Cover page

Official Title: An interactive advance care planning intervention to facilitate a good death for cancer patients

NCT number: NCT01912846

Date of the Document: 2018/1/24

Specific Aims: The primary objectives of this 5-year randomized controlled trial (RCT) of a theory-based, tailored, multifaceted, interactive advance care planning (ACP) intervention are to examine the extent to which the proposed ACP intervention will (1) increase the congruence between terminally ill cancer patients' preferred and actual end-of-life (EOL) care, (2) improve quality of life (QOL), depressive and anxiety symptoms of patients and caregivers during the patient's dying process, and (3) enhance family caregivers' bereavement adjustment. The secondary objectives are to determine the effectiveness of the proposed ACP intervention in facilitating patients' prognostic awareness and EOL care discussions among patients, families, and physicians; in increasing patient-caregiver agreement on preferences for EOL care; and in reducing aggressive EOL care treatments for terminally ill cancer patients.

A randomized controlled trial with a tailored, multifaceted ACP intervention will be conducted on a convenience sample of 231 dyads of terminally ill cancer patients and caregivers with the same number of attention controlled group to evaluate the intervention's effectiveness.

We hypothesize that the proposed intervention will (1) facilitate terminally ill cancer patients' prognostic awareness; EOL care discussions among patients, family caregivers, and physicians; and patient-caregiver agreement on preferences for EOL care as death approaches; (2) reduce aggressive healthcare resource utilization at EOL; (3) increase congruence between the patient's preferred and actual EOL care; (4) improve QOL, depressive and anxiety symptoms of patients and family caregivers during the patient's dying process; and (5) enhance family caregivers' bereavement adjustment. We also hypothesize that the proposed intervention will facilitate patients' prognostic awareness and EOL care discussions among patients, families, and physicians; increase patient-caregiver agreement on preferences for EOL care; and reduce aggressive EOL care treatments for terminally ill cancer patients.

Eligibility criteria for terminally ill cancer patients: (1) diagnosed with a terminal stage disease that continues to progress with distant metastases and judged by their oncologists as

unresponsive to current curative cancer treatment, (2) cognitively competent, (3) able to communicate with data collectors, (4) age>20 years, and (5) having a designated family caregiver who agrees to participate in the survey. Family caregivers will be recruited if they are: (1) family members of cancer patients with a terminally ill disease as defined by this proposed study, (2) identified by patients as the primary person caring for the patient without financial reimbursement for that care, (3) age>20 years, and (4) agree to participate and can communicate with data collectors. Patients and family caregivers will be excluded if they participate in other research to facilitate prognostic awareness, ACP, QOL, or psychological well-being.

Sample size calculation: There was no interventional study directly investigating the effectiveness in increasing the extent of congruence between patient preferred and actual end-of-life (EOL) care received by terminally ill cancer patients; therefore sample size estimation will be based on the effectiveness of holding EOL care discussions between patients and physicians on the extent to increase congruence between the patient's preferred and actual EOL care received. Patients who reported having EOL care discussions with their physicians significantly more likely to receive EOL care consistent to their preferences (OR=2.26; p<.0001) and received significantly fewer aggressive medical interventions near death, with lower rates of CPR (0.8% vs 6.7%; AOR, 0.16; 95% CI, 0.03-0.80), mechanical ventilation support (1.6% vs 11.0%; AOR, 0.26; 95% CI, 0.08-0.83), and ICU care (4.1% vs 12.4%; AOR, 0.35; 95% CI, 0.14-0.90), respectively. A sample size of 124-195 dyads per group achieves 80% power to detect a difference between the interventional and control group by a two-sided hypothesis test with a significance level of 0.05. In compensating the 18.5% of attrition rate found in our previous longitudinal study, 147-231 dyads per group are needed. The proposed sample size will be targeted on 231 dyads per group to ensure adequate power to detect the hypothesized effects of the proposed intervention. Approximately 8-10 new dyads of terminally ill cancer patients and their family caregivers were recruited in each month. In order

to recruit the targeted 462 dyads (231 dyads in each treatment group) of subjects. After development of detailed study protocol, subjects will start to enter into the study at the beginning of the 6th month of the study through the 54 th month and be followed through the 5th year of the proposed study period.

