Online Information and Support for Distance Caregivers

NCT02666183

12.13.21

Study Protocol and Statistical Analysis Plan

DISTANCE CAREGIVER STUDY PROTOCOL

OBJECTIVES

The primary goal of this RCT is to compare outcomes (anxiety, distress, depression) for DCGs of patients with advanced cancer and/or patients receiving ongoing care from a medical oncologist who are randomly assigned to either the full intervention arm (Closer), the video-only intervention arm (Video-C Only), or the Web-Only group. The goal is to determine which is most efficacious in improving outcomes over time for these caregivers.

RESEARCH SUBJECT SELECTION AND ELIGIBILITY

The sample will consist of patients with advanced cancer and/or patients receiving ongoing care from a medical oncologist and distance caregivers of these patients. Patients with any metastatic solid tumor will be recruited for participation in the study. Subject(s) selection will involve two phases: first eligible patients must be identified and second, they must have eligible DCGs as well.

Inclusion and exclusion criteria include:

Patient inclusion criteria are: 1) a new diagnosis (within 3 months) of advanced cancer and/or patients receiving ongoing care from a medical oncologist (solid tumors) or a new recurrence of the primary cancer in an advanced stage; 2) receives ongoing care from a medical oncologist at the Seidman Cancer Center (SCC); 3) has English as the primary language; 4) has a life expectancy of >6 months; 5) provides consent for his/her own treatment and procedures; and 6) identifies a DCG involved in his/her care, support, or care planning.
Exclusion: The patient sample is limited to patients with advanced cancer and/or patients receiving ongoing care from a medical oncologist because the full intervention is tailored to meet the needs of DCGs of patients with advanced cancer and/or patients receiving ongoing care from a medical oncologist.

The second stage of selection and eligibility will involve DCGs.

DCG inclusion criteria are: 1) is an adult family member (at least 18 years old) of a patient with an advanced-stage cancer; 2) identifies himself/herself as a DCG for the patient; 3) lives >1 hour travel time away from the patient; 4) has English as his/her primary language; 5) is capable of providing informed consent; and 6) will be able to access Internet (phone, computer, etc.). The sole **exclusion** criterion is cognitive impairment.

For this study, DCGs will be defined as anyone who self-identifies as providing informal, unpaid care to a family member with advanced cancer and/or patients receiving ongoing care from a medical oncologist, who provides support to the patient, and who lives >1 hour away in travel time; a definition commonly used to define DCGs [1,2,4,77].

RESEARCH SUBJECT ENTRY

Subject recruitment: Potential **patient subjects** will be obtained from a list of patients who have appointments to be seen in the outpatient clinic at the Seidman Comprehensive Cancer Center (main campus). Research Assistants (RAs) will obtain a list of patients who meet eligibility criteria each week from the outpatient clinic staff. RAs will review subject charts to confirm eligibility of these subjects prior to their outpatient appointment.

Informed Consent for patient and DCG: At their outpatient clinic visit, all subjects who meet eligibility criteria will be approached by the RA and asked if they have a DCG. For those who have a DCG, the RA will describe the study and ask if the RA if he/she (RA) can contact the DCG to talk about the study and to invite participation. The RA will then obtain contact information from the DCG and contact them, describe the study, and ask for consent. Only after the DCG consents, will the RA obtain written consent from the patient. The RA will contact the DCG by telephone within a week of meeting with the patient. If the patient does not give the RA permission to contact the DCG or if the DCG does not consent to participate then neither the patient nor the DCG will be enrolled in the study. In our pilot, 90% of patients agreed to let the RA contact the DCG. Using

this procedure in our pilot study, we were able to obtain consent and enrollment data from the patient and the DCG within 7 days of one another.

Subject randomization: Once consent has been obtained, the DCG subject will be randomly assigned by the Project Director to one of three arms of the study. Randomized to one of the three study groups will involve using the minimization stratified randomization technique. Minimization is designed to balance pre-identified stratifying covariates across treatment assignments more effectively than simple randomization[79]. Stratification variables will be DCG age, gender and patient cancer stage. We will use the free online program MinimPy[97].

Allocation concealment: For DCGs assigned to the Closer or Video-C Only groups, the Project Director will email the link to download the free WebEx application that will be needed for all videoconference sessions. For subjects in the Web-Only group, the Project Director will email them to download an application that will allow the DCG to click on an icon and be directly connected to the DCG website used for this group. This procedure will blind RAs to group assignment.

