participants, any spouse/partner of a currently enrolled patient who is also a patient at SFHN/ZSFG, meets the eligibility criteria, and therefore, is also a potential patient participant, will be excluded from being a patient participant. This will avoid a situation where 2 closely related people living in the same home could be randomized to different study arms and result in unblinding. In addition, an individual who is named as an enrolled patient's potential surrogate decision maker (regardless of cohabitation or spousal status), who is also a patient at SFHN/ZSFG, meets the eligibility criteria, and therefore, is also a potential patient participant, will only be eligible to be a surrogate participant in our study and will be excluded from being a patient participant. In addition, we are excluding any

patient who has been enrolled in a previous PREPARE-related study or is known to have previously been exposed to PREPARE (e.g. note in medical record).

To save research staff considerable time and effort, potential participants who miss an interview (i.e. no show) more than 2 times (for the same baseline interview appointment) without prior notification and rescheduling with study staff will be considered ineligible, unless there are extenuating circumstances.

Inclusion and Exclusion Criteria

Inclusion Criteria	55 years of age or older
	Obtains care in the primary care clinics at in the San Francisco Health Network (SFHN).
	Has been seen at least twice in the last year by a primary care provider (a marker of established primary care) and had at least two additional visits to SFHN in the past year (a marker of illness)
Exclusion Criteria	Clinician is the PI, Co-I or member of the Patient-Clinician Advisory Board
	In a prior PREPARE-related study, such as a focus group or pilot study
	Dementia by ICD-9/ICD-10 codes, clinician assessment, chart review or self-report
	Blindness or poor vision by ICD-9/ICD-10 codes, clinician assessment, chart review, self-report of blindness or the inability to read print on a newspaper[45]
	Deafness by ICD-9/ICD-10 codes, clinician assessment, self-report, chart review or research staff assessment
	Cognitive impairment as assessed by research staff of any deficits on the validated Short Portable Mental Status Questionnaire (SPMSQ)[46] and the mini-Cog[41,47]
	Delirium or psychosis as assessed by a clinician or research staff
	Does not report speaking English or Spanish “well” or “very well”
	No phone for additional study contacts and follow-up interviews
	Active drug or alcohol abuse within the past 3 months determined by clinician assessment, self-report, chart review or research staff assessment.
	Patients who report they will be out of town during their scheduled follow-up interview dates outside of a window of 3 months.
	Report being a spouse or surrogate of another enrolled participant
	Patients who cannot answer consent teach-back questions after three attempts
	2 or more no-show baseline interview appointments without rescheduling

RECRUITMENT METHODS

Data Extraction:

To facilitate recruitment, we obtained a Health Insurance Portability and Accountability Act waiver to access patients' names, age, primary language, phone numbers, addresses, medical record numbers, as well as dates of outpatient primary care clinic appointments in the past year and up to 3 months in the future, other appointments and hospitalizations and emergency room visits in the past year, and the name of patients' outpatient primary care providers. From these data, we obtain a list of potentially eligible patient participants and send a secure email to their primary care providers asking for permission for our study team to tell their patients about the study through a recruitment opt-out study letter, followed by phone or in-person recruitment. Weekly administrative data pulls from the electronic health record identify patients with upcoming primary care appointments and are used to target patient recruitment efforts.

Clinician Permission to Contact Patients:

Upon completion of the administrative data pulls, providers from all recruitment sites are sent a letter/e-mail informing them about the research study and asking them to review a list of their patients, to refer patient(s) on their patient list who would be appropriate for the study, and to obtain permission to contact their patients to tell them more about the study. Clinicians are also informed that if the study team receives their approval, their eligible participants will receive a letter describing the research study and offering them the opportunity to decline to be contacted by research personnel and/or will be contacted in clinic. Additionally, clinicians are informed that if they do not respond one week after the 3rd attempt to contact them by the study team (including by email, phone, and/or in-person), we will assume assent to contact their patients and a letter describing the study will be sent to patients on behalf of the study team. We obtain permission from all of the Service Chiefs before their clinicians are contacted.

Recruitment Methods and Materials:

Study-related fliers written at a 5th-grade reading level in English and Spanish are posted in approved areas in SFHN/ZSFG-affiliated primary care clinics. Because many patients may be too ill to come to frequent clinic appointments and to be interviewed or hear about the study in busy clinic waiting rooms, we include several recruitment strategies. Therefore, in addition, recruitment letters and postcards written at a 5th grade reading level in English and Spanish are mailed and describe the research study as well as provide a telephone number to either opt-out or to hear more about the study. Although patients can opt out at any time, those who do not call study staff to decline participation within 1 week of the mailings are deemed eligible to be contacted to describe the study, assess willingness to participate and assess study eligibility. To standardize the timing between intervention exposure and primary care follow-up, we schedule patients for the baseline interview and exposure to PREPARE or the control intervention 1 to 3 weeks prior to their upcoming primary care appointment. Weekly administrative data pulls from the electronic health record identify patients with upcoming primary care appointments and are used to target patient recruitment efforts. Potential participants are then contacted by phone or in the clinic.

Patients who consent and enroll are paid $50 for the baseline interview and given $10 in MUNI (municipal transportation vouchers) to help participants come back to follow-up interviews in person if they desire. Participants are also reimbursed $25 for each of the 1-week, 3, 6, and 12-month interviews.

Diverse, vulnerable populations are often difficult to recruit for research studies. We employ several strategies to enhance our recruitment. First, we attempt to hire individuals who have experience with diverse populations and individuals who are bilingual (native Spanish-speaking) and bicultural. Furthermore, we conduct extensive sensitivity training with all research staff and

require staff to use approved study scripts when speaking to patients. These study scripts and all study materials used for recruitment are vetted, updated and approved by both our patient advisory and clinical advisory boards. All materials and study scripts are written at a 5th grade reading level and are provided to patients in their preferred language (i.e., English or Spanish).

CONSENT PROCEDURES

We use a modified consent process that several co-authors designed for vulnerable populations.[28,29] Consent forms written at the 5th grade reading level are provided and read to participants in English or Spanish. This review is then followed by standardized "teach-to-goal" questions to ensure understanding. If potential participants cannot correctly complete the teach-back process after 3 attempts, the patient is deemed ineligible.

The consent form is approved by the UCSF and ZSFG Institutional Review Boards, the patient/clinical advisory board, and the Data and Safety Monitoring Board (DSMB). The consent form states the following for the purpose of the study: "Why is this study being done? Sometimes patients and their families have to make hard medical decisions. We want to design and test an easy-to-understand handout to help. This handout will help people think about their values, or what is most important to them in their life. It will also help prepare patients to make medical decisions." We use the word "handout" because, in pilot testing, both groups are given handout materials and written advance directives. For randomization we explain, "We will ask you to look over a handout and answer some questions about your experience with making medical decisions. There will be two groups that will be given different handouts. You will have a 50/50 chance of being in either group."

Due to exclusions based on several missed baseline appointments and for staff safety and the need to exclude or withdraw participants who were intoxicated, psychotic, or threatening, the

consent also explains, “We also may ask you to stop taking part in this study if we feel it is in your best interest or if you do not follow the study rules.”