Components of the proposed study arms

ACP Intervention: The goal of this theory-based, tailored, multifaceted, interactive ACP intervention is to facilitate discussions among terminally ill cancer patients, their family caregivers, and their primary physicians about the patient's preferences for EOL care and to honor the patient's wishes. To that end, the ACP intervention will clarify each participant's understanding of the patient's prognosis and treatment options and her/his readiness to engage in ACP, help participants appropriately weight the benefits and burdens of medical treatments at EOL, and clearly define and document the patient's preferences for the primary physician to use later to guide EOL care decision-making that honors the patient's preferences. The intervention constitutes dynamic and multiple interactions between patients, family caregivers, and primary physicians and a tra**in**ed, master's-prepared ACP interventionist with experience in oncology nursing and palliative care. The ACP interventionist will use two decision aids (a workbook and a video) to enhance participants' understanding of the essential elements in ACP and aggressive EOL care.

The major components of the proposed ACP intervention include: (1) repeated assessments of participants' readiness to engage in ACP; (2) specific interventions tailored to the participants' readiness to engage in ACP; (3) facilitating prognosis communication and EOL care discussions among patients, family caregivers, and physicians, and (4) use of a workbook and a video educational aid to facilitate understanding of ACP and life-sustaining treatments at EOL.

The trained ACP interventionist will begin each course of the ACP intervention by independently and separately assessing each patient's and family caregiver's readiness to

engage in ACP. The ACP interventionist will assess participants' understand**in**g of how the illness is likely to progress, preferences and goals for EOL care, and readiness to engage in ACP. "Course" refers to each repetition of the four major intervention components. Each course will assess participants' readiness for ACP and preferences for EOL care to determine if they have changed over time and to adjust the intervention accordingly. The participant's stage of readiness to engage in ACP will be determined according to the Transtheoretical Model (TTM).[128] The TTM integrates key constructs from other theories to describe how people acquire a positive behavior. Indeed, the TTM has served as the basis for developing many effective interventions to promote health behavior change.[128] The model's central organizing construct is that a behavioral change occurs in five stages. In this study, we propose that in the first stage, precontemplation, the participant is unaware of the prognosis or has no desire to engage in ACP planning. In the second stage, contemplation, the participant understands the relevance of ACP to his/her life and begins to consider his/her values and future treatment preferences. In the third stage, preparation, the participant commits to engage in ACP soon, but is not yet ready to do so. In the fourth stage, action, the participant overtly engages in ACP, e.g., discusses and clarifies his/her preferences for EOL care with family members and healthcare professionals. In the fifth stage, maintenance, the participant has made EOL care decisions and can periodically evaluate these decisions given changes in her/his life status.[99,129]

The intervention protocol in this trial will not follow a script for discussing pre-specified topics. Rather, the trained ACP interventionist has the flexibility to provide participant-centered care tailored to the participant's specific needs at each stage of readiness to engage in ACP.[130] For participants in the precontemplation stage, the goal of the individualized intervention is to address participants' lack of readiness to engage in ACP and to motivate them to think of the relevance of ACP. For participants in the contemplation stage, the ACP interventionist will discuss life-sustaining treatments and palliative care that may be applicable to that patient, explain the benefits and burdens of each treatment, and encourage patients and

families to evaluate benefits and burdens from their own perspective. For participants in the preparation stage, the ACP interventionist will help them to determine specific preferences for EOL care and to communicate their preferences and concerns to primary physicians. For participants ready to take action in ACP, the ACP interventionist will communicate patients' and family caregivers' preferences for EOL care to the primary physicians, thus facilitating EOL care discussions to achieve a consensus of goals for EOL care and specific treatments that will be used or withheld. For participants who have made EOL care decisions, the ACP interventionist will continually support and reassure them that their goals and EOL care plan will be periodically reviewed based on changes of the patient's health status and their preferences.[130] (Detailed protocol for each stage will be developed in the first year of the proposed study).

To enhance consensus in perceptions of the prognosis and goals/preferences for EOL care among terminally ill cancer patients, their family caregivers, and physicians, the ACP intervention protocol will be designed to facilitate discussions about these topics throughout the dying process. Since patients' preferences and concerns fluctuate over the dying process,[117] a basic tenet of this intervention is that ACP will be revisited periodically to ascertain any changes in participants' values regarding an acceptable QOL and desirable EOL care as the patient's death approaches. After the initial intervention course, the ACP interventionist will interact with participants at least every month until the patient dies. If the patient's health status declines as assessed by the primary physician or he/she experiences sentinel events, such as initiating a new chemotherapy regimen, deciding to undergo major surgery, admission to an ICU, initiating mechanical ventilation, or new hemodialysis, and diagnosed with CNS metastasis,[78] the next intervention course will be scheduled immediately to readdress the participant's goals and preferences for EOL care. The tailored intervention will be provided according to the participant's specific needs.