STUDY DESIGN AND METHODS

Design/Study Type

This proposed three group RCT will examine the effects of videoconference technology (information) during patient-oncologist office visits and the added effects of from RN coaching sessions (information + emotional support) using videoconference technology. The study will use an experimental design with random assignment of DCGs to groups.

Selection of Instruments

Study measures will be obtained at enrollment and 4 months later (Table 1).

Table 1. Study Tools and Measures

Variable	Measure	Time of measure Enroll	4M	Reliability
Outcome Variables				
Distance Caregiver	PROMIS^{R*} (SFv1.0-ED-Anxiety-SF4a)	X	X	r=.96
Distance Caregiver	NCCN Distress Thermometer	X	X	r=.80 test-retest
Distance Caregiver	PROMIS^{R} (SFv1.0-ED-Depression-SF4a)	X	X	r=.83
Distance Caregiver Health Status	MOS-SF12** (GSRH-Item 1)	X	X	r=.79 test-retest
Patient Anxiety	PROMIS^{R} (SFv1.0-ED-Anxiety-SF4a)	X	X	r=.96
Patient Distress	NCCN Distress Thermometer	X	X	r=.80 test-retest
Patient Depression	PROMIS^{R} (SFv1.0-ED-Depression-SF4a)	X	X	r=.83
Appraisal Variable				
Caregiver Burden	Zarit Burden Interview-12	X	X	α=.88-.99
Covariates		Enroll	4M	
Distance Caregiver demographics (age, race, gender)	Enrollment form	X		NA
Mechanisms of Intervention Variables				
Self-Efficacy	Caregiving Self-Efficacy Scale	X	X	α=.82-.91
Emotional Support	PROMIS^{R}(Item Bankv2.0-Emotional support)	X	X	α=.90-.99
Descriptive Variables		Enroll	4M	
Patient: Age, gender.	Enrollment form	X		NA
Distance Caregiver: Socioeconomic & marital status, work productivity, computer competence/literacy.	Enrollment form		X	
Recovery Experience Questionnaire: Psychological Detachment Subscale	Enrollment form	X		

*PROMIS^{R}: Patient Reported Outcomes Measurement Information System; **MOS-SF: Medical Outcomes Study Short-Form 12; GSRH: General self-rated health (Item 1).

Description of Intervention

***Closer* Intervention**. The full intervention (*Closer*) is a tested intervention that uses videoconferencing technology (WebEx) for delivery and delivers the highest dose of the intervention. This arm of the intervention will deliver personalized information (aimed at enhancing self-efficacy) and emotional support via RN or SW

coaching as well as the opportunity to talk with the oncologist and patient in "real time" during a minimum of four patient-oncologist office visits over a 4-month period (at least once/month). For patients who have more than one oncologist-patient meeting/month, we will use the videoconference technology to allow the DCG to join as many of the oncologist-patient office visits as desired.

After study enrollment, DCGs will be contacted by the interventionist who will conduct baseline assessments. Afterwards, each DCG will schedule a videoconference coaching session with the interventionist (each lasting 20-30 minutes)[46,51] approximately once/month depending upon caregiver's need and availability.