It was determined with our Patient-Clinician Advisory Board that clinicians of patients should be contacted in the event that the patient reports severe depression or anxiety. Our DSMB agreed and our consent forms explain:

“We would need to contact your regular doctor or a medical provider for the following reasons:

- You report or we observe that you are having a medical emergency,
- Such as a serious medical illness
- Or, a serious mental illness, such as major depression
- You report that you may harm yourself, you may harm someone else, or someone is harming you.”

INTERVENTION AND COMPARISON CONDITIONS

PREPARE arm

As previously described, PREPARE is an easy-to-use, patient-centered, interactive website that is available in English or Spanish, is written at a 5th grade reading level, includes voice-overs of all text for the reading-impaired and closed-captioning of all videos for the hearing impaired (www.prepareforyourcare.org).[27,28] The conceptual framework for PREPARE has been previously published and is based primarily on Social Cognitive Theory, [48,49] with elements from the Health Belief Model,[50] the Theory of Planned Behavior,[51] and Behavior Change Theory.[49,52] In these theories and in behavioral studies, modeling of behaviors helps people change their behavior. Successful behavioral change interventions model skills, enhance self-efficacy, and address perceived barriers,[53,54] especially literacy-appropriate interventions.[8] Modeling behaviors (as in PREPARE) can also improve patients’ ability to communicate with clinicians and improve outcomes,[55,56] such as increased question asking behavior and a sense of control during a clinical visit,[56,57] an increased desire to participate in decision making, and even

improved affect and functional status.[53,58-60] PREPARE incorporates these successful teaching methods through the modeling of behaviors in videos. Video and interactive websites are more powerful mediums to teach information and change behavior than written materials, especially for those with language/literacy barriers.[61-67] PREPARE includes a training and goal setting component which has been shown to be effective in changing outpatient behaviors, such as exercise.[68]

In the design of the PREPARE website, we included essential, theory-based health education strategies, such as the use of video modeling of ACP behaviors and tailored and interactive content based on patients' values and decision preferences. To ensure PREPARE is easy to read and understand, we use clear health communication principles (e.g., targeting text to the 5th grade reading level) informed by extensive formative research and cognitive interviewing with the target population (i.e., racially and ethnically diverse older adults with limited health literacy and English proficiency) to ensure PREPARE content is acceptable to individuals from diverse cultural backgrounds.[27] The PREPARE website leads people through a 5-step ACP process that ranges from choosing a surrogate decision maker to asking their clinicians the right questions. While going through the website, PREPARE also helps individuals answer personal values questions about their medical care, and helps them create an action plan to engage in some form of ACP. Patient-generated action plans have been shown to help patients engage in other preventative and disease management activities in the outpatient setting.[69]

After the baseline interview, participants in the PREPARE arm review all 5 steps of the PREPARE website in English or Spanish in our research offices. Participants are asked to review PREPARE on their own and in its entirety. Research assistants are available to answer questions only if needed, but do not go through the website with the participants. At the end of the program, a summary of the patient's medical wishes and action plan are automatically

generated from the PREPARE website in written format. This information along with the participant's PREPARE website login information is included in a take-home folder that also contains PREPARE information in pamphlet, booklet, and DVD format. We include PREPARE content in non-website formats because some patients may not have access to the internet at home. PREPARE arm participants are also given an easy-to-read advance directive in English or Spanish to review and consider completing.[8,70] Participants are asked to review the advance directive form for at least 5 minutes and up to 15 minutes in research offices, and then to take the form home to discuss with their potential surrogates and/or their clinicians. The time frame of 5-15 minutes was chosen because our goal is only to introduce the advance directive and allow participants to ask questions. The goal is not to have patients complete the form on the day of the study, before potential discussions with clinicians or surrogates, unless the participant would like to do so.

AD-only arm

Participants in the control arm are only given the easy-to-read advance directive, are asked to review it for at least 5 minutes and up to 15 minutes, and to take the form home to discuss with their potential surrogates and clinicians.

Both arms: Reminder of primary care appointments

One to 3 days before the patient's next scheduled primary care appointment, research staff call the PREPARE arm participants to remind them to bring in their study materials (i.e., action plan and advance directive) and to talk to their clinician about ACP. For the control arm, research staff members only remind patients about their upcoming appointment and do not provide additional encouragement about ACP.

RANDOMIZATION PROCEDURES

A statistician not involved in recruitment or data collection uses a computer-based random number generator to create a randomization scheme using block randomization by health literacy (adequate health literacy versus limited health literacy, as determined by a validated question concerning confidence with medical forms).[71] Random block sizes of 4, 6, and 8 are used to ensure an equal number of patients with limited health literacy in each group. Randomization information is associated with a unique patient identification number and is kept separate from other patient data. Due to the need to secure interview rooms for the duration of the baseline questionnaire and intervention (i.e., approximately 2 hours for the AD-only arm and 3 hours for the PREPARE arm), randomization occurred prior to scheduling a baseline interview.

BLINDING

Clinicians are blinded to patient group assignment. Although we obtain clinicians' permission to recruit their patients, the interventions are not described, and no clinician education is provided. Participants could not be blinded to the intervention; however, they are told during consent there is a "50/50 chance" of getting one of two different ACP guides, and the non-assigned intervention is not described. Because each group obtains ACP materials, such as the easy-to-read advance directive, blinding is enhanced. The research assistant who administers the intervention cannot be blinded to the study arm, but all follow-up outcome assessments are conducted by different and blinded staff. At the start of all follow-up interviews, participants are reminded not to discuss the study materials they reviewed with assistants recording if they became unblinded. If unblinding occurs, a different blinded assistant conducts all subsequent interviews.

INTERVENTION FIDELITY

All staff members are rigorously trained and are required to read and adhere to a standardized study protocol manual, standardized study scripts, and standardized checklists for each contact and interview with participants. Several training videos have also been developed for staff. Research staff are not allowed to conduct study tasks independently until they have reviewed all written and video training materials and can demonstrate complete mastery of all scripts and checklist items. In addition, a 10% random sample of all interviews is observed by senior research staff to ensure study fidelity.

DATA COLLECTION METHODS

Live capture of research data are collected through Research Electronic Data Capture (REDCap) software. REDCap is managed by the UCSF Academic Research Systems Team and is stored behind strong-string password protected firewalls on UCSF servers, not on individual laptops or desktops. All patients are given a unique, non-identifying patient identification number that is removed from any personally identifying information (PII) or personal health information (PHI). All PII and PHI are stored in a Microsoft ACCESS database behind strong-string password protected firewalls on UCSF and ZSFG servers. To reduce missing data, REDCap has been programmed to not allow study staff to progress if data fields are left blank. We retain the use of paper surveys in the event the RedCap system is down. All paper files continue to be stored in secure, locked research offices in secure, locked file cabinets.

FOLLOW-UP AND RETENTION:

We conduct follow-up interviews one week and 3, 6, and 12-months after the primary care visit in the clinic, by phone, or in the home if needed due to patient functional limitations. We utilize several measures to help ensure follow-up. Each follow-up interview takes between 30 to 45 minutes and participants are reimbursed $25.

Method of contact for follow-up surveys:

Upon enrollment, we ask participants to provide alternative phone numbers (e.g., cell or work numbers) and one to three additional phone numbers of close contacts who may know how to contact the patient in the event our study staff is unable to reach them. Many patients in safety net settings are marginally housed, have intermittent phone access, and may change locations and phone numbers during the study period. We also ask participants if they prefer a text message or an email to schedule follow-up visits and will use their preferred mode of communication. If these other modes of communication fail, we send out reminder letters. If needed, we also attempt to contact patients during scheduled clinic visits or make home visits.

