PEACe
compare

Patient-centered and efficacious advance care planning in cancer: the PEACe comparative effectiveness trial

Grant number: 1R01CA235730-01

Protocol Number: STUDY19080337

Principal Investigator: Yael Schenker, MD, MAS, FAAHPM

ClinicalTrials.gov: NCT03824158

April 17th, 2024

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STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice (ICH E6), the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the NIDCR Clinical Terms of Award. All personnel involved in the conduct of this study have completed human subjects' protection training.

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Principal Investigator:

Signed: _____ Date: _____

Name: Yael Schenker, MD, MAS

Title: Principal Investigator

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LIST OF ABBREVIATIONS

ACP	Advance care planning
AD	Advance directive
CEQUEL	Caregiver evaluation of the quality of end-of-life care
CITI	Centralized IRB Training Initiative
CONSORT	Consolidated Standards of Reporting Trials
ECOG PS	Eastern Cooperative Oncology Group – Performance Status
EOL	End of life
eSYSDM	Electronic system for data management
GLMM	Generalized linear mixed model
HADS	Hospital Anxiety and Depression Scale
HRPO	Human Research Protection Office
ICU	Intensive care unit
IRB	Institutional Review Board
NQF	National Quality Forum
PI	Principal investigator
PTSD	Post-traumatic stress disorder
QOPI	Quality Oncology Practice Initiative
RN	Registered nurse
SAE	Serious adverse event
SW	Social worker
UAP	Unanticipated problem
UPMC	University of Pittsburgh Medical Center

PROTOCOL SUMMARY

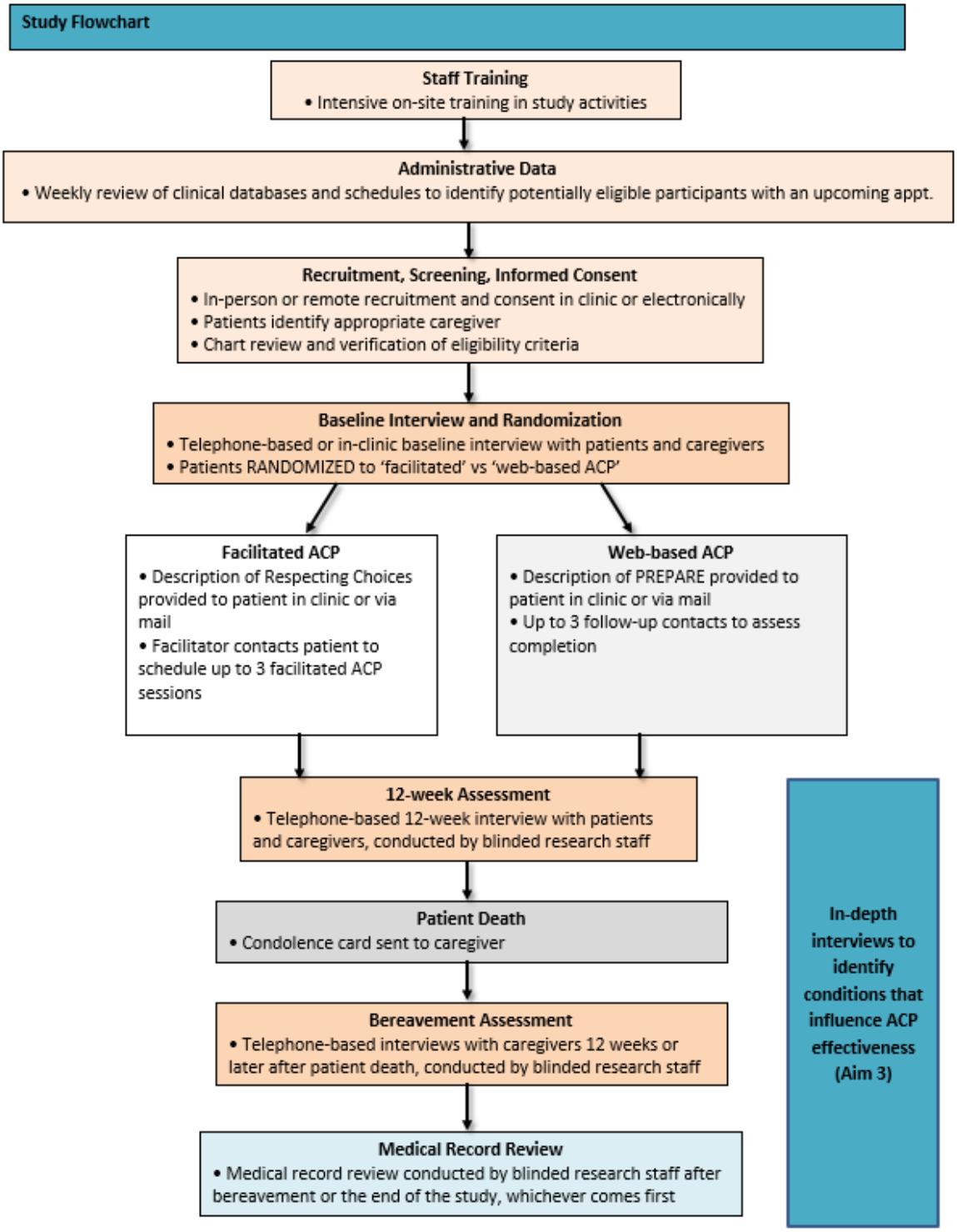
Title:	Patient-centered and efficacious advance care planning in cancer: the PEACe-compare trial
Précis:	PEACe-compare is a single-blind, patient-level randomized trial to compare the effectiveness of facilitated ACP vs web-based ACP among patients with advanced cancer and their family caregivers.
Objectives:	Aim 1: To compare the effectiveness of facilitated ACP versus web-based ACP on patient and family caregiver outcomes. Aim 2: To assess implementation costs and the effects of facilitated ACP and web-based ACP on healthcare utilization at end of life. Aim 3: To identify contexts and mechanisms that influence the effectiveness of facilitated ACP versus web-based advance care planning.
Population:	400 adult patients with advanced cancer and their caregivers
Sites:	The study will be conducted at UPMC Hillman Cancer Center clinics in Western Pennsylvania.
Description of Interventions:	Facilitated ACP will be conducted using the Respecting Choices® facilitated ACP conversation model. Patients randomized to this arm will participate in an in-person or remote (telephonic or video) facilitated ACP discussion led by a trained facilitator using a structured interview tool designed for adults with chronic, incurable illness. Web-based ACP will use the PREPARE for Your Care tool, an online ACP tool that includes 5 ACP steps using interactive videos. Patients randomized to this arm will view PREPARE on a home computer or on a tablet in the oncology office.
Study Duration:	5 years
Subject Participation Duration:	up to 5 years
Estimated Time to Complete Enrollment:	3 years

