

Project Number: NRI 15-456-1

Project Title: Palliative Care Interventions for Outpatients Newly Diagnosed with Lung Cancer: Phase II

Principal Investigator: Lynn F. Reinke, PhD, ARNP; VA Puget Sound Health Care System

Primary Site: VA Puget Sound Health Care System

Secondary Sites: Birmingham VA Medical Center, Portland VA Medical Center

DATA ANALYSIS PLAN (DAP)

A. Study sample size rationale

Power Calculation

Sample size calculations for the study were calculated in order to be well-powered to evaluate the main primary outcome in Aim 1, the Functional Assessment of Cancer Therapy - Lung Scale Trial Outcome Index (FACT-L TOI) assessed at baseline and completion of the study post-randomization. This measure assesses functional and physical well-being and lung cancer specific symptoms, and is the most well described measurement of quality of life in lung cancer patients and has been used extensively in clinical trials. We calculated sample sizes assuming a minimum clinically meaningful difference of 5 points in the intervention arm as compared to the usual care arm, corresponding to an effect size of 0.45, considered a moderate effect size in the Cella study [1]. We assume a maximum standard deviation of 11 in both arms, an estimate taken from a study done in a similar population of patients and matching our pilot study data [2]. We use a conservative estimate 15% attrition rate based on our previous recruitment experience with patients with lung cancer. Correlation within subject between baseline and outcome measures is estimated to be between .4 and .6. We base our study on a correlation of 0.5. To have 80% power (with a two-tailed alpha of 0.05), we require 69 patients per group for a total of 138 patients*.

Correlation (ρ)	$\rho=0.4$	$\rho=0.5$	$\rho=0.6$
Required Total Sample Size*	154	138	118

Further details of our sample size calculation can be found below:

For a randomized control trial, the hypothesis that will be tested is $H_0: \delta = \mu_c - \mu_I = 0$ vs. $H_a: \delta = \mu_c - \mu_I \neq 0$. According to Friedman et al [3], the sample size needed for each group for conducting a two-tailed test of size α with power of $1-\beta$ is

$$n = \frac{2 \sigma^2 (Z_{\alpha/2} + Z_{\beta})^2}{\delta^2}$$

Where δ/σ is equivalent to Cohen's d and $Z_{\alpha/2}$ and Z_{β} are critical values for the standard normal distribution at $\alpha/2$ and β respectively.

The final n required for each group to adequately power the study is then:

$$n_{final} = \frac{n(1 - \rho^2)}{1 - attrition}$$

Where $(1 - \rho^2)$ is the design factor for an ANCOVA design [4] and $\frac{1}{1-attrition}$ accounts for the highest expected attrition in the study.

B. Data collection

Setting

The study will be performed at the three VA Medical Centers, Puget Sound Health Care System (VAPSHCS), Birmingham VA HCS, and Portland VA Medical Center, all university-affiliated tertiary medical centers. VAPSHCS receives approximately 100 new diagnoses of lung cancer annually and provides care to patients with lung cancer for the northern alliance of VISN 20 that includes all of Washington State, Alaska, and Idaho. VAPSHCS provides full diagnostic and treatment services for lung cancer including pulmonary medicine, oncology medicine, cardiothoracic surgery, and radiation oncology. VAPSHCS has only in-patient palliative care consult service and no outpatient palliative care clinic. The Birmingham VA receives approximately 150 new diagnoses of lung cancer annually and provides care to patients with lung cancer within VISN 7. The Birmingham VA offers in-patient palliative care consult services and no outpatient palliative care services. The Portland VA receives approximately 150 new diagnoses of lung cancer annually and provides care to patients with lung cancer within VISN 20. The Portland VA offers in-patient palliative care consult services and no outpatient palliative care services. Ancillary care services for all centers include social service, Chaplain service, nutrition, home care, and referrals for hospice.

Subjects

Our study population includes Veterans diagnosed with non-small and small cell lung cancer receiving care at the VAPSHCS, Birmingham VA HCS and Portland VA HCS.

Identification and recruitment process

We will recruit individuals (n=138) with lung cancer over a 2.5 year period using a similar approach that we used for our NRI pilot study. We will target recruitment activities to identify all patients at both VA PSHCS and Alabama VA with lung cancer who will receive therapy other than solely surgical resection. Virtually all patients undergoing evaluation for lung cancer at the both VAs are presented at the Tumor Board, or are evaluated in the chest (thoracic surgery and pulmonary), oncology and radiation oncology clinics. As members who regularly attend the tumor board, we are well acquainted with other Tumor Board attendees, including physicians, social workers, and other support staff. Each week, we will review patients who are to be presented at Tumor Board, or seen in the Chest (includes pulmonary and thoracic surgery) and Oncology Clinics for patients with new diagnoses of lung cancer.