Table 2: Key Components of *Closer* Intervention

Videoconference Coaching & Office Visit Sessions	Information to Enhance Self-Efficacy as a DCG	Emotional Support
Session 1 [At study enrollment]	• Interventionist performs baseline assessment of DCG using **PAL-23-25** Guidelines from NCCN[62] (understanding of course of disease, amount of information desired, values with respect to QoL).	• Interventionist performs baseline assessment of caregiver distress, practical, family, emotional concerns (**NCCN Assessment: DIS-A**) & caregiver spirituality (**Facit-Sp Assessment**)
Sessions 2 – 4 [Focus & amount of services provided over time is determined by assessment and caregiver need and will vary over time]	• Based upon assessment results: 1. Develop a plan of care for DCG to provide tailored information and assistance that is needed. 2. Provide information (after HIPAA release provided by patient) regarding test results, changes in treatment plan, and care transition information. 3. Provide referrals for information or other community services as needed. 4. Assist the DCG with coordinating services or care for patient among multiple providers (if needed). 5. Discussions related to advance care planning.(See **NCCN Guide: PAL-27**) 6. Provide any information needed in terms of what to expect along the disease trajectory, additional information as patient's disease progresses, and resources that may be needed in the future. Assist DCG in obtaining information about resources. 7. Demonstrate online resources such as NCCN (www.nccn.org/patients/resources/life_with_cancer/distress.aspx) 8. Provide information & discuss self-care strategies that may be of help to DCG (e.g. diet, exercise, stress reduction). (**NCCN Guide: PAL-25**)	• Based upon assessment results: 1. Make referrals for spiritual and/or psychological counseling if indicated. (See **NCCN Guide: DIS 16, 20-28**) If no referrals available locally for DCG, arrange videoconference meetings with SCC social workers, spiritual counselors, chaplin etc. 2. Provide emotional support to DCG as needed. 3. Provide anticipatory grief support and end-of-life education as needed. (**NCCN: DIS-22**). 4. Identify resources for ongoing emotional and social support (online groups, local support groups, ways to utilize existing support systems). (e.g. www.nccn.org/) 5. Conduct *ongoing assessment* in key areas identified at baseline as areas of concern to monitor. Provide additional feedback, support, or guidance as needed for DCG to obtain various types of support as needed. (See **NCCN Guide: PAL-25**)
Videoconference Office Visit Meetings with Oncologist, Patient, DCG	1. Interventionist will be linked via videoconference to the oncologist-patient-DCG meetings and will provide the DCG feedback at subsequent coaching sessions regarding ways to enhance the caregiver's role as	1. Interventionist will be able to provide emotional support to DCG as needed as it relates to discussions that occurred in the oncologist-patient-DCG videoconference meetings.

(minimum 1/month x 4 months)	patient advocate and ways to communicate with the healthcare team should these issues be of concern. 2. Interventionist will follow up in subsequent coaching sessions with DCG on clarifying any information discussed at the meetings, providing more information as relevant to issues discussed with patient and oncologist at the prior office visit meeting	2. Topics discussed at the videoconference meetings that have raised emotional issues with the DCG or that the Interventionist feels might warrant follow-up discussion (e.g. EOL issues) can be further explored at subsequent coaching sessions.

Video-C Only. This arm will involve the delivery of information solely via the use of videoconference technology during the patient-oncologist-DCG visit. As with the Closer intervention, the DCG will be able to participate in the patient-oncologist visit in "real time" during a minimum of four office visits over the 4-month study period (total dose ~5 hours). The procedure for these meetings will be the same as outlined for Closer (above) but will not involve having the interventionist involved.

Web-Only. This group will be provided access to a website that will provide the following major links: a) Caregiving Resources (links to "National Family Caregiver Association", etc), b) Resources for DCGs (links to "Caregiving from a Distance", etc), c) Cancer Information (links to National Cancer Institute, etc.). DCGs will be told that we will track usage of the website in order to assess which areas of the website are used most frequently. Any questions or concerns regarding use of the website can be sent online to the study's technical site, and the support staff will respond within 24 hours.

Data Collection

As seen in Table 1, data (patient and DCG) will be collected by the RA at student enrollment (after consent is obtained from patient and DCG) and 4 months later (after the end of the intervention period).

Description of Study Process

At study enrollment, patient demographic information will be obtained through a brief 5 minute interview conducted by the RA during an outpatient clinic visit. Instruments for patients will be interviewer-administered (10-20 minutes maximum). Interviews with patients will be conducted in person when possible at the time of the patient oncology visit, and the order of tool administration will be randomized. If this is not feasible, patients will be interviewed by phone. Instruments for DCGs will be conducted by the RAs via telephone at a time convenient for the DCGs. Interviews will be scheduled to take place at the time of enrollment, and then 4 after enrollment. The interviews will include administration of study tools (Table 1) in a random order. The RAs (blind to study arm assignment) will use established interview protocols from our prior research that have shown a minimum of subject burden. From prior work, these interviews are estimated to last 10-20 minutes[46].

Adverse Reactions and Their Management

As they occur, all unanticipated events and adverse events will immediately be reported to the principal investigator who will report them to the IRB according to the IRB protocol for both serious and non-serious adverse event and unanticipated problem reporting. These will be summarized in the twice annual reports Annual progress reports to the IRB and NINR/NIH will include a summary of the Data and Safety Monitoring Committee's activities and findings as well as any adverse events regarding human subjects. Program officials at NINR will be informed within 3 business days of unanticipated problems (e.g. data breach) or unexpected serious adverse events that may be related to the study protocol or IRB-approved revisions to the study protocol that indicate a change in risk for participants.