Physicians caring for participants in the intervention group will receive individualized 1-page patient- and family caregiver-specific feedback forms, based on interview responses, to facilitate EOL care discussions with terminally ill cancer patients and their family caregivers. The patient- and family caregiver-specific feedback forms will be generated using an automated, computerized process that reflects the patient's or family caregiver's reported responses, including whether he/she knows the patient's prognosis, her/his desire/readiness to engage in ACP, and preferences for specific EOL care treatments,[122] including goals of EOL care (comfort-oriented or life-prolonging) and when or if the patient/family caregiver prefers to receive ICU care, CPR, intubation with mechanical ventilation support, intravenous nutrition or hydration, hemodialysis, and hospice care. The trained ACP interventionist will build rapport with physicians caring for participants in the intervention group to provide feedback and to reinforce physicians' communication with participants, help them manage patients' and family caregivers' negative emotional reactions, and minimize their time constraints in delivering sensitive information by facilitating and coordinating EOL care discussions.

Terminally ill cancer patients often poorly understand EOL treatments, including ICU care, CPR, and intubation with mechanical ventilation support, and may overestimate their probability of survival. [7,110,115] One focus of this proposed ACP intervention is to promote realistic and achievable goals for EOL care and to improve patients' and family caregivers' understanding of the patient's medical situation and the efficacy of life-sustaining treatments proposed at EOL. The ACP intervention will therefore include a workbook and a video to enhance participants' understanding of the essential elements in ACP. The two-part workbook is derived from Pearlman and colleagues'[120] work. The first part contains basic information on ACP, including life-prolonging and comfort-oriented care, and facts about the probability of survival after and consequences of ICU care, CPR, and intubation with mechanical ventilation support. This information is designed to motivate participants in the precontemplation and contemplation stages of readiness to engage in ACP. The second part contains four subsections:

(1) a glossary describing health states that may cause decisional incapacity and where life-sustaining treatments or palliative care may be beneficial, (2) exercises to elicit preferences for EOL care, (3) advices about how to discuss one's understanding of prognosis and preferences for EOL care with family members and healthcare professionals, and (4) documents for recording treatment preferences.

The proposed ACP intervention will draw on the power of healthcare information technology by using a 5-minute video to provide visual information that captures complex medical treatments that are highly emotionally charged. This video, adopted from Jawahri and colleagues' work,[131] portrays life-prolonging and comfort-oriented care for terminally ill cancer patients. Participants will view the video on a laptop computer when they are ready, as assessed by the ACP interventionist. One scene of life-prolonging care will show a patient with advanced non-small cell lung cancer on a ventilator in an ICU, being cared for by nursing staff, and with multiple intravenous lines to supply nutrition and antibiotics. In another scene, a different patient will appear in a simulated code situation with physicians administering CPR and intubating the patient, and nurses administering vassopressors. Comfort-oriented care will be portrayed by scenes of a terminally ill patient with non-small cell lung cancer on hospice care and receiving patient-controlled analgesia for pain and supplemental oxygen with a nasal cannula, a nurse assistant helping the patient with self-care, and family members surrounding and interacting with the patient. Participants will be offered the opportunity to re-view the video upon request.

The attention-control group is designed to compare the effects of the multifaceted, interactive ACP intervention to those of attention care and a passive symptom-management educational intervention to rule out the Hawthorne effect. The attention-control protocol will include prognostic disclosure and discussions of EOL care as needed according to current clinical practice. This study arm will be provided by a bachelor's-prepared attention-control interventionist. In the initial session for this group, the attention-control interventionist will

give terminally ill cancer patients and family caregivers a workbook and a video with educational materials on how to manage common symptoms and a list of available resources, including patient support organizations, as well as support and financial assistance through the hospital's social work department. We hypothesize that using a workbook and a video with content on symptom management alone will not impact the outcomes, but parallelize education received by the control group as much as possible with that of the intervention group. This hypothesis is based on a recent systematic review that found using passive informative material in isolation was an ineffective method for promoting use of ACP.[119] The attention-control interventionist will visit and interact with participants in the attention-control group according to the same schedule as for the ACP intervention group to assess their symptom distress and general well-being. Necessary referrals to physicians or social workers will be made for further management.