Participant Appointment Reminder Sheet

We created an appointment reminder sheet as a reference for patient participants. This sheet shows the dates and times for upcoming appointments that the patient participant will have with us.

Reminders for the primary care visit:

Participants receive a brief reminder call one to 3 days before their next primary care visit. Participants in the AD-only arm are reminded to come to their scheduled appointment while participants in the PREPARE arm are reminded of their appointment and to bring the PREPARE materials to the visit.

Reminders for study interviews:

For all follow-up interviews, participants in both arms receive reminders of their upcoming study interview by phone or in person. To help participants follow along during the interview, the participant can receive a Participant Version of the survey via mail or email, as

preferred. No survey responses or information are collected by mail or email. We use 14-point font and color-coded, standardized, large font response options to help with understanding.

Participants who miss their primary care appointment:

Participants who cancel or miss their primary care appointments and do not reschedule within 30 days of the cancelled appointment receive a courtesy phone call to remind participants to reschedule the primary care appointments in order to move on with the study schedule. For participants who cancel or miss their primary care appointments after they have been enrolled and randomized:

- If they have rescheduled and attend their primary care appointment within 6 months from when they were randomized, they receive a brief reminder call one to 3 days before their primary care appointment date. We conduct follow up assessments at 1 week, and at 3, 6, and 12 months from this primary care appointment date,
- If they do not reschedule or attend their primary care appointment within 6 months from when they were randomized, they receive a brief reminder call one to 3 days before their new primary care appointment date. We conduct follow up assessments at 6 and 12 months from the originally scheduled primary care appointment date.

Ascertaining reasons for loss of follow-up or withdrawal: For participants who want to withdraw, we ask them why in open-ended questions. If they cannot provide an answer, we prompt them from a list of reasons we obtained from prior advance care planning trials, such as the study is too long, they are too busy, the study topic is too upsetting, they are too ill, etc.[35]

MEASURES

Overview

Because ACP ideally is a process that occurs over time, we felt it important to measure a full range of ACP measures including ACP documentation (primary outcome) over time, and several behavior change constructs and several additional ACP actions over a 12-month period (secondary outcomes). All study measures used in this analysis, including validity and reliability information in English and Spanish and the schedule of administration (i.e., baseline, 1-week or 3, 6, or 12-months), are included in the Outcome Measures table below. All outcomes, including secondary outcomes not used in our main analysis, are included in our published protocol.[36] The main outcome measures are described in detail below.

Primary Outcome

The primary outcome is new documentation of ACP wishes in the ZSFG/SFHN medical record (Table of Outcome Measures below). ACP documentation for the purposes of this study includes the easy-to-read advance directive or other valid advance directives or living wills, a durable power of attorney for health care document (DPOAHC), a Physicians Orders of Life Sustaining Treatment form, or other documentation of discussions concerning patients' wishes for medical care (i.e., documentation of oral directives by a physician or notes describing patients' goals for medical care by clinicians).

We assess baseline and 15-month new ACP documentation rates and the date of documentation to determine the length of time from study enrollment to subsequent documentation. Patients in our study are enrolled, randomized, and exposed to the intervention 1 to 3 weeks prior to a primary care appointment. ACP documentation is timed to the date of intervention exposure as patients may have engaged in ACP prior to seeing their primary care provider. The patient-reported outcomes in the follow-up surveys (1 week, 3, 6, and 12-months), however, are timed to the primary care visit because those questions concern engagement in discussions with clinicians (see secondary outcomes below). This same timeframe for ACP

documentation was determined from a prior PREPARE trial conducted within the VA to take into account and to standardize the expected time from intervention exposure to the primary care visit and the anticipated time to schedule and complete the final patient interview.[35]

Because legal forms and documented discussions can be used to direct medical care, we created a composite variable of any ACP documentation (forms and/or discussions); we also plan to report the percentage of forms and discussions separately. All medical review data is double coded by 2 independent, blinded research assistants. Discrepancies are adjudicated by the principal investigator (R.L.S.).

Secondary Outcomes

Main Patient-Reported Outcome

The main patient-reported secondary outcome, the validated Advance Care Planning Engagement Survey,[27,28,37] was chosen to measure the full process of ACP. The Advance Care Planning Engagement Survey measures both ACP Behavior Change Processes, such as knowledge, contemplation, self-efficacy, and readiness on a validated 57-item scale. The ACP Behavior Change Process scale is measured on a 5-point Likert scale and average 5-point scores will be calculated. We will also measure ACP actions on the validated 25-item Action scale, which assesses ACP activities (yes or no) such as identifying a surrogate decision maker, identifying values and goals for medical care, choosing the level of leeway in surrogate decision making, discussing one's wishes with clinicians and surrogates, and documenting one's wishes in an advance directive. Validity and reliability of the ACP Engagement Survey, as well as the questionnaire's ability to detect change in response to an ACP intervention, have been previously described.[27,28,37]

Feasibility and Satisfaction

To evaluate whether and how PREPARE will be used in clinical practice and in the community, we also assess acceptability of the PREPARE website compared to an advance directive alone using validated scales of ease-of-use (10-point scale, “On a scale of 1 to 10, with 1 being very hard and 10 being very easy, how easy was it to use this guide?”) and satisfaction (comfort: “How comfortable were you viewing this guide?”, helpfulness: “How helpful was this guide?”, and recommendations: “How likely are you to recommend this guide to others?” assessed on a 5-point Likert scale (not-at-all to extremely) from our prior work.[8] For the PREPARE arm only, and at the end of the 12-month interview and after unblinding, we also ask how likely patients are to recommend the PREPARE intervention to others.[72]

Clinical and Patient-Advisory Board Requested Outcome

Our Patient-Advisory Stakeholders requested we quantify the number and percentage of patients who increased their ACP activities overtime. Our stakeholders perceive any increase in an ACP activity over time as clinically meaningful. Thus, in addition to mean change in ACP Engagement scores, they wanted to know the percent of patients who improved (i.e., had an estimated slope > 0) over time for both Behavior Change scores, Actions scores, and both combined. We therefore created this exploratory variable post-hoc.

Adverse Event Outcomes

In addition, to ensure that the PREPARE program does not cause undue harm, we also assess both depression[73,74] and anxiety.[75,76] We measure depression using the validated Patient Health Questionnaire (PHQ)-8 (scores 0-24) and anxiety Generalized Anxiety Disorder (GAD)-7 (scores 0-21) at baseline and each follow-up.[74,75] Scores of 5, 10, 15, and 20 represent mild, moderate, moderately severe and severe depression or anxiety.