We will mail potential candidates invitation letters and include pre-paid postcards providing an opportunity for patients to opt out of the study or to be contacted if they are interested in learning more about the study. We will contact patients initially by telephone to introduce the study. Among interested patients, we will take two approaches to obtain informed consent and conduct the initial study visit based on patient preference. First, if the patient has an upcoming clinical appointment, we will coordinate the initial study visit with that clinic visit. Second,

because of the travel and clinical burden, we will also offer to perform the informed consent process and initial interviews by telephone. For several of our pilot studies we have conducted informed consent over the telephone and have not experienced any unforeseen challenges. Given the frequency at which patients are seen in clinics, we anticipate that the majority of these initial interviews will be performed in person. If a patient elects to participate in this study, we will document this in the medical record to inform all medical providers of their patients' involvement.

Patients will receive \$50 following randomization into the study, \$25 after completing 8 weeks in the study and \$25 after completion of the final assessment for a possible total of \$100.

Measures

Outcome measures will be collected on all enrolled participants by a research coordinator at baseline and the final visit. Outcome measures will be collected through surveys over the telephone. Prior to data collection, we will mail the surveys to the patient so they can visually follow while the research coordinator asks the questions and records their response. The estimated time for completion of the six surveys is approximately 30-45 minutes based on our pilot study. Subjects did not commonly report being overly burdened by the surveys.

C. Method of randomization

The unit of randomization will be the patient, performed at a ratio of 1:1 within strata using the permuted-block method with block sizes of 4 [3]. Given three stratifying variables of cancer stage (early and late), site (Seattle, Birmingham, Portland) and COPD (yes or no), there will be eight strata. Patients from each strata will be assigned to the intervention (I) or the control (C) in randomly generated sequences ICIC, IICC, CIIC, and so forth as they enter the trial.

Randomization will be conducted by a statistician on our study team. Providers will not be specifically informed of patients' treatment allocation. However, providers cannot be masked in this intervention trial and will have access to the research notes entered into CPRS by the study nurse. The research coordinator collecting baseline and final visit outcome measures will be blinded to the subject's treatment allocation.

D. Interim analysis of the data

Stopping rules

There are no formal stopping rules for safety, efficacy, and futility for the study. This determination was made based on previous studies incorporating palliative care interventions into routine care finding improvements in quality of life and depression for patients with advanced cancers. ER visits, hospitalizations, and death are expected for patients with advanced cancers. These events are due to the underlying disease or side effects from cancer treatments, not from a palliative care intervention. This study does not involve investigational medications or devices. Patients will continue to receive standard of clinical care for their lung cancer during the study.

During our pilot study, no complaints were received from study participants regarding the study procedures and there were no reported unanticipated serious adverse events due to study participation. Therefore, the study's sample size should not be impacted.

The data safety monitoring board will assess and respond to complaints and monitor all deaths,

hospitalizations, and ER visits. In the unlikely event that any unanticipated adverse events are identified, they will be reported appropriately to the facility's IRB. As stated in the consent forms, a provider may also withdraw specific patients without their consent for medical or other reasons.

If at any time during the course of the study, the DSMB judges that risk to subjects may significantly outweigh the potential benefit, the DSMB shall have the discretion and responsibility to request all necessary information for detailed analyses, and if warranted, recommend that the study be terminated. Reason to stop the trial may include a significant number of adverse events that can reasonably be attributed to participation in the study, inability to recruit and measure the required number of participants to conduct the primary outcome analyses, serious deviation from study protocols, or other circumstances that would render the study unlikely to produce scientifically valid findings. The DSMB will carefully weigh the risk of completing the trial as planned against the risk of prematurely stopping the trial for safety or futility.

E. Missing data

We will make every effort to obtain complete data on each study participant at all data collection points. Collecting survey data via telephone with the study coordinator documenting responses will facilitate complete data. However, some missing data is inevitable and creates a risk for selection bias that can skew results. Prior to evaluating our primary and secondary aims, we will perform multiple imputation (MI) which relies on the assumption that the outcome measure is missing at random (MAR) [5]. Datasets resulting from the multiple imputation procedure will be analyzed separately and the results from each data set will be summarized into one summary set of findings the ease of which is facilitated by statistical software.