FUNDING
This trial is funded through a National Cancer Institute R01 grant: 1R01CA235730-01.

CLINICALTRIALS.GOV INFORMATION
This trial is registered at ClinicalTrials.gov: NCT03824158, registered on January 31, 2019.

ETHICS AND ADVISORY COMMITTEES
The study is approved by the University of Pittsburgh IRB: STUDY19080337.

SCHEMATIC OF STUDY DESIGN



1. BACKGROUND AND RATIONALE

Failure to deliver care near the end of life (EOL) that reflects the needs, values and preferences of patients with advanced cancer remains a key shortcoming of our cancer care delivery system.[1, 2] National organizations including the National Academy of Medicine and American Society of Clinical Oncology have called for increased attention to advance care planning (ACP) to improve patient-centered care near EOL.[1-4] A critical barrier to progress in the field is a lack of evidence about the most effective and efficient ACP strategy to improve treatment decisions near EOL and ensure patients' wishes are honored. Two widely-used patient-facing ACP interventions entail sizeable differences in costs and complexity to deploy: (1) discussions with trained facilitators[5] and (2) web-based advance care planning using interactive videos.[6, 7] These approaches have never been compared directly; it is therefore unclear whether one form of ACP is more potent—and if so, for whom and under what circumstances.[8, 9] Understanding the relative effectiveness of facilitated versus web-based ACP is important because facilitated ACP requires far more resources. This proposal addresses this evidence gap, using mixed methods to compare the effectiveness of facilitated ACP vs web-based ACP among 400 patients with advanced cancer and their caregivers.

2. AIMS AND OBJECTIVES

The purpose of this study is to compare the effectiveness and implementation costs of two different patient-facing ACP interventions among patients with advanced cancer and their caregivers: (1) facilitated ACP using the Respecting Choices® model versus (2) web-based ACP using the PREPARE online ACP tool. The study includes longitudinal outcomes that define successful advance care planning based on a recent international consensus panel[10] and incorporates a qualitative evaluation to identify factors that influence ACP effectiveness.

Aim 1 will compare the effectiveness of facilitated ACP versus web-based ACP on patient and family caregiver outcomes. Using a validated, patient-reported measure, we will compare the interventions' impact on ACP engagement at 12 weeks (1° outcome), ACP discussions with caregivers and clinicians, advance directive (AD) completion, and caregiver symptoms of depression and anxiety. For patients who die during the study period, we will use validated, caregiver-reported measures to compare perceived quality of EOL care, patients' EOL goal attainment, and bereaved caregiver symptoms of depression, anxiety, and post-traumatic stress.

Aim 2 will assess implementation costs and the effects of facilitated ACP and web-based ACP on healthcare utilization at end of life. To inform future dissemination efforts and aid in understanding optimal financing models, we will calculate implementation costs of each intervention and determine effects on healthcare utilization at EOL, including hospitalizations, chemotherapy use, and hospice use.

Aim 3 will identify contexts and mechanisms that influence the effectiveness of facilitated ACP versus web-based ACP. We will conduct a qualitative evaluation, using in-depth interviews with patients, caregivers, and clinicians, and perform thematic analysis to understand for whom, how, and in what circumstances facilitated ACP versus web-based ACP are most effective.

3. STUDY DESIGN

The study is a single-blind, patient-level randomized trial, using mixed methods to compare the effectiveness of facilitated ACP versus web-based ACP among 400 patients with advanced cancer and their caregivers.

3.1 Study Setting

The trial will be conducted with patients seen at the UPMC Hillman Cancer Center, one of the largest integrated community networks of oncologists in the United States with over 60 locations throughout Western Pennsylvania, Ohio, and New York. Within this network, we will focus recruitment at up to six sites representing a mix of academic and community practice models and a range of clinic sizes.

