RESEARCH PROTOCOL

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Background and Purpose:

Our long-term goal is to improve spiritual care outcomes for elderly patients with cancer. We will use a spiritual intervention, Dignity Therapy (DT), to help these patients maintain pride, find spiritual comfort, enhance continuity of self, and ultimately make meaning of their life threatening illness. However, to date, DT has not been viewed as a spiritual intervention or studied with chaplains as the interventionist. Our thesis is that DT will systematize spiritual care processes and improve patient outcomes (spiritual and cancer prognosis awareness). The spiritual outcomes are important because people with advanced illness report that being at peace with God is as important as freedom from pain.[1] Spiritual concerns are issues for 86% of patients with advanced cancer.[2] Unfortunately, little research guides interventions for spiritual care. We will address this gap by testing efficacy of DT in a rigorous, multi-site, randomized controlled trial (RCT).[3]

Previous studies of DT demonstrated clear feasibility and inconsistent efficacy of DT with virtually no evidence of its mechanism of action. Specifically, the 12 studies of DT (8 uncontrolled feasibility; 4 mostly small sample efficacy RCTs) show DT to be an important intervention when delivered by nurses and mental health professionals, but effects on patients' distressing physical or emotional symptoms of life-threatening illness have been inconsistent. Taking a spiritual perspective for reanalysis of data from the one large RCT,[5] we found that compared to usual care, patients who received DT reported significantly higher dignity impact ratings, which is consistent with the DT focus on meaning making, preparation for death, and life-completion tasks. Evidence from our pilot study also suggests that awareness of cancer prognosis outcomes and will-to-live is facilitated by DT.[4] One possible explanation of the lack of DT effect on physical symptoms could be that symptoms only moderate the DT effect, so conceptualizing symptoms as the relevant outcome is mismatched to the operative DT elements. It is also possible that spiritual distress could moderate the DT effect on patients' sense of meaning and purpose,[5] which is an important part of dignity impact. Two disciplines typically part of the palliative care team are known for their focus on spiritual concerns—nurses and chaplains. A nurse-led or chaplain-led DT study of patients receiving outpatient palliative care is needed to determine the efficacy of DT on key spiritual-related patient outcomes (dignity impact, existential tasks, cancer prognosis awareness) and explore possible moderators (physical symptoms and spiritual distress) of DT's effects on patient outcomes.

We propose a pre/posttest, RCT with a 4-step (12 months per step), stepped-wedge design[3] to compare effects of usual outpatient palliative care (usual care) and usual care along with either nurse-led or chaplain-led DT on patient outcomes (dignity impact, existential tasks [preparation for death, life completion], cancer prognosis awareness [peaceful awareness, treatment preferences]). We will assign 6 outpatient palliative care sites to usual care during the first-step, and randomly assign two sites per step to begin and continue DT led by either a nurse or a chaplain during each of the next 3 steps. During the usual care steps, 280 patients will complete pretest measures (patient outcomes, covariates [physical symptoms, spiritual distress], and satisfaction with palliative spiritual care services), receive usual palliative care, and complete posttest measures (patient outcomes, covariates, satisfaction). During the experimental steps as part of routine palliative care service delivery, 280 patients will complete pretest measures, receive nurse-led or chaplain-led DT, and complete posttest measures. Using mixed level analysis with site, provider (nurse, chaplain) and time (step) included in the model, we will compare the usual care and each of the DT groups for effects on dignity impact, existential tasks, and cancer prognosis awareness and explore the moderating effects of physical symptoms and spiritual distress. We will also determine the effect of usual care and DT on the patient's satisfaction with palliative spiritual care services and the report of the patient's unmet spiritual needs.

Specific Aims:

In a diverse sample of 560 elderly cancer patients, the specific aims are to:

Aim 1. Compare usual care and usual care with nurse-led or chaplain-led DT groups for effects on:

a) patient outcomes (dignity impact, existential tasks [preparation for death, life completion], cancer prognosis [peaceful awareness, treatment preferences]). We hypothesize that, controlling for pretest scores, each of the DT groups will have higher scores on the dignity impact (1° outcome) and existential tasks (2° outcome) measures than the usual care group. Also patients in each of the DT groups will report better peaceful awareness and treatment preferences more consistent with their cancer prognosis (2° outcomes) than the usual care group; and

b) processes of delivering palliative spiritual care services (satisfaction and unmet spiritual needs; 2° outcomes). We hypothesize that each of the DT groups will show increased patient satisfaction with spiritual care services and fewer unmet spiritual needs compared to the usual care group.