F. Definition of covariates included in adjustment models

Prior to the analysis of the specific study aims, descriptive statistics, means and standard deviations for the quantitative variables, and frequencies and percentages for the categorical variables, will be calculated. All surveys will be scored according to the instructions. Differences between the intervention and control groups in baseline characteristics and clinical outcomes will be assessed using chi-squared tests for categorical variables and t-tests for continuous variables. The primary hypotheses we will test the effect of the intervention on improving quality of life scores (includes symptoms).

Analysis of Aim 1

H1: Among patients newly diagnosed with lung cancer, provision of a telephone-based palliative care intervention will be associated with a change in FACT-L TOI.

The outcome measure for this hypothesis is quality of life as measured by the FACT-L TOI. FACT-L TOI includes functional and physical well-being and lung cancer specific symptoms. We will assess the difference in FACT-L TOI between the intervention and control subjects. Patient will be the unit of analysis and we will use a multiple linear regression model to estimate the effect of the treatment group on patient outcome, adjusting baseline FACT-L TOI as well as for randomization grouping variables (site, cancer stage and diagnosis of COPD). This approach is referred to as analysis of covariance (ANCOVA). A multiple linear regression model will be constructed using FACT-L TOI as the outcome variable and include treatment

group as a covariate. The intervention will be considered a success if the indicator variable for the intervention group is significantly associated with an increase in the FACT -L TOI score. The linear model for this analysis takes the following form:

$$Y_1 = a + b(\text{treatment group}) + c(Y_0) + d(X_{i-j}) + \varepsilon$$

Where Y_1 = FACT-L TOI at the end of the study period, treatment group = intervention or control group, Y_0 = baseline FACT-L TOI, and X_{i-j} randomization grouping variables (cancer stage, site, and COPD).

We will conduct sensitivity analyses to evaluate if a difference exists between inference drawn using the multiple imputed datasets and complete case analyses. Additionally, we will conduct sensitivity analysis by including patient level covariates (race and FEV 1) in the model both together and individually to complement and elucidate primary results.

Secondary Aims

For secondary aim 1, we will evaluate if the intervention is associated with higher satisfaction of care as measured by FAMCARE-P. The evaluation of this aim will take the same form as that described for FACT-L TOI above including multiple imputation and sensitivity analyses.

For secondary aim 2, we will assess if the intervention makes a difference in patient activation to discuss their treatment preferences with their provider from baseline to the final visit. Item responses on the Health Care Communication Questionnaire are ordinal. We will use Wilcoxon rank sum test [6] to analyze the change in the score from baseline to the final visit.

For secondary aim 3, we will assess if the intervention will make a difference in improving the level of concordance between the clinicians' knowledge of the patients' life-sustaining treatment. Item responses for these questions are ordinal. We will use Wilcoxon rank sum test to analyze the difference between the subjects' and providers' responses.

For secondary aim 4, we will determine if the provision of palliative care integrated at the time of lung cancer diagnosis improves appropriate resource utilization (pharmacy, social work, dietician, spiritual care, psychology, and PT/OT) as compared to the usual care group. We will collect data on health care utilization from CDW at the end of the study period (3 years). Measures include: 1) number of hospital admissions (for any reason); 2) number of intensive care admissions; 3) use of mechanical ventilation or no use of mechanical ventilation; 4) the number of Emergency Department visits (for any reason); 5) number of cancer treatments (chemotherapy); 6) number of radiation treatments—definitive or curative; 7) fee service for hospice care; and 8) survival status. Referrals to system interdisciplinary resources (pharmacy, social work, dietician, spiritual care, psychology, and PT/OT) will be monitored on a monthly basis for all enrolled subjects.

G. Prospective tracking of serious adverse events

Data and Safety Monitoring Board

An external and independent data safety monitoring board (DSMB) will be established to examine interim study results on a periodic, scheduled basis and to recommend early termination due to the burden of participation if warranted. The issues that are raised in these interviews bring up sensitive subjects among a terminally ill group of patients and it is

reasonable to expect that the surveys may cause some patients distress. If patients have any questions or do not feel comfortable responding to specific survey questions, they have the right to refuse and will be informed of their right to opt out of any questions.

Specifically, we propose that the data safety monitoring board to assess and respond to complaints and monitor all deaths and hospitalizations.