3.2 Eligibility Criteria

We designed patient eligibility criteria to be broadly representative of the population with cancer for whom ACP is most important. There are no inclusion or exclusion criteria based on gender, race, or ethnicity. There is a lack of good evidence regarding the optimal timing of ACP in advanced cancer[11, 12], but in most prior studies patients and clinicians preferred to delay the introduction of ACP to later in the illness trajectory rather than at the time of diagnosis.[13-15] The validated 'would not be surprised' question is a simple and effective method for identifying patients with cancer at high risk of dying in one year (hazard ratio 7.8).[16, 17] We do not include patients with hematologic malignancies because these diseases have very different trajectories and treatment options near the end of life,[18, 19] and the majority of patients seen at participating practices have solid tumors. We include patients who have previously completed an AD because preferences change and patients may benefit from additional engagement in ACP with changing health contexts.[12] We exclude patients < 18 because children with incurable cancer have unique ACP needs best served by clinicians experienced working with pediatric populations, and our study is conducted at adult oncology practices. Our teach-back method for informed consent is designed to ensure complete comprehension among vulnerable populations.[20]

3.2.1 Patient eligibility criteria

Inclusion Criteria	18 years of age or older
	Solid tumor
	The oncologist 'would not be surprised' if the patient died within the next year
	Eastern Cooperative Oncology Group performance status (ECOG PS) of 0, 1, or 2
	Planning to receive ongoing care at a participating oncology clinic
	Willing to participate in either a web-based or facilitated program
Exclusion Criteria	Does not speak English
	Inability to consent, using a validated teach-back method.
	Hematologic malignancy
	No phone for additional study contacts and follow-up interviews
	Unable to participate in advance care planning, as assessed by clinician
	Unable to complete the baseline interview

3.2.2 Caregiver eligibility criteria

Inclusion Criteria	18 years of age or older
	Family member or friend of an eligible patient
	Primary person involved in patient's care and best able to participate in the study, as assessed by patient
Exclusion Criteria	Does not speak English
	No phone for additional study contacts and follow-up interviews
	Unable to complete the baseline interview

3.2.3 Clinician eligibility criteria

Inclusion Criteria	Clinician of consented patients

3.3 Recruitment Methods

To facilitate recruitment, we use a process for identifying and screening study participants that has been IRB-approved and successful in our prior work.[21-25] Research staff at each clinic will review administrative lists and clinic schedules weekly with oncologists or their designated representatives to identify potentially eligible patients with solid tumors for whom the oncologist 'would not be surprised' if the patient died within one year. These criteria are not shared with patient and caregiver participants. Patients who meet initial criteria will be approached in-person by a clinical member of their oncology team who is already involved in their clinical care and offered a study recruitment brochure, or securely referred to the study team remotely and then contacted via the telephone for study recruitment.

For in-person recruitment, the referring clinician will obtain verbal permission from the patient before introducing a member of the research team. The research team will document that verbal permission has been obtained before approaching a patient. We will not introduce the study at the first

appointment in which a new diagnosis of metastatic disease is discussed, because this is a time of heightened anxiety when patients are unlikely to be receptive to ACP research.[15, 26] If verbal permission is obtained from the patient, this introduction from a member of the clinical team will be followed by a detailed, in-person explanation of the study from a trained research staff member. Patients may decline to hear more about the study and will be informed that their decision will in no way affect their medical care.

Patients referred to the study team remotely will be mailed a letter by the study team, on behalf of their oncologist. This letter will include a brief introduction to the study, inform the patient that they may be eligible to participate, and include instructions to call or email the study coordinator if they do not wish to hear further about the study. If patients do not contact the study coordinator within one week after the letter is sent, a trained research assistant or the study coordinator will call to review key study highlights and assess interest in participating.

A second invitation to participate will be offered to patients who decline initial participation (for example, because they are feeling too overwhelmed), but give permission to be re-contacted (either in person or by phone) at a later date. Study staff will review the tracking system weekly to maintain recruitment fidelity.

Patients who have provided consent to participate will be asked to identify a potential caregiver participant, designated by the patient as the primary person involved in their care and best able to participate in the study. Patients will be encouraged to contact the potential caregiver in advance of the research team to avoid any impression of cold calling. All caregiver participants will provide informed consent (either written or verbal option). Patients unable to identify a caregiver will not be excluded because these patients also face treatment decisions near EOL and may benefit from ACP.

Patients participating in an in-depth interview (Aim 3) will be asked to identify the clinician most involved in decisions about their care. Research staff will approach clinicians to introduce the study and offer a study information sheet. The consent discussion will be done at a time that is convenient for the clinician. All clinicians participating in an in-depth interview (Aim 3) will provide informed

consent.

3.4 Consent Procedures

All consent forms and procedures have been approved by the University of Pittsburgh Institutional Review Board.

Patient participants will provide written informed consent using the validated teach-back method. This is a modified informed consent process developed for vulnerable and low-literate populations.[20] The process involves: using a consent form written below a 6th-grade reading level and in a 14-point font; reading highlights from the consent form to potential subjects; allowing time for questions and discussion; allowing participants to read the form themselves, if desired; and verifying comprehension through repeated and targeted education until comprehension is achieved. If subjects require > 3 passes through the comprehension assessment, they will be deemed ineligible. Only after comprehension will we ask patient participants to sign the consent form. Patients recruited in-person by the study team will be asked to sign a paper copy of the consent form. Patients recruited remotely will be given three options to complete written consent: 1) paper consent form provided via the mail, 2) electronic consent form provided via email, and 3) electronic consent form sent through DocuSign, signed via electronic signature. All recruited study patients will be provided a copy of the completed consent form for their records.

Caregiver participants will also provide informed consent (either written or verbal option) and may participate in the teach-back with the patient if they are present for this discussion.

The study staff will consent clinicians verbally at a time that is convenient for them. Study staff will conduct a consent discussion with the clinician describing study procedures, anticipated risks and benefits, emphasizing the voluntary nature of participation, and eliciting any questions or concerns. After all questions have been addressed to the clinician’s satisfaction, study staff will request verbal consent. Consent will be documented in the study's secure electronic database.