Potential Mediating or Moderating Variables & Participant Characteristics

Based on the previously published conceptual framework of PREPARE,[27] we also hypothesize that PREPARE efficacy may vary across several moderator or mediator variables (e.g., health literacy using the validated Short form Test of Functional Health Literacy in Adults s-TOFHLA, scores 0-36[77] and dichotomized to limited = 0-22 & adequate = 23-36; clinician-patient language concordance (concordant versus discordant); and patient's desired role in decision making with the medical provider using the validated Decision Control Preferences Scale(wants to make their own decision versus wants doctors/family to make decisions for them).[78] We also hypothesize that PREPARE efficacy may be affected by several confounding variables (e.g., self-rated health, "How would you rate your health?" [5-point Likert][79,80] dichotomized as fair-to-poor and good-to-excellent and past experiences with ACP including prior documentation of legal forms and documented discussions. We will also assess a full range of patient-reported characteristics, as these factors may impact patient-clinician communication,[20,81] such as age ("What is your date of birth?"), self-reported gender ("What gender do you consider yourself to be? male, female transgender, other"), finances (able to make ends meet versus not make ends meet), having a potential surrogate decision maker or not, education ("What is the highest educational level you have completed?" less than or equal to high school or greater than high school), internet access in the home (yes or no), and religiosity and spirituality (i.e., "How religious/spiritual do you consider yourself to be?" on 5-point Likert scale from not-at-all to extremely).

Outcome Measures Table

Construct	Measure	# items	English Reliability/Validity	Spanish Reliability/Validity	Baseline	1 week	3 months	6 months	12 months	15 months
	Primary Outcome									
New ACP Documentation	Chart review: ACP documentation (i.e., legal forms and documented goals of care discussions)[35,36]				X					X
	Secondary Outcomes									
The Full ACP Process	ACP Engagement Survey: [27] Behavior Change Process Measures (knowledge, contemplation, self-efficacy, readiness) Action Measures: values identification and discussions	57 25	Behavior Change Measures: Cronbach's α = 0.94 (0.91-0.96), ICC= 0.70 (0.54-0.82)[27] Action Measures: ICC*= 0.87 (0.79-0.92)[27]	-	X	X	X	X	X	
Implementation: Acceptability	Acceptability and Usability (a) Ease of Use and Understanding (b) Usefulness in decisions & discussions (c) Attitudes about norms or expectations	8 6 6	1 factor explained 81-85% of variance/scale. Kuder-Richardson >0.75[8]	1 factor explained 81-85% of variance/scale. Kuder-Richardson >0.75[8]	X					
	Adverse Event Outcomes									
Depression	Patient Health Questionnaire-8	8	Scores ≥10 100% sensitive and 95% specific for major depressive disorder.[73,74]	Scores ≥10 77% sensitive and 100% specific for major	X	X	X	X	X	

Construct	Measure	# items	English Reliability/Validity	Spanish Reliability/Validity	Baseline	1 week	3 months	6 months	12 months	15 months
				depressive disorder[82]						
Anxiety	GAD-7[75]	7	Cronbach's α = 0.92[75] ICC*= 0.83	Cronbach's α = 0.88[76] ICC*= 0.64	X	X	X	X	X	
	Exploratory Outcome									
Percent increase in ACP activities	N (%) participants who increased their Behavior Change or Action scores from baseline (i.e., estimated slope > 0)		-	-	X	X	X	X	X	
	Demographic Information									
Demographic Information	Age, gender, race/ethnicity[83], marital status, and education				X					
Finances	"In general, how do your finances usually work out at the end of the month?"	1	Associated with functional impairment and co-morbidity [84]	-	X					
Socioeconomic Social Standing	Social standing ladder (i.e. place an "x" where you think you stand relative to other people in society)	1	Associated with functional decline[85]	-	X					
	Other Measures									
Health Literacy	Short form Test of Functional Health Literacy in Adults s-TOFHLA, scores 0-36)[77] Continuous & dichotomized to limited = 0-22 & adequate	36	Cronbach's α = .97 Correlation coefficient w/ other literacy tests > 0.80[77]	Cronbach's α >.95[86]	X					

Construct	Measure	# items	English Reliability/Validity	Spanish Reliability/Validity	Baseline	1 week	3 months	6 months	12 months	15 months
	= 23-36									
Patient-clinician language concordance	To clinicians: "How well do you speak Spanish?[87] Fluent, very well (concordant) vs. well, fair, or poor"	1	AUROC† 94% (CI: 90-98%)[87]	AUROC† 94% (CI: 90-98%)[87]	X					
Desired role in decision making	Control Preference Scale (CPS) with clinician[78]	2	Correlation between preferred and actual role in decision making.[12,88,89]	Correlation between preferred and actual role in decision making[90]	X				X	
Internet Access	Do you have access to the internet in your home?	1	-	-	X					
U.S. Acculturation	Based on Acculturation scale (USAS) "How many years have you lived in the U.S.?"	1	Cronbach's α = .98 Associated w/ desire to know prognosis[91]	-	X					
Functional Status	Activities of Daily Living (ADL) (0-16 point scale)& Instrumental (IADL) measure (0-12 item scale)[92,93]	13	Morbidity/mortality correlation.[126,127]	Cronbach's alpha =0.94[94]	X					
Self-rated health status	How would you rate your health? (5pt Likert) [79,80]	1	Cronbach α = .80[80]	-	X					
Prior ACP experience	Prior ACP experiences (e.g., ("Ever had to make life threatening medical decisions?") [8]	5		-	X					
Social support	Modified Medical Outcomes Study Social Support (scores 11-55) [95] Presence of a possible	11 11	Cronbach's α = 0.88-.93[95]	Cronbach's α = 0.94[96]	X					

Construct	Measure	# items	English Reliability/Validity	Spanish Reliability/Validity	Baseline	1 week	3 months	6 months	12 months	15 months
	Surrogate Decision maker									
Religion/Spirituality	Self-reported extent of how spiritual/religious (5-pt Likert) and role play in decision making.[97]	4	Spirituality associated with quality of life. Religiosity associated with wanting all measures to extend life.[97]	-	X					

Only the variables included in the current analysis are listed in the table. All measures including other secondary and exploratory outcomes not included in this analysis are listed in the published protocol.[36]
If a validated Spanish-version of a survey was not available, we translated the English version into Spanish.
*ICC = Intraclass correlation
† Area under the receiver operating curve (AUROC)
‡ While mediator variables, measured at baseline, may explain how or why a particular effect or relationship occurs, these variables may also be affected by the intervention and are therefore also considered secondary outcome variables measured over time (i.e., knowledge, self-efficacy, and readiness, as well as barriers and attitudes).

STATISTICAL ANALYSIS PLAN

Our primary analyses will compare change in ACP documentation between study arms from baseline to 15 months. Secondary outcomes will include ACP Engagement with respect to 5 ACP Actions (yes/no and a 0-25-point scale) and behavior change scores (average 5-point Likert scores) from baseline to 1 week, and 3, 6, and 12 months. Variables will be assessed for distributional and outlier values using standard summary statistics. Baseline comparability will be assessed between groups using unpaired t-tests, Chi-square tests or Fisher's exact tests. Using t-tests or Chi-squared tests, we will also compare patient's age and self-reported gender between those who refused versus those who enrolled and differences between arms of those who withdrew versus those who did not. We will use intention-to-treat analysis using SAS version 9.4 (SAS Institute Inc.) and STATA 15.0 (College Station, TX). All p-values will be 2-tailed and set at .05 for the primary outcome and Bonferroni adjusted for secondary patient-reported outcomes. In addition, because of differences in ACP engagement among English and Spanish speakers,[8] and based on preferences of our stakeholders and granting agencies, we decided, *a priori*, to analyze our results overall and stratified by English and Spanish language. To compare outcomes between the two arms longitudinally, we will use mixed effects linear, Poisson, or negative binomial regression for continuous measures and mixed effects logistic regression for dichotomous measures. The mixed effects models will include fixed effects for the primary modeling terms of time (baseline and 15 months for ACP documentation and baseline and 1 week, 3 months, 6 months, and 12 months for ACP Engagement with time modeled using dummy variables to allow for non-linearity); arm (AD-only versus PREPARE); an interaction term of study arm and time; and a random effect for subjects. We will adjust for the randomization blocking factors limited vs. adequate literacy,[98] and any predictor variables that differ between arms. All models also will also be adjusted for baseline ACP documentation and will include random physician intercepts to account for nesting of patients within physicians. We will use standardized, clinically meaningful effect sizes (i.e., 0.20-0.49 small, 0.50-0.79 medium,