Aim 2. Explore the influence of physical symptoms and spiritual distress on the dignity impact and existential tasks effects of usual palliative care and nurse-led or chaplain-led DT. We hypothesize that physical symptoms and spiritual distress will significantly affect intervention effects. This rigorous trial of DT will constitute a landmark step in gero-oncology palliative care and spiritual health services research.

Study design:

We propose a 6-site, pre/posttest, randomized, controlled 4-step, stepped-wedge design to compare the effects of usual outpatient palliative care and usual outpatient palliative care along with nurse-led or chaplain-led DT on patient outcomes and palliative care processes. We will assign the 6 sites to usual care during the first-step period (10 months), and randomly assign 2 sites per step to begin and continue DT during each of the next 3 steps (10 months each). Figure 1 shows the stepped-wedge study design with projected numbers of completed patients needed per site, step period, and group (usual care, DT led by either a nurse or a chaplain). Dr. Yao, a highly qualified statistician will conduct the randomization of site to steps 2-4. Each step will be 10 months long, with DT training during a 1-week period between steps. For each site/step, a quota of 50% of the participants will report low or high distress on the Personal Dignity Inventory to assure we recruit a sample with a range of problems threatening their dignity. Each patient will participate for 4-6 weeks. Over the 10 months at each step, we expect 23-24 patients to participate at each site (93-94 total patients per site).

Figure 1. Stepped-wedge design

	N per step per site				Total N
Site 6	23	23	23	24	93
Site 5	23	23	23	24	93
Site 4	24	23	23	24	94
Site 3	24	23	23	24	94
Site 2	24	23	23	23	93
Site 1	24	23	23	23	93
Step	**1**	**2**	**3**	**4**	
Patients/ Step Period	142	138	138	142	**560**
Usual Care					280
Nurse-Led DT					140
Chaplain-Led DT					140
Step Period Duration (mo)	10	10	10	10	40

Subject identification, recruitment and consent:

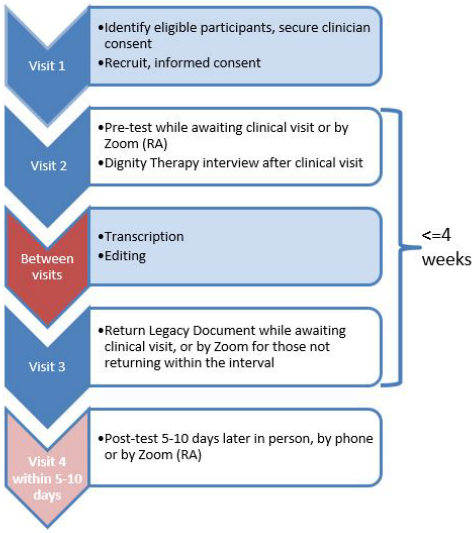
We will recruit the study sample from the population served by the six hospitals participating in this application. The sites represent the South Eastern (Emory University, UF Health Gainesville), North Midwest (Northwestern University, Rush University), South Midwest (MD. Anderson), and Western (University of California at San Francisco) areas of the U.S. The participants will be elders who are diagnosed with cancer and are receiving outpatient palliative care services at the participating sites. At UF Health, we will recruit the sample from the existing outpatient oncology palliative care services and those under development within the UF Cancer Center.

The consent process will be completed in person and in a private area at the outpatient palliative care services of the 6 sites, or at another outpatient palliative care site or other private location chosen by the potential subject to go over the details of the study and informed consent. The consent process may also be conducted by phone with the signed consent form returned by mail in a preaddressed, stamped envelope.

Procedures:

The study will be conducted in the outpatient clinic in spaces available for research or virtually via a HIPAA-compliant video-conferencing platform. The investigators will attend patient care planning meetings and introduce the study to the palliative care team members. Any member of the palliative care team will refer patients to the RA on the day the patient is seen in the palliative care clinic or via a HIPAA-compliant video-conferencing platform.

Figure 2 shows the general flow of patients through the outpatient palliative care clinics and study procedures for this study of nurse-led or chaplain-led DT over 4-6 weeks. Prior to participant recruitment, the research assistants (RA) will be trained in all study procedures. Prior to stepping up to the DT steps of the study, the nurse and chaplains at the sites scheduled to begin the DT will be trained in the DT.