Randomization

We will enroll and randomly assign eligible dyads of terminally ill cancer patients and their family caregivers into either the ACP intervention or the attention-control group in a 1:1 fashion without stratification. Dyad allocations into the two study arms will be concealed from the personnel responsible for recruiting subjects. A randomization schedule using a computerized random number generator will be prepared in advance by a co-PI (LCY) who will have no contact with any participants throughout the trial and will not be involved in recruiting, enrolling, assigning, assessing, or treating them. The sequence of randomization will be sequentially numbered and sealed in opaque envelopes which will be used later by the PI to allocate participants. The PI will be the only person with access to the allocation schedule during the study and will not be involved in recruiting, enrolling, assessing, or treating participants. The sealed opaque envelopes will not be opened until the PI responsible for assigning participants to the two study arms receives a call from the data collector who has completed the recruitment and initial assessment of a patient-caregiver dyad. The PI will then

open the sealed envelope, assign this dyad to the proper study arm, and forward their information from the envelope to the ACP or attention-control interventionist, accordingly.

Blinding

Participants, study investigators, data collectors who administer study instruments, and data analysts will be blinded to intervention assignments. All study investigators, research staff (i.e., those who administer the ACP intervention, attention-control care, and outcome measures), and participants will be blinded to trial results until closure of the study. Blinding will be facilitated by both groups (ACP intervention and attention-control) receiving parallel care, preventing data collectors and participants from differentiating between group assignments. To evaluate participant blinding, randomly selected dyads of terminally ill cancer patients and their family caregivers in each study arm will be interviewed by an independent research staff every 3 months to check which arm they believe they are allocated to.

Research fidelity

Research fidelity will be ensured by several strategies. First, the proposed ACP intervention requires an interventionist skilled in the content, techniques, and delivery of the intervention. The interventionist's training will be built on her experience in oncology nursing and palliative care and will be based on her demonstrated competency. The training will include an overview of the study protocol and procedures, a review of the developed workbook and video, and instruction in motivational assessments. The PI will serve as a role model for the interventionist to coach her in assessing and motivating participants at different stages of readiness to engage in ACP and to cooperate with physicians in coordinating and facilitating EOL care discussions on five patient-caregiver dyads as pilot cases. Before the interventionist can formally deliver the intervention to participants, she must successfully demonstrate predefined competencies and consistency in delivering the intervention to promote ACP. Thereafter, the study team will meet biweekly to review the interventionist's notes on intervention sessions and to provide feedback on difficult subject-management issues. Second,

procedures provided to subjects in the ACP intervention and attention-control groups will be reviewed by an independent research staff every 3 months to check the extent to which they are consistent with the group protocol. To this end, the research staff will interview randomly selected patient-caregiver dyads in each study group. Third, the workbook and video will be created systematically, starting with a review of the ACP literature in advanced cancer. The workbook content and overall video design will be reviewed for appropriateness and accuracy by 2 physicians specializing in cancer care, 1 ICU physician, 1 expert in palliative medicine, and 1 nurse with expertise in clinical decision-making.

Data collection procedures: Assessments will be performed prospectively and continue until patient death, loss to follow-up, study withdrawal, or when the patient can no longer be interviewed. An every-3-week time frame will be used in this study for repeated QOL and other outcomes assessments for both patients and their family caregivers bases on the review of literature to cover the most rapid change of patient physical conditions and demanding period of caregiving until the death of the patient. After each patient's death, a chart review and postmortem interview with patients' caregivers will be performed to confirm the type of medical care received at the EOL. Bereavement interviews will be conducted 1, 3, 6 and 13 months after the time of death in order to avoid contamination on the basis of anniversary grief reactions.

Data safety and management plan

An independent Data and Safety Monitoring Board (DSMB) will be organized to ensure patient safety throughout the trial as well as its validity and scientific merits. The DSMB will comprise a biostatistician experienced in statistical methods for clinical trials, a nursing researcher experienced in conducting randomized controlled trials, and a physician-scientist experienced in cancer care. The DSMB will monitor and address the following issues: (1) sufficient and appropriate enrollment of subjects, including compliance with the eligibility criteria for each dyad of terminally ill cancer patients and family caregivers, (2) appropriate

implementation of randomization, (3) comparability of baseline data between study groups, (4) protocol compliance by research staff, i.e., interventions delivered to each study group and the data collection schemes, (5) protocol compliance by participants, and (6) adverse events (AEs). The DSMB will monitor the progress of subject enrollment every 6 months to ensure adequate subject recruitment and enrollment. To ensure fulfillment of eligibility criteria, the DSMB will monitor the ineligible rate and examine the reasons for refusal to participate in the study, basic demographics, and disease-related characteristics of each recruited dyad of patients and family caregivers.