Patients will be interviewed in person during a clinic visit at the Seidman Cancer Center (SCC) at study enrollment and then 4 months after study enrollment. During these interviews, data will be obtained related to patient anxiety (PROMIS Anxiety-SF4a), distress (NCCN Distress Thermometer), and Patient Depression (PROMIS Depression-SF4a). If, during the interviews, the research assistant (RA) obtains data from the patient that indicates that their NCCN Distress Thermometer score is >5, the RA will refer the patient to the social worker at the SCC for further evaluation and referral as needed. The SCC has this procedure as part of their standard of practice and our research team will utilize this existing pattern of referral. For patients with anxiety scores >60[83] or depression scores $\geq$ 58.6[98] the RA (or a member of the research team) will contact the patient's

primary oncologist and will collaborate to determine the appropriate referral (SCC psychiatrist or other mental health professional) on the day of the interview.

Distance Caregivers (DCGs) will also be interviewed at study enrollment and then 4 months after study enrollment. These interviews will take place on the phone with the caregivers being at varying distances from the SCC. If, during the interview, their scores on the anxiety, depression or distress measures (same as for patient) exceed the thresholds established (same as for patient), the RA will reflect to the DCG that their score(s) indicate distress (or anxiety, depression) and the RA will encourage them to contact their primary care physician or a local mental health professional. We will tell the DCG that if it would be helpful, we could try to identify some contact/facilities in their area and if the DCG is interested, the RA will contact the Project Director who will identify some appropriate contacts for the DCG. The RA will call the DCG and share that information within 48 hours of the interview. If the DCG depression score falls within the "severe" range (>70.3)[98] the RA will follow the protocol outlined but will make a follow-up call within 24 hours.

Serious adverse events that have any possible relation to the study be reported immediately to the IRB. Less significant events and events that have no relation to the study procedures will also be reported to the IRB in a timely fashion.

Anticipated Reactions

A risk involved in the study is that patients and/or caregivers might become tired during the interview or they may find talking about feelings to be upsetting. The interviews will be scheduled at the convenience of the patients and/or caregivers and they may stop the interviews at any time if they become tired or simply wish to stop talking. They can elect to not answer any question they find upsetting and can choose to stop participating completely in the study at any time. Participation or non –participation will have no effect on the type or quality of care that the patient receives. A research assistant who is not employed by the hospital will obtain all research data.

Reaction Management

This study involves an intervention—thus a Data and Safety Monitoring Committee (DSMC) will be formed for this study. This committee will be comprised of members outside the study team and the Chair of the committee will be responsible for submitting reports to NINR within 2 weeks of the meeting. The committee who are outside the study team will review data on the study as provided by the PI. Twice annually throughout the project, this committee will review data on this study regarding: (1) study safety including auditing selected cases for compliance with IRB requirements, (2) conformance with informed consent requirements, verification of source documents, and investigator compliance, (3) minimizing research-associated risk, and (4) protecting the confidentiality of participant data. In addition, it will review all causes of mortality and issues with participation. The rate of recruitment refusal (percent and reasons) and subject attrition (percent and reasons) will be tracked and reported at these reviews. Differential attrition form all study groups will be monitored. If concerns or problems are identified by the DSMC, they will be reported to the IRB and NINR/NIH via email by the Chair of the DSMC within 3 business days after they are identified.

STATISTICAL ANALYSIS

This study is an evaluation of a randomized three group trial. The major aim is listed, followed by hypotheses and analyses.

Aim 1: Compare the direct effects of Closer, Video-C Only, and Web-Only on DCG outcomes (anxiety, distress, depression) over time, controlling for DCG demographic variables.

H1: DCGs in the Closer arm will show significantly greater reductions, over time, in DCG outcomes (anxiety, distress, and depression) and significantly greater improvement in health status than subjects in the Video-C Only and Web-Only groups.

Primary endpoints

The primary purpose of the study is to examine the effectiveness of two videoconference-based interventions (Closer, Video-C Only) when compared to a Web-Only group upon psychological outcomes for DCGs of patients with advanced cancer.