and ≥0.80 large).[99] Per stakeholder request, we will conduct post-hoc mixed-effects regression to calculate the percentage of participants who increased their Behavior Change score, Action scores, or both Behavior Change and Action scores from baseline (i.e., estimated slope > 0) by study arm; p-values adjusted to a significance of 0.017.

For moderator analysis, we will test for interactions by adding interaction terms to the group by time variable for health literacy (limited versus adequate) controlling for prior ACP documentation and clustering effects by clinician. All other interaction terms are adjusted for health literacy (randomization blocking variable) prior ACP documentation and clustering effects by clinician. Additional interaction terms to be added to the group by time variable include language (i.e., English versus Spanish), control preferences for decision making (i.e., makes own decisions versus doctor makes decisions), age (i.e., < 65 years versus ≥65 years of age), sex/gender (i.e., self-reported man versus woman), race/ethnicity (i.e., white versus non-white), health status (i.e., good-to-excellent versus fair-to-poor), presence of a potential surrogate (i.e., yes versus no), internet access at home (i.e., yes versus no), and, for Spanish-speakers, patient-clinician language (concordance vs. discordance). A p-value for interaction <0.05 is considered significant.

Missing data for the primary outcome will be assessed. If there is 10% or more of missing data, we will use a mean imputation approach. All available data will be included in mixed-effects models. We will assess whether any research staff member became unblinded during follow-up assessment and conduct sensitivity analysis as needed.

SAMPLE SIZE AND POWER CALCULATIONS

We will measure a full range of ACP behaviors including discussions. However, written advance directive completion of legal forms is a primary outcome and is the most well-studied.[100] Power

from longitudinal analyses with repeated measures will be stronger, but to be conservative, we consider power for a single post-intervention time point (e.g., 15 months). A recent meta-analysis of written advance directive documentation studies demonstrated a pooled effect size of 0.50 (95% CI; 0.17 -0.83),[100] as did an RCT of an ACP workbook that included both behavior change constructs and a social work visit,[101] and our prior RCT of an easy-to-read AD at ZSFG which showed an increased AD completion rate from 7% to 15%.[8] Because both the intervention and control arm will receive the easy-to-read advance directive, we assume that both arms will have an advance directive completion rate of ≤ 15%. Based on prior studies, we assume PREPARE will result in additional benefit of advance directive completion with a minimum effect size of 0.5 (two-fold increase) above 15%. A sample of 350, (175 per arm), will afford us 92% power (2-tailed alpha of 0.05) to detect a difference of advance directive completion rates of 15% in controls vs. 30% in the PREPARE arm and 80% power to detect a difference of 15% vs. 27%. Power is also expected to be strong for the ACP behavioral change scale outcomes (preliminary data demonstrated a pre-to-post improvement of 0.5 SD).[27] With a conservative assumption that controls will improve by 0.1 to 0.2 SD, we will have 85% to 98% power, respectively, to conclude that the improvement is better in the PREPARE arm. We expect a 15% drop out rate at 12 months based on our prior randomized, controlled trial at ZSFG,[8] and will therefore attempt to recruit 402 patients, or 201 in each arm for each language (English and Spanish) for a total recruitment of 804 patients.

Our sample size will also allow adequate power to detect clinically important interactions based on potential moderators (literacy, control preferences, language concordance) for our outcomes. In a prior trial of an easy-to-read advance directive in the same patient population with only 200 patients, we found significant interactions for literacy.[8] Thus, if we consider the power scenario of the control group ACP documentation rate of 15% and the PREPARE group of 28%, and suppose the control group rate is the same (15%) for both levels of the moderating factor, then

for a moderating factor split of 1:1, we would have 80% power to detect an interaction. If the PREPARE arm ACP documentation rate is 18% for one level of the factor and 40% for the other, this corresponds to a relative rate of ACP documentation of 2.2 times as high for one level of the factor compared to the other. A 2:1 split of the moderating factor still allows detection of a 2.4-fold increase in the relative rate of documentation. Power to detect interactions will likely be stronger for continuous outcomes (e.g. engagement/behavioral scales).

ETHICS AND ADVISORY COMMITTEES

This study is approved by the University of California, San Francisco (UCSF) (IRB reference #13-10847). This study is guided by a Patient-Clinical Stakeholder Advisory Board that is comprised of patients and patient advocates (including native Spanish-speakers), surrogates, and ZSFG/SFHN primary care clinic staff and medical directors. It is also guided by a DSMB consisting of 4 experts in randomized trials, human subjects research and consent, vulnerable populations, palliative care, advance care planning, and biostatistics. Both advisory groups reviewed and approved all study protocols and related materials. In addition, we continue to meet with both groups every 4-6 months to review the progress of the trial, make suggestions for recruitment, review any potentially adverse events, and ensure that we are following our study protocols in a way that protects vulnerable patient populations.

HUMAN SUBJECTS PROTECTIONS

Protection of the rights and welfare of participants:

All study staff are required to take annual training regarding the rights and protections of research participants. Additionally, weekly study team meetings will ensure that all study staff are following the research protocol and that all study participants are consented according to our study protocol.

Furthermore, our consent process ensures that study participants have a clear understanding of the study and understand that they can choose to not participate in the study at any point in time, and that the care they receive will not be affected by declining to participate in our study. Our consent process involves using a consent form written below a 6th-grade reading level, reading the form to potential subjects verbatim, allowing time for questions and discussion, and then assessing comprehension using teach-to-goal. If questions are not answered correctly, repeated education and reassessment of comprehension are continued until complete comprehension is achieved. If subjects take more than three passes through the comprehension assessment, formal assessment for cognitive impairment will be completed. If patients are found to be cognitively impaired, they are excluded from the study. If they are not cognitively impaired, we will re-do teach back once more, after which the participant will be deemed ineligible for the study if they are unable to demonstrate comprehension of the study.

Additionally, we include UCSF Clinical Research Office contact information on all consent forms as required for all non-biomedical studies.

Steps taken to minimize risks to subjects:

We have developed a modified research consent process that has been shown to be successful in vulnerable patient populations as described above.[29] All study fliers, consent forms, and questionnaires are read to the subjects in their entirety by native English- and Spanish-speaking research staff. Participants are reminded that they can opt out of the study at any time. All study materials are in an easy-to-read (5^{th} grade reading level, large 14-point font) format. The consent materials and the study interviews are conducted in the language the participant is most comfortable speaking (English or Spanish).