3.5 Intervention Arms

Facilitated advance care planning arm

Participants randomized to the facilitated ACP arm will participate in Respecting Choices®, a facilitated ACP conversation designed for adults with chronic incurable illness. Conversations are led by a nurse or social worker with supportive oncology experience who has been trained as a Respecting Choices® facilitator. Each patient will participate in up to three face-to-face, video, or telephonic visits, lasting 45-60 minutes each. The facilitator initiates contact with a call to each patient to establish rapport, determine the preferred visit mode, schedule the visit, and facilitate overall intervention participation. Visits will include the patient's medical decision maker (health care agent), when available, and any other members of the family and/or caregivers the patient wishes to include. Visits will be held in a private location (oncology clinic, patient's home, or research office) and audio-recorded for fidelity monitoring. During the ACP conversation visit, facilitators will use the "First Steps® ACP Conversation Guide: Adults with Chronic Illness" structured interview tool as a discussion roadmap and provide guidance in choosing a medical decision maker, exploring serious illness understanding and experiences, identifying goals and values, and making future treatment decisions. Facilitators will provide a copy of the AD used throughout UPMC, assist with completion and uploading to the patient's electronic medical record, when appropriate, and make recommendations for communicating goals and sharing written preferences.

Web-based advance care planning arm

Participants randomized to the web-based ACP arm will use the PREPARE web-based ACP tool (available at *https://prepareforyourcare.org)* PREPARE is literacy- and culturally-appropriate and HIPAA-compliant. Instructions for accessing and using a secure, PEACe-compare study version of the PREPARE website, as well as a copy of the AD used throughout UPMC, will be shared with participants upon randomization. Patients and their caregivers review the 5 steps of PREPARE (approximately 10 minutes per step) and create an action plan for each step. After completing the steps, patients have the option of printing out a Summary and Action Plan. The website can be reviewed on a home computer or on a tablet in the patient's oncology practice. Website analytics will be provided to the research staff to gauge patient participation. Patients who have not logged on to the website will be called by study staff to assess and address any technical difficulties. During the check-in call, study staff will offer three options to participants in order to help them overcome any

practical or technological barriers preventing the patient from accessing the website: 1) to review the website on a study-supplied tablet during the patient's next oncology clinical visit, 2) to help walk them through signing up for the website initially, and 3) setting a goal date to review the website. If patients do not choose any of these options, they will be reminded that accessing the website is part of their study participation, and will be called again in a few weeks if they have not logged on to the website.

3.6 Randomization Procedures

Upon completion of baseline patient and caregiver interviews, patient-caregiver pairs will be randomized 1:1 at the patient level to receive either the facilitated ACP or the web-based ACP intervention. We chose patient-level randomization, consistent with most prior ACP trials, because both interventions are at the patient level and do not involve clinician- or system-level changes. The risk of contamination is extremely low because both interventions will be conducted in private and are unlikely to influence systematic changes in physician practices. To further ensure against any potential contamination, we will ask enrolled participants and caregivers not to discuss either intervention with other patients or caregivers once they are told which group they have been randomized to.

The randomization sequence will be generated by the lead statistician who will not be involved in study recruitment or treatment allocation. The statistician will use R (R Foundation for Statistical Computing, Vienna, Austria) to generate a randomization sequence that will be fed into the web-based database portal, so that each patient-caregiver pair will be randomly assigned to a group upon completion of their baseline interview.

3.7 Blinding

All outcome assessments will be conducted by blinded research staff who are not involved in ACP interventions or follow-up contacts to assess intervention completion. At the start of each outcome assessment interview, participants are reminded not to discuss study materials with research staff. It is not possible to blind patient and caregiver participants. However, they are told during the consent process that there is a "50/50 chance" of getting one of two different tools to help patients have a voice in their care, and patient/caregiver participants provide informed consent before randomization.

We obtain clinicians' permission to recruit their patients but do not share information on randomization or involve clinicians in intervention administration. However, it is possible that participants will discuss ACP participation with their clinicians.

3.8 Intervention Fidelity

Training of Respecting Choices® ACP facilitators is overseen by experienced Respecting Choices® staff members. We train nurses (RNs) or social workers (SWs) because these non-physician members of the clinical team are typically trained as ACP facilitators and are widely available in outpatient oncology settings, maximizing feasibility of future dissemination. We select facilitators who do not provide other clinical duties at participating sites to guard against potential contamination. Clinical leaders at participating sites are asked to meet with and approve ACP facilitators to ensure oncology-relevant experience and mutual trust. Selected facilitators complete on-line prerequisite modules and attend a competency-based, in-person Respecting Choices® ACP Facilitator Certification program. Participants demonstrate competency in ACP facilitation through role play demonstration in small group observation and feedback. Participants develop a plan for improvement of identified skill deficits as needed. Upon completion of training, facilitators will conduct several mock ACP sessions using case scenarios provided by Respecting Choices® while being observed by trainers to certify acquisition of key skills. To ensure consistent delivery of facilitated ACP at participating sites, identify any problems in delivery that may require immediate remediation or modifications in future settings, and reduce drift in adherence to ACP protocols over time, all ACP sessions conducted during the study are audio-recorded. Each month, one to two audio-recordings per facilitator are reviewed and scored for fidelity to key constructs per Respecting Choices® evaluation standards. Feedback on reviewed sessions is discussed during regular intervention team meetings and with a consultant from Respecting Choices®.