The DSMB will monitor the dropout rate in each study group every 6 months to detect unexpectedly high dropout rate to clarify or modify the study protocol if necessary.

The study team will record AEs (e.g., complaints of emotional upsets by participating in this study) and submit them monthly in writing to the DSMB, with immediate reporting of serious AEs (SAEs; e.g., suicidal ideation or suicide attempts) to the DSMB and an oncologist with expertise in palliative care. Site reports of AEs/SAEs to its institutional review board (IRB) will be dictated by local requirements.

No data will be analyzed before the study ends. Access to interim results, including baseline data for each group and results from each study arm, will be limited to the DSMB members and the statistician who prepares reports for the DSMB. The DSMB will review study data every 6 months and summarize recommendations for the PI. A summary of reported AEs/SAEs will be sent to the local IRB to ensure that the participating site will be informed of any pertinent safety issues. No favorable or unacceptable benefit-to-risk ratios are expected to find to stop the trial early, thus, no rules for early termination are set.

Statistical analysis plan

All data will be entered into a computer spreadsheet by an administrative assistant. Data will be checked for omissions and outliers to identify potential data entry errors, which will be

clarified with the data enterer. Data will be first descriptively analyzed to check range and distribution of all variables. The baseline equivalence of groups will be tested by differences in their baseline characteristics and outcomes using two-sided Fisher's exact tests and chi-square tests for categorical variables and independent-sample Student's t-tests for continuous variables.

The effectiveness of the intervention will be examined using intention-to-treat analyses with generalized estimating equations (GEE) or hierarchical generalized linear modeling (HGLM). Effectiveness of the intervention will be assessed in terms of (1) facilitating prognostic awareness, EOL care discussions, patient-caregiver agreement on preferences for EOL care, and congruence between patients' preferred and actual EOL care, (2) improving patients' and family caregivers' QOL, anxiety and depressive symptoms before the patient's death, and family caregiver bereavement outcomes, and (3) limiting aggressive healthcare resource utilization at EOL. In the intention-to-treat analyses, all participants will be analyzed in the study group to which they are initially allocated, regardless of whether they complete or withdraw from the study. The GEE/HGLM uses robust standard error estimates to take into account (1) within-subject correlations of the outcome variables during the study period, (2) unequal numbers of assessments among subjects, and (3) potential missing observations. In GEE/HGLM analysis, incompleteness of the outcome variables has only marginal influence on the results of longitudinal data analysis because GEE/HGLM involves fitting a generalized linear model to the marginal distribution of repeated outcomes.[151]

The congruence between terminally ill cancer patients' preferred and actual EOL care will be determined by comparing the agreement between preferences for EOL care elicited at the last assessment and actual EOL care. Preferences for each EOL care treatment will be dichotomized so that those who are "unsure" whether prefer a specific EOL care treatment will be counted as desiring that treatment because in most instances the clinical default is to provide

treatment unless specifically refused.[72] In addition to the percentage of overall agreement, kappa coefficients will be computed to correct for the amount of agreement that can be expected by chance alone.[152]

Subsequently, multivariate logistic regression with the GEE method will be used to examine the impact of the ACP intervention on improving the congruence between patients' preferred and actual EOL care, and on secondary outcomes--increasing prognostic awareness, EOL care discussions, and patient-caregiver agreement on preferences for EOL care, and decreasing aggressive healthcare resource utilization at EOL, with simultaneous adjustment for time-varying and invariant confounding factors. The GEE model will also be used to examine the moderation effects of prognostic awareness, EOL care discussions, and patient-caregiver agreement on preferences for EOL care on the ACP intervention's effectiveness in increasing the congruence between patients' preferred and actual EOL care and in decreasing aggressive healthcare resource utilization at EOL.

Multivariate multiple regression with the GEE/HGLM method will be used to test the effectiveness of the ACP intervention in improving patients' and family caregivers' QOL and psychological well-being (depressive and anxiety symptoms) before the patient's death, and family caregiver bereavement outcomes (including QOL, depressive symptoms, and grief reactions), with simultaneous adjustment for time-varying and invariant confounding factors. The GEE/HGLM model will also be used to examine the moderation effects of prognostic awareness, EOL care discussions, patient-caregiver agreement on preferences for EOL care, aggressive healthcare resource utilization, and the extent of congruence between patients' preferred and actual EOL care on the ACP intervention's effectiveness in improving patients' and caregivers' QOL, anxiety and depressive symptoms before the patient's death and facilitating family caregiver bereavement adjustment.