This study will employ research assistants who are fluent in English or Spanish. Only fluent research assistants will be in contact and will communicate with Spanish-speaking participants. We will also ensure that all study materials are accurately translated into Spanish by having them initially translated from English to Spanish by native Spanish- speakers. We will then have them back translated into English to ensure accuracy. Finally, we will have the final translated documents reviewed for accuracy by third party native Spanish- speakers. To help participants follow along during the interview, they may review a large font Participant Version of the survey at baseline and all follow-ups that can be reviewed while the research assistant is asking research questions verbatim. We use 14-point font and color-coded, standardized, large font response options to help with understanding.

Data security:

- Data are stored securely in the encrypted, secure UCSF MyResearch environment
- Data are coded; data key is kept separately and securely
- Data are kept in a locked file cabinet
- Data are kept in a locked office or suite
- Electronic data are protected with a password
- Data are stored on a secure network
- Data are collected/stored using REDCap or REDCap Survey

Measures to ensure confidentiality and protect identifiers from improper disclosure

Risks to subjects are minimal and may include loss of confidentiality and psychological discomfort about discussing end-of-life issues. Subjects are assured that their answers to study questions will not be directly linked to their names. Instead, any identifying information is coded and separated from the data. The identifying information will only be known to the primary investigators but will not be used in data analysis. In addition, signed consent forms are kept in

locked file cabinets and kept separate from the data collection instruments. Study subjects are also reminded that the information obtained will not be shared with their providers except in non-identifying aggregate form at the end of the study. We also make clear that the responses to the PREPARE guide are only for research purposes and will not be shared with their clinicians or put in their medical record.

We will store all study materials in locked offices and locked storage cabinets. We will utilize UCSF MyResearch and REDCap to enter and maintain data in a secure environment. In order to be more environmentally-conscious, we will attempt to use the LiveCapture function of RedCap and thus reduce the use of paper resources. We will retain the use of paper surveys in case the RedCap system is down. These paper files are stored in secure, locked research offices in secure, locked file cabinets.

As some of the questions concerning end-of-life may cause psychological discomfort for some study subjects, subjects are reminded at the beginning of the interview of their right to refuse to answer any and all questions and their right to terminate the interview at any time. We will also reassure subjects that if they choose not to be in the study or choose to terminate the interview, it will not change the medical care that they normally receive from their clinic or their clinician. In addition, we will reiterate that the information shared within the research interview will not be shared with their clinicians or used in medical care. However, subjects can take home a copy of the PREPARE guide with them and bring it back to their clinicians if they wish. Subjects are given the name and number of the primary investigator and may call if they have questions or are concerned about their participation in the study.

Required reportable information:

As these interviews may be completed in people's home and, in the interviews, we are asking patients to describe their experiences and opinions, it is possible that reportable events such as elder abuse, suicidal or homicidal ideation may be detected. If they are detected, they will be handled according to the American Psychological Association code of ethics. If elder abuse is suspected, the participant will be encouraged to take steps to ensure their safety. They will be offered contact information for local supportive services and informed that the concerns will be discussed with the elder abuse hotline for assistance. When there are concerns about self-harm or harm to others, severity of harm will be assessed. Participants will be offered local support services and officials will be notified as necessary.

Patient Depression/Anxiety Protocols

With input from the Patient-Clinician Stakeholder Advisory Board, and to err on the side of caution, we created a flow diagram with detailed instructions, including study scripts and contact names and telephone numbers for research staff to use in the event scored in the moderately severe depression or anxiety range on the PHQ-8 and GAD-7 or a participant expressed suicide ideation.

DATA SAFETY MONITORITY PLAN

Monitoring will focus on recruitment, baseline comparability of treatment groups, protocol adherence, completeness of data, accrual of primary endpoint data, safety, and follow-up rates. This monitoring will provide the basis for monthly review by the study investigators, review by the ZSFG Patient-Clinician Advisory Committee, and Data Safety and Monitoring Board (DSMB), and yearly reporting to our IRBs. We will implement methods of verifying entered data and of quality control. All study materials data are kept on secure, password-protected, encrypted servers. All consent materials and any identifying information are kept in locked cabinets within locked offices, on password-protected, encrypted servers, on card-key protected

research floors. Dr. Sudore, will be directly responsible for identifying and immediately reporting all adverse events to the IRBs Privacy Officers, and funding agency as appropriate. The ZSFG Patient-Clinician Advisory Committee will ensure participant safety in the clinic and will meet up to 4 times per year. The formal DSMB includes 4 experts in randomized trials, human subjects research and consent, vulnerable populations, palliative care, advance care planning, and biostatistics. The DSMB will review and approve the research protocol and plans for data and safety monitoring; and assess data quality; participant recruitment, accrual and retention; baseline comparability of treatment groups, accrual of primary endpoints; and participant safety (e.g., adverse events, protocol violations). They will also develop stopping rules for the trial. The DSMB will meet up to 4 times per year.

CHARTER OF DATA SAFETY MONITORING BOARD

The Data and Safety Monitoring Board (DSMB) will act in an advisory capacity to the National Institute of Aging (NIA) Director to monitor participant safety, data quality and evaluate the progress of the study. Dr. Sudore, University of California, San Francisco is conducting the "*Improving Advance Care Planning by Preparing Diverse Seniors for Decision Making*" study under a R01 funded by the National Institute of Aging. The DSMB for this study includes 2 outside clinicians with expertise in RCTs and an outside biostatistician. The NIA program officer is also included. The DSMB will review and approve the research protocol and plans for data and safety monitoring; and assess data quality; participant recruitment, accrual and retention; baseline comparability of treatment groups, accrual of primary endpoints; and participant safety (e.g., adverse events, protocol violations). They will also develop stopping rules for the trial. The DSMB will meet 2 and up to 4 times per year.

DSMB Responsibilities

The DSMB responsibilities are to:

- review the research protocol, informed consent documents and plans for data safety and monitoring;
- advise the NIA on the readiness of the study staff to initiate recruitment;
- evaluate the progress of the trial, including periodic assessments of data quality and timeliness, recruitment, accrual and retention, participant risk versus benefit, performance of the trial sites, and other factors that can affect study outcome;
- consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the trial;
- review study performance, make recommendations and assist in the resolution of problems reported by the Principal Investigator;
- protect the safety of the study participants;
- report to NIA on the safety and progress of the trial;
- make recommendations to the NIA and the Principal Investigator concerning continuation, termination or other modifications of the trial based on the observed beneficial or adverse effects of the treatment under study;
- if appropriate, review interim analyses in accordance with stopping rules, which are clearly defined in advance of data analysis and have the approval of the DSMB;
- ensure the confidentiality of the study data and the results of monitoring; and,
- assist the NIA by commenting on any problems with study conduct, enrollment, sample size and/or data collection.

The DSMB will discharge itself from its duties when the last participant completes the study.

Membership

The DSMB includes experts in or representatives of the fields of:

relevant clinical expertise,

clinical trial methodology, and

biostatistics.