We monitor fidelity in the PREPARE intervention arm by using analytics from a secure, study-specific website that allows us to track the number of log-ins and number of ACP steps completed by each participant. Analytics data will be examined by an un-blinded research staff member.

Participants in both arms will receive check-in calls between baseline and the 12 week follow-up. Participants in the Respecting Choices® arm will be called to schedule the Respecting Choices® intervention visits with an ACP Facilitator. Participants in the PREPARE arm will be called (up to

three times) to assess for and troubleshoot any participation issues if they have not logged on to the PREPARE website.

All contacts with study participants follow standardized study scripts. All staff members are rigorously trained to follow study operating procedures and are not permitted to conduct study tasks independently until they have been observed and demonstrated mastery.

3.9 Data Collection Methods

We will use a secure electronic System for Data Management (eSYSDM) for all data entry and management. To minimize participant burden and disruption to clinical activities, baseline surveys may be completed either in-person, by telephone, or by mail. Medical record reviews will be conducted by blinded clinical research staff. Twelve-week and bereavement assessments will be conducted via telephone by blinded research assistants trained in study procedures. In the event a participant is unable to complete the interview by telephone or unreachable after seven attempts, a paper copy will be mailed. All data from paper documents will be entered into the eSYSDM by research staff and verified using standardized data entry procedures. Original paper source documents will be filed and locked in a filing cabinet accessible only by study staff members.

3.10 Follow-up and Retention

Follow-up assessments will be conducted with patients and caregivers at 12 weeks, and with caregivers at bereavement (12 weeks or later after patient's death). To enhance retention, we distribute contact cards with the contact information for study staff, mail reminder cards, mail answer guides prior to telephone assessments, and send condolence cards to referred family caregivers when a patient dies. Our data collection strategy is designed to minimize participant burden by using parsimonious measures previously pilot-tested with this population, administering patient and caregiver interviews by phone, and providing compensation. Enrolled patients and caregivers will be paid $25 each upon completion of the 12-week follow-up assessment. Enrolled caregivers will be paid $25 each upon completion of the bereavement assessment, if applicable.

Enrolled patients and caregivers will be paid an additional $25 each if asked to complete the qualitative in-depth interview.

3.11 Withdrawal

Participants may withdraw from the study at any time. All previously collected information will continued to be used for study purposes until study completion. For participants who wish to withdraw, we will ask them why. For participants who do not have a response to this open-ended question, we will offer a list of reasons for withdrawal from previous studies (e.g., not enough time, no longer interested, no benefit, etc).

4. MEASURES AND ASSESSMENTS

4.1 Overview

Successful ACP influences multiple important outcomes. We selected priority outcomes related to patients, caregivers, and healthcare utilization based on an organizing framework developed by an international panel of ACP experts.[10] We focused on outcomes for which validated and parsimonious measures have been developed for use with seriously-ill participants. We chose a 12-week time-point for patient and caregiver assessments to balance the need to allow sufficient time for ACP to occur without incurring excessive loss to follow up in a seriously-ill population. For patients who die during the study period, we will conduct brief additional interviews with bereaved caregivers 12 weeks or later after a patient's death, allowing assessment of EOL care and caregiver bereavement adjustment while minimizing participant burden. Additionally, we will review medical records for documented care goals and EOL healthcare utilization.

4.2 Primary Outcome

We chose patient-reported engagement in ACP as our primary outcome because this validated measure reflects a patient- and caregiver-centered understanding of ACP as a complex process involving multiple behaviors, rather than simply completion of an advance directive. Importantly, the 15-item version of the ACP Engagement Survey measures a broad range of ACP behaviors, is able to detect change in response to ACP interventions, and can be administered with minimal participant burden.[27]

4.3 Secondary Patient and Caregiver Outcomes

We will additionally measure ACP discussions with caregivers, ACP discussions with clinicians, and AD completion (using both a single question and by reviewing medical records for any new ACP documentation). For patients who die during the study period, we chose caregiver-reported measures of goal-concordant EOL care because these validated measures capture overall receipt of goal-concordant care in the last month of life and incorporate the perspectives of bereaved family members. In contrast, measuring receipt of goal-concordant EOL care based on chart review does not account for frequently-encountered situations in which documented ADs do not reflect the

current, real-time clinical scenario. Similarly, we chose a validated, caregiver-reported measure of quality of EOL care because cancer caregivers provide an important and reliable perspective on this outcome.[28, 29] We include measures of caregiver depression, anxiety, and post-traumatic stress symptoms because many patients cite easing the burden on families as a motivator of ACP and it is possible that family caregivers may experience less distress after participating in a facilitated ACP intervention.