Study Procedures:

I. The RA will recruit the referred and potentially eligible patients for this study, provide and obtain informed consent, determine final eligibility, and schedule time before the next clinic visit or at a time convenient to the patient for the patient to complete the pretest tools via an audio-recorded interview documented on REDCap forms and stored on REDCap for quality control purposes.

II. Then the RA will inform the nurse/chaplain that the patient is available for care (usual care or DT, depending on the study step and site). The nurse/chaplain will provide the designated care on the same day as the pretest data collection, as specified in the following section:

   a. Usual care. Palliative care nurses usually see patients each clinic visit to assess vital signs, function, symptoms, and to provide patient and family education. They document findings and interventions in the electronic health record (EHR). Whereas usual care for palliative care chaplaincy in the outpatient setting varies by site, chaplaincy care for usual care patients in this study will follow the usual practice for inpatient palliative care chaplaincy, which is to visit all new referrals to the clinic and assess their spiritual and religious needs. This assessment is then memorialized in a spiritual treatment plan documented in the EHR.

   b. Dignity Therapy. The DT intervention is detailed in Chochinov's manualized guide; he serves as our co-investigator and will conduct trainings for the team. The basic questions of the DT interview appear in Table 2. The nurse-led or chaplain-led DT intervention involves three sessions, each of which follows a set process (Fig 2). The standardize approach to the delivery of the intervention facilitates a personal process of reflection and recognition that allows the patient to make meaning of their experience.

Table 1. Examples of the Dignity Therapy Question Protocol
1. Tell me about your life history; particularly the parts that you either remember most or think are the most important? When did you feel most alive?
2. Are there specific things that you would want your family to know about you, and are there particular things you would want them to remember?
3. What are the most important roles you have played in life (family roles, vocational roles, community service roles, etc.)? Why were they so important to you, and what do you think you accomplished in those roles?
4. What are your most important accomplishments, and what do you feel most proud of?
5. What are your hopes and dreams for your loved ones?
6. What have you learned about life that you would want to pass along to others?
7. What advice or words of guidance would you wish to pass along to your [son, daughter, husband, wife, parents, other(s)]?
8. Are there particular things that you feel still need to be said to your loved ones, or things that you would want to take the time to say once again?
9. Are there words or perhaps even instructions you would like to offer your family, in order to provide help to prepare them for the future?
10. In creating this permanent record, are their other things that you would like included?

When the nurse/chaplain session(s) are completed, the nurse/chaplain will inform the RA that he/she has completed all nurse/chaplain session(s). The interview will be conducted either in person in the clinic or at a time and place convenient to the patient (e.g., home, community setting), or via a HIPAA-compliant video-conferencing platform.

III. Either in-person if the patient has a clinic visit, by telephone contact or via a HIPAA-compliant video-conferencing platform, the RA will schedule the follow-up appointment at a time and place convenient to the patient (e.g., clinic, home, community setting), and complete the audio-recorded posttest measures within 5-10 days. Upon completion of posttest measures, the RA will provide $50 (cash or card) to the patient for time and travel expenses to complete study measures.

Sample size:

We will recruit 1500 adults with cancer diagnoses who are receiving care from the outpatient palliative care services of the six hospitals. From this sample, 560 patients will complete the study and provide data for analysis, 280 for the DT groups (140 per each of the two DT groups) and the 280 for the control groups. From UF Health, we expect to recruit 94 total patients, 23-24 per year with complete data. We will consent approximately 1,500 (250 total patients per site) for screening over the 4.5 years devoted to data collection and 120 to participate to achieve a completed sample of 94 patients per site.

Anticipated risks:

The risks of this study are primarily those regarding potential for fatigue from completing the questionnaires and the intervention, the emotionally evocative nature of the material shared during the course of the intervention, and loss of privacy. The likelihood of these risks is low, as has been observed and documented in the many previous studies of DT cited in the Background section.

Anticipated benefits:

There may be no benefit to individual participants in any arm since this study is needed to understand how DT can be implemented in a real-world setting and still retain its beneficial impacts. A common perception regarding DT is that it has been sufficiently studied that it should simply be accepted. However, there is minimal knowledge on how DT fares in the real world setting. As our recent systematic review has revealed, results of many feasibility studies are very promising, but only one small efficacy study showed significant effects on study outcomes whereas the other three completed efficacy studies, one with more than 400 patients, did not show significant effects on study outcomes. Our study will fill the gap of inconsistent and inconclusive effects, in turn then allowing for the next step of up-scaling implementation.