If depression or suicidal ideation or intention is detected during the phone conversations, study staff will adhere to the VA suicide protocol.

During the administration of the study questionnaires and during the intervention telephone calls, study staff may detect symptoms of depression. If this situation occurs, we will inform the Primary Care Physician and refer the patient to Mental Health services for further evaluation. In the unlikely but possible detection of suicidal ideation, the following protocol will be followed:

The interviewer will ask, "You mentioned that you have had thoughts that you would be better off dead or hurting yourself in some way. Do you have a plan for how you would hurt yourself?" If the subject says: "I would not actually hurt myself", the interviewer may continue with the interview. If the subject endorses a plan, the interviewer would proceed as follows: "Our highest priority is keeping Veterans safe. I would like to have one of our study doctors call you to make sure you are safe."

If the Veteran indicates he/she is safe, but does not want to be evaluated by a study doctor or mental health provider, let him/her know you will need to contact the mental health provider to ensure his/her safety. In the case of possible suicidal intention or ideation, the Veteran will be provided with the VA Suicide Hotline number.

If the Veteran indicates he/she will wait for an evaluation from the study doctor or mental health provider, thank him/her and let him/her know that a doctor will be seeing him/her soon. Then call the mental health provider/study doctor to see the Veteran and assess his/her suicidality.

DSMB Role

The DSMB will provide the investigators and the IRBs with objective, scientific monitoring of the conduct of the study from the standpoint of ensuring the protection of human subjects and the integrity of the trial. It will do so by regularly monitoring adverse events (AEs) and serious adverse events (SAEs) and the quality of data, as well as reviewing and assessing the performance of the study's operations. The DSMB will convene with the investigators at least semi-annually to review study progress and provide objective recommendations, as appropriate, with respect to:

- Determination of any actions to be taken in response to AEs and SAEs reported during the study;
- Reports related to study operations and the quality of the data;
- Consideration of early termination of the study because of treatment safety concerns or inadequate performance;
- Modifications in the study protocol concerning recruitment, participant retention, data quality, outcome assessment, statistical analysis, or general trial operations.

At the end of each meeting, DSMB members will make a recommendation regarding the continuation of the trial and the date and format of the next meeting. The DSMB's findings and recommendations will be documented in the meeting minutes and transmitted to the

Investigators for their information and action, and will be incorporated into the annual Status Reports to the IRB.

Safety monitoring

Project staff will be trained to identify and report all potential AEs. To ensure unbiased determination across treatment arms, we will systematically identify AEs by query of the EHR and/or patients at each scheduled data collection time-point. AEs discovered will be investigated and reported to the IRB and DSMB according to required timelines. The DSMB may request additional information if it deems additional deliberation is warranted. The project director and/or analyst will prepare a statistical summary of the numbers and types of all AEs (serious or not), by unidentified treatment arms, for the investigators and the DSMB on a quarterly basis. At the discretion of the DSMB, the Chair may request unblinded results in order to determine the nature and extent of effect of the experimental intervention. Should the DSMB make this request, it will be fulfilled following a procedure that will maintain blinding of the investigators and the staff involved in follow-up data collection and analysis. If, at any time, the investigators believe they are seeing an unexpected increase in AEs that is a cause of concern, this will be specifically brought to the attention of the DSMB and their advice will be sought. This systematic, non-biased monitoring process will ensure that any group disparities will be effectively addressed.

References

1. Cella, D., et al., *What is a clinically meaningful change on the Functional Assessment of Cancer Therapy–Lung (FACT-L) Questionnaire?: Results from Eastern Cooperative Oncology Group (ECOG) Study 5592*. Journal of clinical epidemiology, 2002. **55**(3): p. 285-295.
2. Temel, J.S., et al., *Early palliative care for patients with metastatic non–small-cell lung cancer*. New England Journal of Medicine, 2010. **363**(8): p. 733-742.
3. Friedman, L.M., et al., *Fundamentals of clinical trials*. Vol. 4. 2010: Springer.
4. Borm, G.F., J. Fransen, and W.A. Lemmens, *A simple sample size formula for analysis of covariance in randomized clinical trials*. Journal of clinical epidemiology, 2007. **60**(12): p. 1234-1238.
5. Schafer, J.L., *Multiple imputation: a primer*. Statistical methods in medical research, 1999. **8**(1): p. 3-15.
6. Hollander, M., D.A. Wolfe, and E. Chicken, *Nonparametric statistical methods*. 2013: John Wiley & Sons.