Patient and Family Caregiver Outcomes (Aim 1)		
Specific Measure	**Description**	**Timing**
ACP Engagement **(primary outcome)**	15-item ACP engagement survey assessing ACP processes related to choosing a medical decision maker, discussing and documenting preference for care at EOL, flexibility for surrogate decision making, and asking questions of medical providers. Single summary score (range 0-5 with higher scores indicating higher engagement) has high internal consistency (Cronbach's alpha=0.92) and responsiveness to change.[27]	Baseline, 12 weeks
ACP discussions with caregivers	"Have you talked with your family or friends about the kind of medical care you would want if you were very sick or near the end of life?"[27, 30, 31]	Baseline, 12 weeks
ACP discussions with physicians	"Have you talked with your doctor about the kind of medical care you would want if you were very sick or near the end of life?"[27, 30, 31]	Baseline, 12 weeks
AD completion	Single question will assess AD completion. We will additionally assess documented care goals by reviewing medical records for any new ACP documentation, including AD forms or documented discussion.	Baseline, 12 weeks
Receipt of goal-concordant EOL care	Two validated caregiver-reported questions have been used to measure receipt of goal-concordant EOL care for patients with cancer: (1) "In your opinion, to what extent were [the patient's] wishes followed in the medical care received in the last month of life?"; and (2) Caregivers asked about patient's preferred and actual places of death, with questions separated in the survey to minimize conscious comparison.[32]	Bereavement
Quality of EOL care	The Caregiver Evaluation of Quality of End-of-Life Care (CEQUEL) scale is a 13- item instrument (range of scores 13-26) with demonstrated reliability and convergent validity among cancer caregivers.[28] Strengths include brevity and clinical relevance, with inclusion of 4 distinct but related factors (prolongation of death, perceived suffering, shared decision-making, and preparation for death) associated with caregiver bereavement outcomes.[28]	Bereavement

Depression and anxiety symptoms	Hospital Anxiety and Depression Scale (HADS) is a widely-used 14-item instrument measuring symptoms of depression and anxiety.[33] It has been extensively validated for screening emotional distress among advanced cancer patients[34] and family members.[35] Score of ≥ 8 on either domain indicate significant symptoms of depression or anxiety with good sensitivity and specificity.[36]	Baseline, 12 weeks, Bereavement
Post-traumatic stress symptoms	Impact of Events Scale is a 22-item self-report instrument for PTSD symptoms with 3 subscales measuring intrusion (8 items), avoidance (8 items) and hyperarousal (6 items).[37] Subscales have high internal consistency (Cronbach's alpha ranging from 0.79-0.92).[38] A score of 30 or higher is considered a clinically significant burden.	Bereavement

4.4 Healthcare Utilization Outcomes

Using methods refined in our previous work,[21] we will assess healthcare utilization at the end of life via caregiver bereavement interviews and medical record review, allowing us to accurately assess use for participants hospitalized in multiple hospital systems.[39] We will measure intensity of EOL care using the American Society of Clinical Oncology's Quality Oncology Practice Initiative (QOPI)[40] and National Quality Forum (NQF)[41]-endorsed measures: chemotherapy administered within the last 2 weeks of life; hospitalizations (>1) or ICU admission in the last month of life; >1 emergency room visit in the last month of life; hospice enrollment; hospice enrollment within 3 days of death; and number of days in hospice.

We will additionally assess ACP implementation costs by tracking staff time spent on each intervention arm. Staff time costs for each intervention will be estimated by multiplying staff training and patient care time related to the intervention in hours by the average hourly wage for US nursing and social work staff of comparable levels.[42]

4.5 In-depth Interviews

We will conduct in-depth interviews with a subset of patients, caregivers, and clinicians to identify contexts and mechanisms that influence ACP effectiveness. These interviews are based on a realist evaluation paradigm, drawing on qualitative methods to investigate factors and conditions under which certain outcomes will or will not be realized.[43] This contextual evaluation expands on the comparative effectiveness data generated in Aims 1 and 2 to answer the guiding questions (1) "what

makes each ACP intervention work," and (2) "for whom and under what circumstances is each ACP intervention most effective."[44]

Patients and caregivers will be invited to participate in in-depth interviews after completing trial outcome assessments (12-week and bereavement, respectively) to avoid impacting trial integrity. We will recruit equal numbers of participants from each ACP intervention arm. Within each intervention arm, we will include participants for whom the intervention was succesful (defined as an increase in ACP engagement at 12 weeks) and not successful (defined as no increase in ACP engagement at 12 weeks). This sampling strategy will ensure elicitation of a spectrum of experiences regarding what makes each intervention work (or not work) for changing ACP behaviors. We will aim for linked patient-caregiver pairs because caregivers may lend additional perspective on patient EOL experiences. Because ACP also involves clinicians and healthcare systems, we will ask patients to identify a clinician most involved in decisions about their care and interview these stakeholders after patient and caregiver interviews have been completed. As recommended for qualitative research, the sample size is not fixed. Rather, we will conduct interviews until thematic saturation is reached, meaning no new themes emerge from the data. Based on our prior work, we anticipate that this will involve at least 60 patients and 60 caregivers and approximately 60 clinicians.[45-48]

Interviews will be conducted using semi-structured interview guides informed by (1) a theoretical framework for ACP based on behavior change theory and (2) the literature on factors that may affect the ability of ACP interventions to improve ACP outcomes. Interview guides will be developed by a multidisciplinary group (including patient and caregiver representatives) and piloted with 2-3 representative stakeholders prior to use. All interviews will be conducted by an experience qualitative researcher with extensive in-depth interviewing experience, audio-recorded, and transcribed verbatim. Interview questions will be modified as new themes emerge from the data.

4.6 Additional Measures

We will collect basic demographic data from participants at time of enrollment, including age, sex, race/ethnicity, religion, social support (8-item modified Medical Outcomes Study Social Support

Survey[49]), health literacy (single-item question validated among diverse patient populations[50]), length of patient relationship with oncologist, cancer type, and performance status. We will additionally assess illness understanding,[29, 51] care preferences,[52] past ACP and decision-making experiences (prior surrogate, prior experiences making decisions for self or others),[53] distress (single-item distress thermometer),[54] and decisional certainty (decisional conflict scale).[55]

As recommended for trials of complex interventions, we will collect process data to understand ACP implementation in both arms.[56, 57] We will track the timing, length, and content of ACP using standardized checklists and website usage data.