Power Analysis for Sample Size

Using a repeated measures analysis with within-between interaction, 3 repeated measures, Type I error of 0.05, and a correlation among repeated measures of 0.5, 104 subjects in each of the three arms would have a power of .95 to detect a difference in the rate of improvement between the three groups, assuming an effect size of .15 or greater[78].

Stratification factors and intervention allocation plan for randomized studies

Randomized to one of the three study groups will involve using the minimization stratified randomization technique. Minimization is designed to balance pre-identified stratifying covariates across treatment assignments more effectively than simple randomization[79]. Stratification variables will be DCG age, gender and patient cancer stage. We will use the free online program MinimPy[97].

Allocation concealment: For DCGs assigned to the Closer or Video-C Only groups, the Project Director will email the link to download the free WebEx application that will be needed for all videoconference sessions. For subjects in the Web-Only group, the Project Director will email them to download an application that will allow the DCG to click on an icon and be directly connected to the DCG website used for this group. This procedure will blind RAs to group assignment.

Analysis plan

Preliminary steps will include examining the frequencies of items to identify the range of variability of each item (e.g., having a range of responses and not having any one category account for >90% of all possible category responses), determine coding inaccuracies, check for outliers, and missing data, and to verify sample size, and normality of data. Descriptive statistics will include examining means, standard deviations, and testing for normality using skewness and kurtosis.

Prior to testing the Aims, additional correlational analyses will be run as the first step to identifying potential relationships among the components identified in the study model. These correlations will be used to prescreen potential violations of the assumptions of correlation. Additionally, scatter plots between the two variables can help identify influential cases, as well as patterns of nonlinearity and non-constant error variance that may reduce a Pearson's *r*. To remedy the potential violation of the assumptions, influential cases can be removed and models retested to determine Pearson's *r* improvement. Data transformations can be used to remedy issues concerning non-linearity, non-constant error variance, and non-normal error variance. These prescreening techniques will help prevent potential problems that may occur when these relationships are tested in our main analyses.

Analyses. Two types of analyses are planned. The first will be a preliminary analysis using exploratory techniques to examine univariate characteristics and bivariate relationships among covariates and between covariates with outcomes. These exploratory techniques will be based upon proportions, medians and/or means. The change in each of the DCG outcomes (anxiety, distress, depression) with time over the 4-month study period will be examined by a repeated measures multivariate regression analysis with covariates entered into the model. A time variable will be created to represent the time of measurement (enrollment, 4 months); and the intervention variable will be expressed using the indicator variables (representing Closer, Video-C Only, Web-Only). The regression coefficient term representing the interaction between time and intervention will indicate whether there are differences in changes over time between the two intervention groups and the web-only group within the context of each of the outcome.

A preliminary step of the multivariate analysis will be to characterize and estimate the relationship of each outcome as measured in Aim1 with the intervention indicator variable, controlling for DCG demographics (age, race, gender). The intervention indicator variable will be the focal independent variable. For continuous variables that do not have a linear relationship with a specific outcome, appropriate transformations or categorization will be considered. For nominal and ordinal variables, the number and type of categories will be considered to obtain the optimum relationship, if any, with the outcome. After this initial step, any variable found to have a significance level less than 0.30 will be retained for further consideration in the model building process. A backward elimination process will be used to assess the relationship between each outcome and available covariates. Goodness of fit tests will be examined to determine the soundness of the models and the

relative importance of the various factors present on each outcome. Estimates of regression coefficients and their variance-covariance matrix will serve as the basis for testing hypotheses. Once a preliminary model containing significant main factors is obtained, interaction terms between the main factors and the intervention variable will be considered. For the major aim, the outcome variables are: DCG anxiety, distress, and depression. In addition, we will be able to classify differences in outcomes by groups using criteria of minimally important differences for PROMIS scales for patient with advanced stage cancer[93]. This will facilitate our interpretation—not only of statistically significant findings but of clinically significant findings as well.

Handling missing data in the analysis.

Missing data is a problematic issue when dealing with longitudinal data sets. Some individuals may quit the study or not participate at a specific data collection point. AMOS will allow for analysis of incomplete data using Full Information Maximum Likelihood (FIML) estimation. Issues of nonrandom missing data are of particular interest in longitudinal data because dropout rates are not a random process; to the extent this is predicted by variables included in the data analysis, FIML will provide unbiased parametric estimates.

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