The multiple feasibility or efficacy studies have shown that DT is greatly appreciated by participants, families and healthcare providers. So there seems reason to believe that DT's impact on promoting healthy life transitions will result in a patient benefit for those from either of the nurse- or the chaplain-led DT arms.

The study has tremendous potential to inform future studies on DT and advancing DT to clinical palliative care practice involving elderly patients with cancer. There tends to be a bias regarding psychosocial interventions, which includes the idea that these interventions ought to be resource neutral i.e., without any cost whatsoever. However, the availability of resources should be driven by efficacy and the evidence to support the application of DT in a given setting. This study will provide needed data on how to apply DT in specific services – by the nurse or chaplain.

The study also has tremendous potential to help the scientific community understand ways for spiritual palliative care services to be implemented systematically to affect patient outcomes and care processes. Very few spiritual care interventions have been systematically developed, protocolized, and studied. DT is one of them. Until we understand how much of DT's impact is spiritual, we do not know how to use DT as a tool to study spiritual care needs.

The knowledge also has potential to add to the understanding of mechanisms that may influence the effect of DT for elderly patients with cancer and receiving palliative care. In particular, in our study, we will be including patients from the palliative care service regardless of prognosis and so we will have exploratory data on the use of DT for people who have every reason to expect to survive for prolonged periods, including promoting the will to survive cancer therapies as findings from one small study suggests.

Inclusion criteria:

Criteria for study participation require that the patient:
(1) has a cancer diagnosis (receiving cancer therapy or cancer control care, responsive to NOT-CA-14-016)
(2) is receiving outpatient palliative care
(3) is age 55 years or older (responsive to PAR-13-354)
(4) is able to speak and read English
(5) is physically able to complete the study (Palliative Performance Scale [PPS]>50,[6-11] suggesting a mean in life expectancy of 53 days at the time of enrollment),[11] each patient is expected to participate in the study for 28-42 days maximum (4-6 weeks).

Exclusion criteria:

Patients will be **excluded** if they:

(1) are legally blind
(2) are cognitively unable to complete study measures (Mini Mental Status Exam [MMSE] does not correctly spell the word world backwards)
(3) have history of psychosis (medical record review)
(4) have Patient Dignity Inventory and Spiritual Distress scores that indicate their distress levels fall outside the remaining quota for a given step (quota is 50% of sample/site/step with low distress ≤ 2 problems rated >2 & 50% with high distress ≥ 3 problems rated >2 on each scale)
(5) are participating in another psychosocial intervention study that is focused on concepts similar to the proposed study.

Data collection and management:

This study is an intervention study with data collected before and after the intervention. We will obtain data from patients completing self-report questionnaires (dignity impact, existential tasks, cancer prognosis awareness, physical symptoms, spiritual distress, death anxiety, satisfaction with spiritual care, demographics) on a tablet device connected to the study's REDCap site. We also will obtain data via patient interview (performance, mental status, DT interview) and medical record review. The DT interview will be recorded, deposited on a secure server for transcription by a qualified transcriptionist and editing by a trained, professional editor. Following upload to REDCap, the video-conference recording will be deleted from the device.

Chaplains will document their usual care in the health record.

To ensure confidentiality, each subject and provider (nurse or chaplain interventionist) will be assigned a code number. All data are coded with the code numbers and linked to the patient's name. The patient's name is removed from the database when statistical analyses are conducted. Demographic information, chart review information, and other self-report outcomes are entered into data forms in REDCap, an Internet-based data management system. The REDCap system has strong password protection and is located on a reliable and secure research server at UF. Access to the server is password restricted and only the pertinent research staff can access the data via an application designed for data download. Only the data manager and statistician will have authority for direct access to the database server files. Participants or study staff will enter data through the REDCap system designed specifically for this study on a tablet computer with strong password protection. The team members in the Center for Palliative Care Research and Education at the UF are skilled in developing and deploying user-friendly, secure, and reliable programs for data collection and tracking. The staff members in the nursing information systems office are well-trained and responsible for maintaining the network security and adhering to UF policy regarding security for research data and protected health information. The UF Health Sciences research servers have firewall protection and access through the firewall is restricted and closely monitored. Data on the server will be backed up each night; backups are stored nightly in water- and fireproof cabinets. The tablets used for data collection will be locked in a secure cabinet when not in use. The project statistician will monitor the safety of the data continuously.