5. STATISTICAL ANALYSIS PLAN

5.1 Baseline Data

We will evaluate the statistical properties of baseline and follow-up outcome measures, including potential outliers, normality, and missing data, using summary statistics and graphical tools. Participant demographics and clinical characteristics will be presented as frequency (%) for categorical variables and mean (standard deviation) for continuous variables (or median and range for continuous variables with heavily skewed distributions). Results will be reported following the CONSORT guideline.

5.2 Primary and Secondary Outcomes

All analyses for treatment group comparisons will use an intention-to-treat approach.

The primary outcome is ACP engagement. We will test the effect of treatment assignment on the primary outcome using linear mixed models. The model will include treatment group, and baseline ACP engagement as fixed effects. To adjust for possible clustering of patients seen by the same facilitator or provider, we will include random effects for facilitators (for patients in the facilitated ACP group only) and oncologists.

The same analytic approach will be used for secondary outcomes: perceived quality of EOL care and caregiver symptoms of anxiety, depression and PTSD. Binary outcomes such as ACP discussions, AD completion, documented care goals, and receipt of goal-concordant EOL care will be compared using mixed effect logistic regression with the same set of fixed effects and random effects as in the models for continuous outcomes. We will also compare the rates of completion of intervention between the two intervention groups, using the same model as for other binary outcomes.

Analyses of health care utilization data will use GLMM (generalized linear mixed model), with logit link (binary distribution) for dichotomous (yes/no) health care outcomes such as chemotherapy within last 2 weeks of life. Again, we will use intervention group and baseline ACP as fixed effects and oncologist and clinic as random factors.

5.3 Handling of Missing Values

We will prevent and monitor missing data by using an eSYSDM, which will automatically produce an error message notifying the user that the field must be completed when required fields are left blank. The eSYSDM also performs important tracking duties by monitoring screening information, eligibility status, follow-up interviews due, and study group assignment to ensure that the required data collection instruments are administered within the time constraints dictated by the study protocol. We will compare baseline characteristics between patients with complete follow-up to those without by randomization group, in order to assess potential biases that may exist in the complete case analysis. We will also record and report all reasons for study drop-out using a withdrawal/termination form to assess the missing data mechanism (missing completely at random, missing at random, or non-ignorable missingness, meaning the data missingness is related to the actual value). We will conduct sensitivity analyses for primary and secondary outcomes using several validated methods: (1) complete case analyses, which assumes missing completely at random; (2) multiple imputation using M=10 imputations, which assumes missing at random; and (3) assigning poor scores and good scores for missing values differentially by treatment group, which aligns with non-ignorable missingness.

5.4 Interim & Final Analyses

We will not have any planned interim looks for stopping for efficacy. The final analyses will be conducted once study follow-up is complete, after all data is cleaned and the study database is locked.

5.5 Sample Size and Power Calculations

We selected our sample size to provide ample power to assess differences in the primary outcome—ACP engagement—as well as secondary patient, caregiver, and healthcare utilization outcomes. All calculations were conducted using $\alpha=0.05$, based on two-sample t-tests for continuous outcomes and chi-squared tests for binary outcomes. To adjust for possible clustering effect within each oncologist, we used the design effect ($DE=1+[(1+CV^2)m-1)]\rho$), where CV=the coefficient of variation for cluster size[58] and m=the number of patients per oncologist. Conservatively estimating a 25% loss

to follow-up for patient-reported outcomes, our sample size will provide >98% power to detect a moderate effect size (Cohen's d=0.5) in our primary outcome—ACP engagement.[27] While any increase in ACP engagement may be associated with clinically meaningful improvements in EOL outcomes,[27] a minimal clinically important difference has not been established. A moderate effect size (0.35 on a 5-point score, based on a SD of 0.7),[27] ensures that we will be able to detect a difference comparable to the changes seen with ACP interventions in prior trials.[6, 27] We will have >78% power to detect a 15% difference in rates of ACP discussions with family and physicians between groups (assuming discussion rates of 25% in the web-based arm) and >99% power to detect a 20% difference in rates of AD completion (assuming an AD completion rate of 50% in the web-based ACP arm). Power is similarly adequate for all caregiver-reported outcomes, assuming a 75% caregiver participation rate and 15% loss to follow-up, which results in an effective sample size of 254. For caregiver-reported quality of EOL care we will have 97.6% power to detect a moderate effect size[28], and for caregiver anxiety and depression we will have 83.2% power to detect a clinically meaningful difference (Cohen's d=0.368).[59] Anticipating that 90% of patients will die during the study period (resulting in an effective sample size of 360), we will have >73-78% power to detect an 8% absolute decrease in ICU admissions and chemotherapy use at the EOL and >80% power to detect a 15% decrease in no hospice or hospice ≤ 3 days before death, based on national data.[60]

5.6 Qualitative Analysis Plan

We will perform iterative, thematic analysis to illuminate key contexts and mechanisms influencing outcomes for each ACP strategy. Preliminary coding will be done by the interdisciplinary investigative team, with robustness assessed through a kappa statistic. Once the coding scheme is standardized, the remainder of coding will be conducted by research staff using qualitative analysis software, with supervision from investigators and cross-checking to ensure confirmability. Regular interdisciplinary meetings will be held to identify themes emerging from the data and revise the initial conceptual model. The final product of this Aim will be a detailed conceptual model providing plausible explanations about how, for whom, and in what circumstances each ACP intervention influences outcomes.