The DSMB members:

- In addition to the NIA program officer members include:
- Dr. David Bekelman, MD, MPH, an internist, psychiatrist, and palliative medicine physician at the University of Colorado School of Medicine and is an expert in health communication and medical decision making
- Dr. Nathan Goldstein, MD, a geriatrician and a national expert in palliative care, communication, and medical decision making at Mt. Sinai School of Medicine,
- Dr. James Wiley, PhD a statistician and Professor in the Institute for Health Policy Studies at the University of California, San Francisco. Dr. Wiley has extensive experience with RCTs and working with safety net populations. Although Dr. Wiley is at UCSF, he does not otherwise work with Dr. Sudore. Membership have no financial, scientific, or other conflict of interest with the trial.

Written documentation attesting to absence of conflict of interest has been obtained.

Dr. Nathan Goldstein, Mount Sinai School of Medicine, has been appointed by NIA to serve as the Chairperson and is responsible for overseeing the meetings, developing the agenda in consultation with the NIA Program Official and the Principal Investigator. The Chair is the

contact person for the DSMB. The University of California, San Francisco shall provide the logistical management and support of the DSMB. Dr. Nathan Goldstein is also the safety officer and contact person for serious adverse event reporting. A log of all potential adverse events and protocol violations will be kept and reviewed quarterly by the DSMB. Procedures for notifying the Chair of the DSMB and the NIA Program Official will be discussed and agreed upon at the first meeting.

Board Process

At the first meeting the DSMB will discuss the protocol, suggest modifications, and establish guidelines to study monitoring by the Board. The DSMB Chairperson in consultation with the Principal Investigator and the NIA Program Official will prepare the agenda to address the review of study materials, modifications to the study protocol and informed consent document, initiation of the trial, appointment of a safety officer, as needed, reporting of adverse events, statistical analysis plan including interim analysis and stopping rules, etc.

Meetings of the DSMB will be held 2-4 times per year at the call of the Chairperson and / or NIA Program Official to ensure patient safety and to review stopping rules for the trial. The NIA Program Official or designee will attend most of the meetings. An emergency meeting of the DSMB may be called at any time by the Chair or by the NIA should participant safety questions or other unanticipated problems arise.

Meetings are closed to the public because discussions may address confidential participant data. Meetings are attended by the Principal Investigator and members of his/her staff. Meetings may be convened as conference calls as well as in-person.

Meeting Format

Each meeting must include a recommendation to continue or to terminate the study and whether the DSMB has any concerns about participant safety made by a formal DSMB majority or unanimous vote. Should the DSMB decide to issue a termination recommendation, the full vote of the DSMB is required. In the event of a split vote, majority vote will rule and a minority report should be appended. The DSMB Chair provides the tiebreaking vote in the event of a 50-50 split vote.

A recommendation to terminate the study may be made by the DSMB at any time by majority vote. The Chair should provide such a recommendation to the NIA immediately by telephone and email. After the NIA Director makes a decision about whether to accept or decline the DSMB recommendation to terminate the study, the PI is immediately informed about his decision.

Meeting Materials

DSMB interim report templates will be prepared by the study staff, to be reviewed by the DSMB members at each meeting. The reports will list the study aims, the status of the study, and summarize safety data.

Reports from the DSMB

A formal report containing the recommendations for continuation or modifications of the study will be prepared by the DSMB Chairperson, NIA Program Official or its designee. The draft report will be sent to the DSMB members for review and approval.

Confidentiality

All materials, discussions and proceedings of the DSMB are completely confidential. Members and other participants in DSMB meetings are expected to maintain confidentiality.

PATIENT-CLINICAN STAKEHOLDER ADVISORY COMMITTEE ROLE

This study is guided by a Patient-Clinical Stakeholder Advisory Board that is comprised of patients and patient advocates (including native Spanish-speakers), surrogates, and ZSFG/SFHN primary care clinic staff and medical directors. These individuals are paid key personnel on the study and have agreed to meet up to 4 times per year to oversee all aspects of the study. Native Spanish-speaking staff will be present to translate for our Spanish-speaking patient stakeholders during advisory meetings. All study materials will be translated into Spanish. The advisory committee will be involved in providing ongoing advice about the following important study related activities:

Recruitment, including study scripts, fliers, methods

- Eligibility and exclusion
- Patient safety and research staff safety
- Clinic workflow and clinical champions
- Informed consent
- Research outcomes
- Presentation of findings
- Dissemination of results

Summary of Changes to the Protocol: The listed topics follow the outline and headers of the protocol

Topic	Date	Summary of Changes
Funding	Feb 3, 2014	We obtained funding from the National Institute on Aging (R01AG045043) to start recruitment of English-speakers. We then also obtained Patient-Centered Outcomes Research Institute (PCORI) funding (R-1306-01500) to add Spanish-speakers to our established trial infrastructure and protocol.
Funding	Mar 8, 2017	Dr. Sudore became funded, in part, by a NIA K24 (K24AG054415).
ClinicalTrials.gov registration	Feb 27, 2014	When PCORI funding was obtained, PCORI required a separate Clinical.Trial.gov number. Thus, it was added in February 2014. Although English- and Spanish-speaking recruitment was supported by two funders, this was one trial with the same staff, locations, procedures, IRB, and protocol.[36]
Background	Apr, 2016	We updated the background to included updated references.
Preliminary Studies	May, 2017	We updated the preliminary studies to include the findings from our published VA trial. The name of hospital was changed on May 3rd, 2015 from SFGH to Zuckerberg San Francisco General Hospital (ZSFG). This change was made throughout the protocol.
Overview of Trial	Jan 4, 2016	We updated the protocol to include our study flow diagram for our records.
Eligibility screening	Jan 16, 2014	Eligibility screening in busy, loud, outpatient clinics was often difficult. With our patient-clinicians stakeholders, we decided to include the ability to recruit and screen by phone. See below under recruitment.
Exclusion criteria	Jul 15, 2014	To minimize potential contamination, we excluded participants who may have been exposed to the PREPARE website from other sources such as being in a PREPARE-related focus group or pilot study.
Exclusion criteria	Oct 3, 2014	To ensure the safety of our research staff, we excluded potential participants with evidence of active drug or alcohol abuse within the past 3 months determined by clinician assessment, self-report, chart review or research staff assessment.
Exclusion criteria	Jan 16, 2014	To minimize the risk of unblinding by fellow research participants, any spouse/partner of a currently enrolled patient or an individual who is named as an enrolled patient's potential surrogate decision maker (regardless of cohabitation or spousal status), who is also a patient at SFHN/ZFG will be excluded from being a patient participant. This will avoid a situation where 2 closely related people living in the same home could be randomized to different study arms and result in unblinding.