Completing the self-report measures and the DT intervention are low risk. Continuous, close monitoring by the Multiple Principal Investigators (MPIs) will be an adequate and appropriate format for monitoring, with prompt reporting of adverse effects to the IRB and NIH Program Officer. As a low-risk study, data monitoring by the MPIs would meet the NIH requirements for

data safety and monitoring for a clinical trial. The co-investigators, site directors, and other team members are well positioned clinically to identify any adverse event and report it to the MPI Wilkie, who will report it to other MPIs, the IRBs and NIH program officer.

The MPIs (Wilkie, Emanuel, Fitchett) will evaluate the progress of the study, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, and other factors that could affect study outcomes. The MPIs also monitor for scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the study. The MPIs make recommendations to the IRB and the site directors concerning continuation or conclusion of the trial.

Data analysis:

Data management and preliminary data analysis procedures will be supervised by MPI Wilkie and conducted by Dr. Yao, the Co-I and statistician, using statistical software R. Data will be stored in a REDCap database and will be exported to R. In the case of missing data, multiple imputations will be used to generate multiple complete datasets on which statistical inference will be performed. Missing at random assumption will be assessed and if necessary sensitivity analysis will be performed using pattern mixture methods. We will consider a p value less than .05 as statistically significant.

Descriptive statistics (ranges, frequencies, means, and standard deviations) and graphic summary (box plots, histograms, bivariate scatter plots, etc.) will be first generated for both patient covariates and outcome measures. We will check patient characteristics to see if there is notable imbalance between the three arms, as well as whether there is significant variations between sites or over time. Descriptive statistics of patient outcomes and process data will reveal patients' spiritual state, identify potential areas for improvement in nurse and chaplain service, and provide information on nurses' and chaplains' workload both in usual care and when dignity therapy is added and on family-related variables (e.g., legacy document disposition, etc.).

Aim 1. Linear mixed effects models will be used to compare the effects of usual palliative care with usual palliative care with nurse-led and chaplain-led DT groups on (a) patient outcomes and (b) processes of delivering palliative spiritual care services. Random effects terms will be used to model the variations between sites. A main challenge of data analysis of a stepped-wedge design is the modeling of potential time trends. We plan to treat time as a continuous variable and utilize smoothing splines to model potential time trends. Smoothing splines is a nonparametric method that allows flexibility to model different time trends without overfitting by enforcing a smoothness constraint. Likelihood ratio tests will be used to determine the statistical significance of the intervention effect on various outcome measures. We hypothesize that, controlling for pretest scores, patients in both nurse-led and chaplain-led DT groups will have higher dignity impact scores, higher preparation for death and life completion scores, better peaceful awareness, and treatment preferences more consistent with their cancer prognosis than the usual care groups. We also expect the patients in the DT groups to be more satisfied with the palliative care and have fewer unmet spiritual needs than the usual care groups. We do not expect significant difference between nurse-led and chaplain-led DT interventions. Note that, this does not necessarily mean that the two interventions are equally effective. We do not seek to test the equivalence of the two intervention arms. At this point, it is premature to speculate on their relative efficacy. We expect most patients in this study to have metastatic cancer. If a sizable portion of our sample has non-metastatic cancer, we will explore if they respond to DT differently than those with metastatic disease.

Aim 2. The effect of physical symptoms and spiritual distress on the dignity impact and existential tasks will be modeled nonparametrically using smoothing splines. Our models will include both main effect for physical symptoms and spiritual distress and their interactions with the intervention. This analysis will provide insight on the type of patients most in need of and most likely to benefit from the DT intervention. Likelihood ratio tests will be used to determine the significance of the interaction. We hypothesize that patients' levels of spiritual distress and physical symptom scores will moderate the intervention effect.

Safety monitoring:

The study is low risk. However, the research team will monitor the safety of subjects during study procedures. In the event of injury related to this research, treatment will be available through the UF Health or the health system associated with the data collection site. However, the patient or third party payer, if any, will be responsible for payment of this treatment. Patient subjects will remain under the care of their usual provider, who will be available to give them usual care if needed. Any unanticipated problems related to the study procedure will be immediately reported to the IRB and NCI Program Officer.

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