6. MONITORING

6.1 Human Subjects Protections

All study staff will be required to complete standard CITI modules related to research ethics and compliance training in human subjects research. Certificates of completion are kept on file, and checked monthly for upcoming expiration. Study staff will be required to renew expiring certificates before continuing involvement in the study. Weekly project management meetings are held with study staff to ensure that research protocols are followed. Our informed consent process ensures that participants have a clear understanding of the study and can freely choose not to participate without affecting their care or relationships with UPMC or the University of Pittsburgh in any way.

6.2 Minimizing Risks to Participants

The potential risks to patient and caregiver participants in both arms of the trial consist mainly of concerns about invasion of privacy and perceived burden or emotional upset from completing questionnaires about personal physical and mental health and/or the health of a loved one. In addition, there are potential risks to participants in both arms of emotional upset caused by the experience of thinking and talking about serious illness and advance care planning. However, based on prior experience with both interventions, these potential risks are quite small. For example, in a prior trial of the PREPARE web-based ACP intervention, there were no adverse events and there was no increase in depression or anxiety when compared to written ADs alone.[6] In a prior trial of facilitated ACP using the Respecting Choices® model, facilitated ACP was associated with less stress, anxiety and depression among bereaved family members when compared to a control group.[5] Participants in the facilitated ACP arm may feel self-conscious about having facilitated ACP sessions audio-recorded and may additionally experience inconvenience or burden if additional appointments are required for facilitated ACP sessions.

We take several steps to ensure confidentiality and avoid invasion of privacy. All study personnel will be properly trained in the protection of human subjects. To maintain confidentiality of all study materials, we will record names and other personally identifying information only on the tracking forms; all other material will use unique identification numbers. Identifying information and de-identified study records will be kept in separate locked file cabinets and separate files on password

protected computers. All study databases will be maintained on password protected servers and routinely backed up to an encoded password protected file. All facilitated ACP visits will be conducted in a comfortable and private or semi-private setting. Telephone interviews will be conducted from a private or semi-private research office. Study staff will not re-contact patients who initially decline to learn more about the study or be re-contacted.

To reduce the risk of emotional distress, we will adhere to the following standardized procedures. First, to address potential emotional upset from answering questions about personal physical and mental health and/or the health of a loved one, study staff will remind participants of the voluntary nature of study participation and notify them at the start of administration of each questionnaire that they are free to skip or decline any questions they wish or to discontinue participation at any time, if desired. If a participant's emotional upset escalates while completing study procedures over the phone, the study coordinator/research assistant will follow a safety protocol that we have successfully deployed in our prior work (see Telephone Safety Protocol in Appendix).

If a participant experiences emotional upset while in the clinical setting undergoing study procedures, the ACP facilitator will be with participants. These ACP facilitators are experienced nurses who will receive additional training in supportive care in their role as Respecting Choices® ACP facilitators. In addition, they will have a palliative care physician investigator available at all times by telephone for any questions or concerns. They will therefore be capable of handling these issues appropriately.

Participants will be given the option of in-person or remote (telephonic or video chat) intervention delivery. Remote intervention delivery will be completed utilizing secure, HIPAA-compliant audio and visual platforms. In order to decrease the burdens of travel and scheduling, we will make every attempt to schedule in-person facilitated ACP sessions at a time and place that is convenient for patients. Directions and parking information will be provided to participants prior to the date of their scheduled session to facilitate an easier travel plan. Participants will receive parking vouchers, if they choose to complete study procedures at the research office. Additionally, participants randomized to the Respecting Choices® arm of the study will have the option of having the ACP facilitator come to their homes to conduct the study visit, when appropriate and advisable.

If the research staff or investigators learn that the patient or caregiver participant or someone with whom they are involved is in serious danger or potential harm, they will inform the appropriate agencies, as required by Pennsylvania law. The requirement to report such information is referenced in the study patient and caregiver participant informed consents. This research is covered by a Certificate of Confidentiality from the National Institutes of Health, which is explained in detail in the patient and caregiver participant informed consents.

6.3 Data and Safety Monitoring Plan

Data and safety monitoring will be the shared responsibility of the research team, led by the PI, Dr. Schenker. A Data and Safety Monitoring Board is not required for this minimal risk trial. The study PI and co-investigators will meet monthly to review study progress and any new developments or changes to the risk-benefit ratio. In addition, data quality will be reviewed quarterly by the full study team.

The data and safety monitoring plan will address the following areas: (1) the progress of the research study, including assessment of data quality and timeliness, and participant recruitment, accrual, and retention; (2) review of adverse event data to determine whether or not there is any change to the anticipated risk-benefit ratio of study participation, and whether or not the study should continue as originally designed, or be changed or terminated; (3) assessment of external factors or relevant information; (4) review of study procedures designed to protect the privacy of the research participants and the confidentiality of their research data. A yearly summary will be submitted to the University of Pittsburgh Human Research Protection Office (HRPO) during annual IRB renewal.

6.3.1 Adverse Event Monitoring

All adverse events will be tracked by the study coordinator and urgent problems (major complaints about the intervention or safety protocol triggers) will be brought to the PI in real time. The statistician will run a mortality report for review at quarterly data quality meetings.

Adverse events, serious adverse events (SAEs), and unanticipated problems (UAPs) will be monitored using standard definitions. Deaths (other than those resulting from suicide) and

hospitalizations will not be tracked as adverse events in this population. All SAEs and UAPs will be reported to the University of Pittsburgh HRPO as per their policy and procedures.

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8. APPENDIX

Telephone Safety Protocol