Exclusion criteria	Jan 27, 2014	To save research staff considerable time and effort, potential participants who initially scheduled but then missed the baseline interview (i.e. no show) more than 2 times without prior notification and rescheduling with study staff will be considered ineligible, unless there were significant extenuating circumstances.
Spanish Translation	Nov 13, 2014	All translated and back-translated study materials were approved by the UCSF IRB.
Recruitment methods	Nov 13, 2013	We initially sent opt-out letters to potential participants. However, many SFHN/ZSFG patients are marginally housed, had incorrect mailing addresses, or have limited literacy. We also discovered that many patients were confusing the opt-out letters for bills from the hospital. With input from our Patient-Advisory Board and DSMB, we switched to more engaging recruitment letters and postcards that allowed patients to call and hear more about the study or to opt-out. They could also opt-out at any time.
Recruitment methods	Jan 16, 2014	It was determined by our patient-clinician stakeholders that it would be acceptable to recruit patients by phone in addition to in clinic recruitment. In addition, because we were attempting to enroll patients 1-3 weeks prior to a primary care visit, it was proving difficult to approach patients in clinic ahead of their primary care appointments. In addition, our primary care stakeholders felt it would be better for their clinic workflow to not have research staff always in the clinic. Therefore, we expanded our recruitment options, after receiving permission from the clinician and sending recruitment letters, to both approach potential participants in clinic as well as recruit by phone.
Recruitment-reimbursement	Jan 16, 2014	We initially reimbursed $25 separately for the screening interview and $25 for the baseline interview that included intervention exposure. We realized that the screening interview was brief and often occurred over the phone because it was difficult to conduct in busy clinic settings. We also realized, in collaboration with our patient-clinician advisory board, that it made more sense to reimburse participants for $50 for the baseline interview since these interviews were longer and in our study offices. We also changed from taxi vouchers to municipal transportation tokens because of the increased surcharge associated with taxi vouchers and participant preference.
Consent forms	Jan 27, 2014	For staff safety and the need to exclude or withdraw participants who were intoxicated, psychotic, or threatening, the consent also explains, “We also may ask you to stop taking part in this study if we feel it is in your best interest or if you do not follow the study rules.”
Consent forms	Jan 27, 2014	Clinicians needed to be contacted if their patient reported severe depression or anxiety. We updated our consent forms to fully explain this to participants:

		"We would need to contact your regular doctor or a medical provider for the following reasons: -You report or we observe that you are having: • A medical emergency such as a serious medical illness • Or, a serious mental illness, such as major depression • You report that you may harm yourself, you may harm someone else, or someone is harming you
Randomization	Jan 16, 2014	The initial IRB application was a Just-in-time submission for an NIH proposal. We initially planned to block randomize, as we did for a recent VA trial,[35] by both health literacy and race/ethnicity. However, given the diversity of patients at SFHN/ZSFG (over 50% non-white), in comparison to the VA, we decided to only block randomize by health literacy.
Data Collection Methods	Jan 16, 2014	To be more environmentally-conscious, we switched from paper surveys to use the LiveCapture function of RedCap. We retained the use of paper surveys in the event the RedCap system was down. All paper files continued to be stored in secure, locked research offices in secure, locked file cabinets.
Follow-up & Retention	May 28, 2014	We created an appointment reminder sheet to show the dates and times for upcoming primary care appointments as well as upcoming study appointments to help with retention.
Follow-up & Retention	Jan 16, 2014	We expanded the options for follow-up interviews to be not only in the clinic or by phone, but also in the home if needed as many of our patients had functional limitations.
Follow-up & Retention	Jul 15, 2014	For all participants who missed their primary care appointment and did not reschedule, we provided a courtesy phone call to remind participants to reschedule the primary care appointment.
Follow-up & Retention	Jul 15, 2014	Patients were enrolled based on upcoming primary care appointments. All follow-up interviews were timed to this primary care appointment. Some primary care appointments were subsequently missed or cancelled. In consultation with our stakeholder advisory committee and the DSMB, we decided that for participants who reschedule and attend their primary care appointment within 6 months, we would still conduct interviews at 1 week, and at 3, 6, and 12 months from the primary care appointment date. If participants do not reschedule within 6 months, we will conduct follow up assessments at 6 and 12 months from the primary care appointment date.

Follow-up and Retention	Jan 16, 2014	All data capture was by verbal survey administration and many of our follow-up interviews occurred over the phone. To help participants follow along during the interview, we mailed out a Participant Version of the survey to be used during the phone call if desired. No data were collected by mail.
Measures & Data Collection	Jan 4, 2016	We created a table displaying all study oucome measures, including validity and reliability information in both English and Spanish, number of survey items, references and the schedule of administration for our records and protocol.
Measures & Data Collection	Mar 12, 2013	Correction*: A priori*, we planned to collect ACP documentation data at 15-months (not 12 months as stated in our original and published protocol) to mirror the methods used in our previously published trial of PREPARE in the VA setting.[35] We fixed this typo in our final protocol. From the prior VA trial,[35] it was estimated that the time from the intervention to the primary care visit and the average time to schedule and conduct the final patient interview would be 3 months. Therefore, we standardized this window for all participants in this and our prior published trial.[35]
Measures & Data Collection	Jan 16, 2014	We initially proposed to screen for depression and anxiety using the -Patient Health Questionnaire-2 item (PHQ-2) and the Generalized Anxiety Disorder-2 item (GAD-2). Our DSMB felt more precise versions of this survey should be used. Therefore, we updated our methods to reflect assessment of depression and anxiety using the Patient Health Questionnaire-8 item (PHQ-8) and Generalized Anxiety Disorder-7 item (GAD-7).
Measures & Data Collection	Sept 20, 2017	Our Patient-Advisory Stakeholders requested we quantify the number and percentage of patients who increased their ACP activities overtime. Our stakeholders perceive any increase in an ACP activity over time as clinically meaningful. Thus, in addition to mean change in ACP Engagement scores, they wanted to know the percent of patients who improved over time for Behavior Change scores, Actions scores, and both combined. We defined improvement as an estimated overall slope > 0. Therefore, we created this exploratory variable post-hoc and used Bonferroni corrections to set the p-value of significance at 0.017.
Human Subjects Protections	May 28, 2014	Because we were assessing depression and anxiety as part of the trial, to err on the side of caution, the Patient-Clinician Stakeholder Advisory Board helped us create a flow diagram with detailed instructions, scripts, and telephone numbers for how staff could refer participants who report severe depression/anxiety if that were to occur. As above, this potential disclosure of participant information was provided on the informed consent form.

Summary of Changes to the Statistical Analysis Plan

Topic	Date	Summary of Changes
Refusals & withdrawal comparisons	Sep 30, 2016	We added a description of our planned analysis to compare participants who refused based on age and self-reported gender. We also added a description of our planned analysis to compare reasons for withdrawal between study arms.
Bonferroni corrections	Sep 30, 2017	We added Bonferroni adjusted p-values for all secondary and exploratory outcomes.
Stratifying results by language	Mar 1, 2014	Our PCORI grant was funded on Mar 1st, 2014 and allowed us to add Spanish-speaking participants to the trial. *A priori* and based on prior literature and the preferences of our stakeholders and grant funders, we added information about stratifying our analysis based on English and Spanish-speaking participants.
Models	Sep 30, 2016	We explain more fully the modeling terms in the mixed effects models.
Variable added to adjusted models	Sep 30, 2016	In addition to health literacy and clustering by clinician, we also adjusted all mixed effects models for baseline ACP documentation because, in consultation with our stakeholders, it was felt that these patients may be different from ACP naïve participants. This also mirrors the analysis in the prior VA PREPARE trial.[35]
Effect Size Definitions	Sep 30, 2016	We added information and references concerning clinically meaningful effect sizes.
Exploratory Outcome	Sep 30, 2016	Based on stakeholder request, we included a description of an added exploratory outcome to calculate the percentage of participants who increased their ACP Engagement scores. Bonferroni adjusted p-values for this post-hoc analysis were adjusted to a significance level of 0.017.
Interactions	Sep 30, 2016	We more clearly defined the variables used to test for interactions and how these variables were dichotomized for analysis.

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